Title: A Phase 3 Study of Relacorilant in Combination with Nab-Paclitaxel in Patients with Metastatic Pancreatic Ductal Adenocarcinoma (RELIANT)

NCT Number: NCT04329949

Date: 30 March 2022

STATISTICAL ANALYSIS PLAN (SAP)

Title	**A Phase 3 Study of Relacorilant in Combination with Nab-Paclitaxel in Patients with Metastatic Pancreatic Ductal Adenocarcinoma (RELIANT)**
Study Protocol	CORT125134-553
Phase	3
Investigational Product	Relacorilant (CORT125134)
Indication	Metastatic Pancreatic Ductal Adenocarcinoma
Protocol Version	Amendment 1
Protocol Version (date)	20 January 2020
Sponsor	Corcept Therapeutics Incorporated 149 Commonwealth Drive Menlo Park, California 94025 USA (650) 327-3270
IND Number	145582
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SAP Version / Date	V1.0 / 30 March 2022

Confidentiality Statement

APPROVAL SHEET

STATISTICAL ANALYSIS PLAN

SAP for Protocol: CORT125134-553
SAP Version / Date: V1.0 / 30 March 2022
Reviewed and Approved at Corcept Therapeutics by:
[redacted]

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	asparate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
BICR	blinded independent central review
BOR	best overall response
BSA	Body surface area
CA-125	cancer antigen 125
CA19-9	cancer antigen 19-9
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum concentration
COX2	cyclooxygenase 2
CR	complete response
CNS	central nervous system
CT	computed tomography
CYP	cytochrome P450
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DOR	duration of response
DLT	dose-limiting toxicity
DUSP1	dual-specificity phosphatase 1
ECG	electrocardiogram
eCRF	electronic case report form
EORTC	European Organization for Research and Treatment of Cancer
FACT	functional assessment of cancer therapy
FDA	food and drug administration

Abbreviation	Definition
FDG	fluorodeoxyglucose
FDG-PET	fluorodeoxyglucose-positron emission tomography
FOLFIRINOX	folinic acid, fluorouracil, irinotecan, and oxaliplatin
FOLFOX	folinic acid, fluorouracil, and oxaliplatin
GC	Glucocorticoid
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GR	glucocorticoid receptor
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HOMA-IR	homeostatic model assessment of insulin resistance
IA	Interim assessment
IA1	Interim assessment during the Open-Label Treatment Period (Part 1)
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
K_i	inhibition constant
KPS	Karnofsky performance status
MedDRA	Medical Dictionary for Regulatory Activities
mPDAC	metastatic pancreatic ductal adenocarcinoma
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NFHSI	NCCN/FACT hepatobiliary-pancreatic symptom index
OR	objective response
ORR	objective response rate

Abbreviation	Definition
OS	overall survival
PD	progressive disease
PDAC	pancreatic ductal adenocarcinoma
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred term
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious AEs
SAP	statistical analysis plan
SAS	Statistical analysis software
SOC	System organ class
SD	stable disease
SI	standard international
SUV	standardized uptake value
TEAE	treatment-emergent AEs
TTP	time to progression
ULN	upper limit of normal
US	United States
WHO	World Health Organisation
WHODD	WHO drug dictionary

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1 INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis populations and endpoints, outlines the timing of statistical analyses, and provides a comprehensive description of statistical analyses to be implemented to assess the clinical efficacy and safety of protocol CORT125134-553, amendment 1, dated 20 January 2020: A Phase 3 Study of Relacorilant in Combination with Nab-Paclitaxel in Patients with Metastatic Pancreatic Ductal Adenocarcinoma (RELIANT).

This SAP will be developed and approved prior to database lock and data analysis. Any deviations from the SAP will be documented as such in the clinical study report.

2 STUDY OVERVIEW

2.1 Overall Design

This is a Phase 3, single-arm, open-label multicenter study to assess the safety and effectiveness of relacorilant in combination with nab-paclitaxel in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC).

This is an open-label single-arm study in which patients are treated with relacorilant in combination with nab-paclitaxel to evaluate the efficacy, safety, pharmacokinetics (PK), pharmacodynamics, patient-reported outcomes (PRO) and quality of life (QoL). There is a pre-planned interim assessment after approximately 40 patients have enrolled.

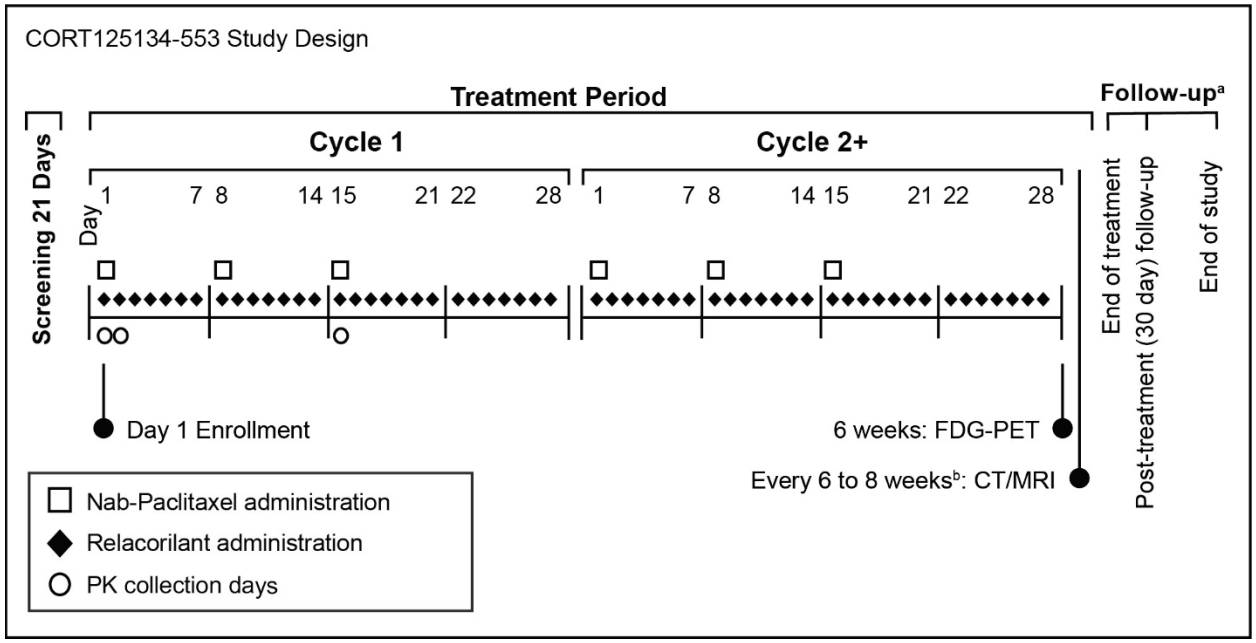
Patients who have received at least 2 prior lines of therapy for PDAC in any setting, including at least 1 prior gemcitabine-based therapy and at least 1 prior fluoropyrimidine-based therapy, and have metastatic disease are eligible for the study. Patients will enroll at approximately 30 centers in the US.

Radiographic tumor assessments will be conducted using computed tomography (CT) with contrast of the chest, abdomen, and pelvis using standard multiphasic (pancreas) CT imaging protocol guidelines. Magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis is acceptable, with Medical Monitor approval, if CT with contrast cannot be done. Imaging for other areas of suspected metastatic disease (e.g. neck, brain or bones) not covered by the required imaging should also be performed. The same method should be used for each assessment for a particular patient. Prior to initiating therapy, a baseline tumor scan is required within 21 days prior to the first dose of study treatment. This includes brain CT/MRI for patients enrolled with brain metastasis/central nervous system (CNS) metastasis disease and for patients with symptoms that may be indicative of CNS metastasis. Subsequent CT/MRI scans will be obtained every 6 weeks (±7 days) from Cycle 1 Day 1 for 24 weeks. After Week 24, subsequent CT/MRI scans will then be obtained every 8 weeks (±7 days). CT/MRI scans will continue per this schedule until unequivocal disease progression is documented, including in patients who prematurely discontinue therapy. In addition, a baseline fluorodeoxyglucose-positron emission tomography (FDG-PET) scan will be obtained prior to initiating therapy and a post-baseline FDG-PET scan will be obtained 6 weeks (±7 days) from Cycle 1 Day 1.

Tumor response will be assessed by blinded independent central review (BICR), and by the Investigator, using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Complete response (CR) and partial response (PR) will be confirmed with a subsequent scan at least 4 weeks from the first response. Tumor response by FDG-PET at 6 weeks will be assessed by BICR only per European Organization for Research and Treatment of Cancer (EORTC) criteria.

Patients will remain on treatment until unequivocal progressive disease (PD) per RECIST v1.1, as determined by the Investigator, or until meeting other criteria for discontinuation of the study regimen. Patients will return for a Post-Treatment Follow-Up Visit approximately 30 days after the patient's final dose of relacorilant or nab-paclitaxel, whichever is latest, for a final visit. Patients will be followed for survival information (i.e., date and cause of death) and information on subsequent treatments (i.e., date/duration of treatment, response, and subsequent PD). Survival follow-up will continue every 3 months until the endpoint of death, the patient is lost to follow-up, or until 2 years following the final dose of study treatment in the final patient enrolled.

Figure 1 CORT125134-553 Study Design



CT, computed tomography; FDG-PET, fluorodeoxyglucose-positron emission tomography; MRI, magnetic resonance imaging; PK, pharmacokinetic.

a Patients will return for a Post-Treatment Follow-Up Visit approximately 30 days after the patient's final dose of study treatment. Patients who discontinue treatment prior to disease progression will continue radiographic tumor assessments (CT/MRI) every 6 to 8 weeks until unequivocal disease progression. Patients will continue to be followed for survival information every 3 months.

b Patients will have CT/MRI scans every 6 weeks (±7 days) from Cycle 1 Day 1 for 24 weeks. After Week 24, subsequent CT/MRI scans will then be obtained every 8 weeks (±7 days).

2.2 Study Phases or Treatment Periods

The study consists of the following study periods:

- **Screening Period:** Within 21 days prior to the first dose of study treatment.
- **Treatment Period:** Both relacorilant and nab-paclitaxel will be administered during the Treatment Period, starting on Cycle 1 Day 1 and continuing until disease progression, unacceptable toxicity, or other treatment discontinuation criteria are met. Relacorilant (starting dose 100 mg, titrated in increments of 25 mg per cycle to a potential maximum dose of 150 mg) will be taken once daily in the morning and nab-paclitaxel 80 mg/m^2 will be administered on Days 1, 8, and 15 of each 28-day cycle.
  All patients, with exception of patients with absolute neutrophil count (ANC) >10,000/mm^3, will receive prophylactic G-CSF to reduce the risk of neutropenia starting 1 day after each nab-paclitaxel infusion. A minimum of 2 doses of granulocyte colony-stimulating factor (G-CSF) (filgrastim [5 µg/kg/day]) is recommended.
- **Safety Follow-Up Period:** Patients will return for a Post-Treatment Follow-Up Visit approximately 30 days after the patient's final dose of study treatment. Patients who discontinue treatment prior to disease progression will continue radiographic tumor assessments per the Schedule of Assessments (SoA) (every 6 to 8 weeks) until unequivocal disease progression.
- **Long-Term Survival Follow-Up Period:** All patients will be followed every 3 months after the end of treatment, (to document dates and responses to subsequent treatment, and for survival). Per protocol Section 7.6, survival information and post-therapy information will be collected at 3 month intervals (or as requested by the Sponsor to support data analysis) beginning on the date of progression and continuing until the endpoint of death, the patient is lost to follow-up, or until 2 years following the final dose of study treatment in the final patient enrolled.

3 STUDY OBJECTIVES

All study objectives apply to patients with mPDAC treated with relacorilant in combination with nab-paclitaxel.

3.1 Primary Objectives

To evaluate the objective response rate (ORR), defined as the percentage of patients with measurable disease at baseline who achieve confirmed CR or PR per RECIST v1.1, according to BICR

3.2 Secondary Objectives

3.2.1 Efficacy Objectives

- To evaluate the ORR per RECIST v1.1, as assessed by the Investigator

- To evaluate best overall response per RECIST v1.1 according to BICR and Investigator assessment
- To evaluate the duration of response (DOR) according to the Investigator and BICR
- To evaluate disease control rate (DCR) (CR, PR, or stable disease [SD]) at 18 weeks, as assessed by the Investigator
- To evaluate progression-free survival (PFS), as assessed by the Investigator
- To evaluate overall survival (OS)
- To evaluate PFS rate at 3, 6 and 12 months
- To evaluate OS rate at 3, 6 and 12 months
- To assess cancer antigen 19-9 (CA19-9) response at 8 and 16 weeks, in patients who have elevated CA19-9 at baseline
- To assess tumor response based on changes in FDG-PET scan at 6 weeks per EORTC criteria, according to BICR
- To evaluate the time to progression (TTP) on study treatment (relacorilant + nab-paclitaxel). The duration of disease control on prior nab-paclitaxel therapy (if applicable), and on the most recent therapy will also be described.

3.2.2 Safety Objectives

- To characterize the exposure-toxicity of relacorilant in combination with nab-paclitaxel
- To assess the safety and tolerability of relacorilant in combination with nab-paclitaxel

3.2.3 Pharmacokinetic Objectives

- To assess the PK of relacorilant in combination with nab-paclitaxel

3.3 Exploratory Objectives

- To assess the impact of relacorilant in combination with nab-paclitaxel on body composition, via CT/ MRI scans for sarcopenia
- To integrate changes in CA19-9 with tumor response rates by FDG-PET scan, in patients who have elevated CA19-9 at baseline
- To assess the changes in carcinoembryonic antigen (CEA) and cancer antigen 125 (CA-125) at 8 and 16 weeks in patients who do not have elevated CA19-9 at baseline
- To assess changes in Karnofsky performance status (KPS) score

3.3.1 Pharmacodynamics/Biomarkers Objective

- To explore molecular, cellular, and soluble markers in peripheral blood and/or tumor tissue that have possible relevance to the mechanism of action of, or response/resistance to, relacorilant in combination with nab-paclitaxel

3.3.2 Patient-Reported Outcomes/Quality-of-Life Objective

- To assess PRO and QoL in terms of physical function, symptoms, and utilization of health care resources

4 STUDY ENDPOINTS

4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is ORR, defined as the percentage of patients with measurable disease at baseline who achieve confirmed CR or PR per RECIST v1.1, according to BICR.

4.2 Secondary Endpoints

4.2.1.1 Secondary Efficacy Endpoints

Efficacy will be assessed by evaluating the following endpoints:

- ORR per RECIST v1.1, according to Investigator assessment
- Best overall response (BOR), defined as the best response recorded from the date of enrollment across all time points during study observation period, per RECIST v1.1 according to BICR
- BOR per RECIST v1.1 according to Investigator assessment
- DOR as measured from the date that the criteria are met for CR or PR until the first date that PD is objectively documented and determined by the Investigator
- DOR as measured from the date that the criteria are met for CR and PR until the first date that PD is objectively documented and determined by BICR
- DCR, defined as the percentage of patients who have achieved CR, PR, or SD for ≥18 weeks, as determined by the Investigator and BICR
- PFS, defined as the time from the date of enrollment to the date the patient experiences unequivocal disease progression per RECIST v1.1, as determined by the Investigator, or death (all causes of mortality). Disease progression as determined by BICR will also be assessed.
- OS, defined as the time from date of enrollment until the date of death from any cause
- PFS rate (proportion of patients who have not progressed) at 3, 6, and 12 months
- OS rate (proportion of patients surviving) at 3, 6 and 12 months
- Change in CA19-9 from baseline at 8 weeks and 16 weeks in patients who have elevated CA19-9 (CA19-9 > upper limit of normal [ULN]) at baseline
- CA19-9 response, at 8 weeks and 16 weeks, defined as the percentage of patients with elevated CA19-9 at baseline who have ≥50% reduction in CA19-9
- Tumor response assessed by FDG-PET at 6 weeks per EORTC criteria, according to BICR
- TTP on study treatment, defined as the time from enrollment to disease progression per RECIST v1.1 as determined by the Investigator

4.2.1.2 Safety Endpoints

Safety will be assessed by evaluating the following endpoints:

- Study drug exposure
- Exposure-toxicity exposure-response of relacorilant and nab-paclitaxel

- Adverse events (AEs) (including frequency, severity, and relationship to study treatment) and deaths
- Change from baseline in clinical laboratory tests
- Change from baseline in vital signs (including blood pressure, heart rate)
- Interpretation of electrocardiogram (ECG) assessments (normal, abnormal clinically insignificant, or abnormal clinically significant)
- Physical examination findings

4.2.1.3 Pharmacokinetic Endpoints

PK will be assessed by evaluating the following:

- Primary PK parameters of relacorilant and nab-paclitaxel estimated from PK sampling on Cycle 1 Days 1, 2, and 15

4.3 Exploratory Endpoints

4.3.1.1 Exploratory Efficacy Endpoints

- Presence of sarcopenia by CT/MRI scans of body composition (i.e., skeletal muscle mass)
- Change in CEA and CA-125 from baseline in patients who do not have elevated CA19-9 at baseline
- Change from baseline in KPS score

4.3.1.2 Pharmacodynamic Endpoints

Baseline assessment of:

- Homeostatic model assessment of insulin resistance (HOMA-IR)
- Immune and GC function-related cytokines
- Markers of sarcopenia or cachexia
- Hematology parameters, such as differential complete blood count
- RNA analyses from circulating cells and tumor tissue of immune, tumor, and GC-related genes such as cyclooxygenase 2 (COX2) and dual-specificity phosphatase 1 (DUSP1)
- Tumor somatic DNA mutation panel
- Tumor IHC: immune infiltrate, programmed death-ligand (PD-L1) and other exploratory markers

Change from baseline of:

- HOMA-IR
- Immune and GC function-related cytokines
- Markers of sarcopenia or cachexia
- Hematology parameters, such as differential complete blood count
- RNA analyses from circulating cells of immune, tumor, and GC-related genes such as COX2 (PTGS2) and DUSP1

4.3.1.3 Patient-Reported Outcomes and Quality-of-Life Endpoints

Changes from baseline of PRO and QoL scores according to the following instruments:

- National Comprehensive Cancer Network/FACT-hepatobiliary-pancreatic symptom index (NFHSI-18) (Butt et al. 2012)
- Patient-Reported Outcomes Measurement Information System (PROMIS) (Cella et al. 2007) short form
- EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L/VASc)
- A questionnaire for healthcare service utilization

5 SAMPLE SIZE CONSIDERATIONS

In this estimation study, the efficacy analysis will include the calculation of a 95% Confidence Interval (CI) around the ORR point estimate in the Intent-to-Treat (ITT) Population treated with relacorilant + nab-paclitaxel.

A total of approximately 80 patients in the ITT Population treated with relacorilant + nab-paclitaxel are expected in this study to provide sufficient precision for the interval estimates for the ORR. The Independent Data Monitoring Committee (IDMC) will perform an interim assessment of safety and efficacy after 40 patients have enrolled and either (1) completed at least 12 weeks of treatment, including the second radiographic tumor assessment and have at least 1 post-baseline tumor assessment with a result other than nonevaluable; or (2) discontinued the study due to disease progression or toxicity. Decision rules for the interim assessment, as described in the IDMC charter, were based on a sample size of 40 patients.

In Table 1, the 95% CI estimates around ORR were obtained using the Clopper-Pearson method (Clopper and Pearson 1934) for the interim assessment. Patients with no post-baseline radiographic tumor assessments available will be considered non-responders.

Table 1 Two-Sided 95% Confidence Intervals of Objective Response Rates with 40 Patients Treated with Relacorilant+Nab-Paclitaxel in the Intent-to-Treat Population

Number of ORs	ORR Estimate (%)	95% CI of ORR (%)
4	10.0	2.8 – 23.7
7	17.5	7.3 – 32.8
8	20.0	9.1 – 35.6

Abbreviations: CI, (Clopper-Pearson) confidence interval; OR, objective response; ORR, objective response rate.

6 ANALYSIS POPULATIONS

6.1 Intent-To-Treat Population/ Safety Analysis Population

ITT / Safety Analysis Population: ITT /Safety population will include all patients enrolled and treated with at least 1 dose of study treatment. This population will be used for all safety endpoints of the study.

6.2 Evaluable Population

Evaluable Population (Evaluable): Evaluable population will include all patients in the ITT Population who have at least one post-baseline radiographic tumor assessment (with results other than non-evaluable).

6.3 Pharmacokinetic Analysis Population

Pharmacokinetic Analysis Population (PK Population) will include all enrolled patients who have PK data collected and available for analysis.

7 DEFINITIONS, COMPUTATIONS AND CONVENTIONS

The statistical principles applied in the design and planned analyses of this study are consistent with International Council for Harmonisation (ICH) E9 guidelines (ICH 1998) and the Food and Drug Administration (FDA) Guidance for Industry: *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (2018). All statistical analyses detailed in this SAP will be conducted using SAS version 9.4 or higher.

7.1 Definitions

Enrollment date: Enrollment date is the date of first dose of study treatment (relacorilant+ nab-paclitaxel), i.e., Cycle 1 Day 1.

Study day: Study day for safety will be calculated in reference to the date of the first dose of relacorilant (study treatment). For assessments conducted on or after the date of the first dose of study drug, study day will be calculated as (assessment date - date of first dose of study drug + 1). For assessments conducted before the date of the first dose of study drug, study day is calculated as (assessment date - date of first dose of study drug). There is no study day 0.

Treatment-emergent period: The treatment-emergent period is defined as the period of time from the date and time of the first dose of study drug (relacorilant or nab-paclitaxel whichever is earliest) through 30 days after the final dose of study drug (relacorilant or nab-paclitaxel whichever is latest).

The treatment-emergent period will be used in the summaries of treatment-emergent adverse events (TEAEs).

Baseline and postbaseline value: Unless otherwise specified, a baseline value is defined as the most recent value prior to the first dose of study treatment including baseline characteristics. A postbaseline value is defined as an assessment obtained after the first dose of study treatment.

Baseline and postbaseline value for safety analyses: Unless otherwise specified, a baseline value for safety analyses is defined as the last value before the date/time of first dose of study treatment for laboratory tests, vital sign assessments, and ECG data. A postbaseline value for safety analyses is defined as a measurement taken after the date/time of first dose of study treatment. If multiple toxicity grades are present for the same date, the worst toxicity grade will be used in the summaries of toxicity grade by laboratory tests. For triplicate measurements of ECG, average of these values will be used in the summaries presented by visit. For all other

safety parameters, if multiple measurements are present for the same date, latest available value will be considered for summaries.

Last dose date: Last dose date is defined as the date of last dose of study treatment (relacorilant or nab-paclitaxel, whichever is last) from the end of treatment – relacorilant and nab-paclitaxel electronic case report forms (eCRFs).

7.2 Reporting Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- Mean and median values will be formatted to 1 more decimal place than the measured value. Standard deviation values will be formatted to 2 more decimal places than the measured value; minimum and maximum values will be presented to the same number of decimal places as the measured value.
- Percentages will be rounded to 1 decimal place. Number and percentage values will be presented as xx (xx.x%).
- Listings will be presented for relacorilant + nab-paclitaxel and will be sorted for presentation in order of patient identifier and date of procedure or event.
- Analysis and summary tables will have the analysis population sample size (ie, number of patients).
- Laboratory data will be reported using standard international (SI) units; as local laboratories are used for this study, conversion factors from conventional units will be listed in the clinical study report.
  For example 1 inch = 2.54 cm.
- Time-to-event or duration of event endpoints will be based on the actual date the radiographic scan was obtained rather than the associated visit date.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with non-missing data as the denominator unless otherwise specified.
- For time-to-event right-censored data, the summary statistics and descriptions will include Kaplan-Meier plots and/or life tables.
- For other continuous endpoints, the summary statistics will include mean, standard deviation, median, and range (minimum and maximum).
- For categorical endpoints, the summary statistics will include frequency counts and percentages.
- Confidence intervals (CIs), when presented, will generally be constructed at the 95% level. For binomial variables, exact methods will be employed unless otherwise specified.
- Medical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v 23.0. Adverse event severity will be evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v.5.0).
- Prior therapies and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and summarized by Anatomical Therapeutic Chemical (ATC) therapeutic subgroup and preferred drug names.

7.3 Conventions for Dates

Conventions for calculations with dates are as follows:

- Dates will be stored as numeric variables in the statistical analysis software (SAS) analysis files and reported in DDMMMYYYY format (ie, the Date9. datetime format in SAS).
- Dates recorded in comment fields will not be imputed or reported in any specific format.
- Intervals that are presented in weeks will be transformed from days to weeks by using the following conversion formula, and rounding to 1 decimal place:
  WEEKS = DAYS / 7
- Intervals that are presented in months will be transformed from days to months by using the following conversion formula, and rounding to 1 decimal place:
  MONTHS = DAYS / 30.4375

7.4 Treatment Group Presentation

Patient disposition, protocol deviations, demographics and baseline characteristics, medical history, prior medications and procedures, efficacy and safety data summaries will be presented using ITT population.

7.5 Handling of Missing Data

Missing data will not be imputed unless otherwise specified.

In safety analyses, for incomplete date of last dose of study drug or incomplete start date of a new antitumor treatment that are missing the day of the month, the 15th of the month will be used to impute the missing data. When imputing partial last dose dates, the last assessment date and death date will be taken into consideration.

Adverse Events and Concomitant Medications

Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures. The imputed dates will be used to determine the treatment emergent period. For adverse events with a partial date, available date parts (year, month, and day) of the partial date will be compared with the corresponding date components of the start date and end date of the treatment-emergent period to determine if the event is treatment emergent. When in doubt, the adverse event will be considered treatment emergent by default. The following rules will be applied to impute partial dates for adverse events:

If start date of an adverse event is partially missing, impute as follows:

- If both month and day are missing and year = year of treatment start date, then set to treatment start date
- If both month and day are missing and year ≠ year of treatment start date, then set to January 01
- If day is missing and month and year = month and year of treatment start date, then set to treatment start date

- If day is missing and month and year ≠ month and year of treatment start date, then set to first of the month
- If only year is missing or start date is completely missing, set to treatment start date as long as adverse event end date is not before treatment start date

If end date of an adverse event is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If only year is missing or end date is completely missing, do not impute

When the start date or end date of a medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant (or both). The following rules will be applied to impute partial dates for medications:

If start date of a medication is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month

If end date of a medication is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month

If only year is missing or start date or end date of a medication is completely missing, do not impute.

Primary Cancer Diagnosis

If the diagnosis date of primary cancer is partially missing, the following rules will be applied to impute partial dates:

- If both month and day are missing and year = year of treatment start date, then set to treatment start date.
- If both month and day are missing and year ≠ year of treatment start date, then set to December 31.
- If day is missing and month and year = month and year of treatment start date, then set to treatment start date.
- If day is missing and month and year ≠ month and year of treatment start date, then set to the last day of the month.

7.6 Visit Windows

Visit windows will be used to associate assessments with a scheduled visit for summarizing data by visit.

Study visits will align with nab-paclitaxel infusion days during the Treatment Phase. Screening hematology and chemistry laboratory tests can be used for the Cycle 1, Day 1 values if collected within 48 hours of the first dose of study treatment. For all other visits, hematology and

chemistry should be performed within the prior 24 hours (relative to the study visit/nab-paclitaxel infusion).

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

The Long-term follow-up assessments should be done every 3 months (±7 days) until the endpoint of death, the patient is lost to follow-up, or until 2 years following the final dose of study treatment in the final patient enrolled.

For efficacy assessments and AEs, data from both planned visits and unscheduled visits will be assessed and summarized.

For all other by-visit safety assessments, unscheduled visits will be mapped into analysis visit windows as shown in Table 2. If more than one assessment occurs within a given analysis visit window, (1) the planned visit will be always used in summaries for the given visit; (2) if all visits are unscheduled visits, the assessment closest to the target date will be used.

Table 2 Analysis Visit Windows for Safety Assessments

Visit Name	Start Day	Target Day	End Day
Baseline/Cycle 1 Day 1	----	1	----
Cycle 1 Day 8	2	8	11
Cycle 1 Day 15	12	15	22
Cycle 2 Day 1	23	29	32
Cycle 2 Day 8	33	36	39
Cycle 2 Day 15	40	43	50
Cycle 3 Day 1	51	57	60
Cycle 3 Day 8	61	64	67
Cycle 3 Day 15	68	71	78
----	----	----	----
EOT		Study Day of Final Dose of Study drug	
Follow-up	>Study Day of Final Dose of Study Drug (relacorilant or nab-paclitaxel, whichever is latest)	Study Day of Final Dose of Study Drug + 30	Study Day of Final Dose of Study Drug + 31

8 TIMING OF ANALYSES

An Independent Data Monitoring Committee (IDMC) will be established to conduct periodic and ad hoc medical and/or statistical reviews of available data to protect the safety and ethical interest of patients and protect the scientific validity of the study. The IDMC will comprise independent consultants (medical and statistical) with relevant expertise. The IDMC will be provided with data from this study, including safety and efficacy variables, for periodic review.

The IDMC will review data as follows.

1) An interim assessment will occur after approximately 40 patients have enrolled and have met at least one of the following criteria:
    1. Completed at least 12 weeks of treatment, including the second radiographic tumor assessment and have at least 1 post-baseline tumor assessment with a result other than nonevaluable.
    2. Discontinued the study due to disease progression or toxicity.

Enrollment will be paused such that the interim assessment can be conducted by the IDMC before additional patients are enrolled.

Subsequent reviews of safety will occur as specified by the IDMC, with a minimum frequency of approximately every 12 months. The IDMC may recommend changes in the protocol based on futility, toxicity, or compelling evidence of efficacy.

Final analyses will be performed after completion of safety follow-up of the final patient enrolled in the study.

9 STATISTICAL METHODS

Analysis populations will be specified for each of the endpoints.

9.1 Patient Disposition

Patient populations will be summarized for all patients enrolled and will include the number and percentage of patients in the ITT/safety, evaluable and PK populations.

Disposition summaries will present number of patients enrolled, number treated, and among those treated, number who completed and discontinued treatment. Primary reason for discontinuation of treatments (relacorilant or nab-paclitaxel), including any of the following, will be summarized:

- Adverse event
- Disease progression as defined by RECIST 1.1
- Clinical disease progression
- Non-compliance with study drug
- Patient decision to discontinue treatment
- Patient withdrew consent for study
- Physician decision
- Lost to follow-up

- Protocol deviation
- Pregnancy
- Study terminated by sponsor
- Death
- COVID-19
- Other

Counts and percentages of patients who complete the study and those who discontinue for any of the following reasons will also be calculated:

- Death
- Protocol non-compliance
- Withdrawal of consent for study
- Investigator decision
- Pregnancy
- Lost to follow-up
- Termination of study by sponsor
- COVID-19
- Other

9.2 Protocol Deviations

Protocol deviations will be categorized as "Important" or "Other" according to the protocol deviation specification document. Important protocol deviations that occur during the study will be summarized by deviation category for all patients in the ITT population. A by-patient listing of all deviations will be provided.

Patient eligibility including inclusion and exclusion criteria that were not met will be summarized for all patients in the ITT population.

9.3 Demographic Characteristics

The following patient characteristics collected will be presented in data listings and summarized for the ITT Population:

- Age (in years) at informed consent (continuous and categorical variables: < 50, 50 to 65, > 65; <65 and ≥65) will be summarized
- Sex
- Of childbearing potential (Yes/No)
- Ethnicity
- Race

9.4 Disease Characteristics and Previous Therapies

Disease characteristics at baseline will be listed including date and stage at study entry, presence of regional nodal metastasis, sites of metastatic disease along with other relevant data collected in the eCRF. Sites of visceral disease (liver, lung, peritoneum, and brain) and number of

metastatic sites (1, 2, 3, >3) will be summarized. Laboratory tumor markers including CA19-9, CA-125 and CEA will also be summarized.

Prior cancer treatments include surgeries, systemic and radiation therapies will be summarized for ITT population.

Prior cancer surgeries: Number of patients reporting at least one prior surgery will be summarized and listed which include type and date of surgeries.

Prior systemic therapies: Number of patients reporting systemic therapies, line of therapies number, line of therapy setting and best overall response, reason for discontinuation will be summarized. Number of prior systemic lines (2, 3, >3), prior taxane, and prior nab-paclitaxel will be summarized. Listings include all relevant data including start/stop dates and medications included in the prior systemic therapy collected in the eCRF.

Prior Radiotherapy: A listing will display all entries for prior radiotherapies received by date of first dose. Patients who received at least one prior radiotherapy, tumor location, total dose received, and disease progressed in the area will be summarized.

9.5 Medical History

Medical History: All medical history verbatim terms will be coded using the MedDRA version 23.0 and ordered by system organ class (SOC) and preferred term (PT). At each level of summation (SOC, PT), patients reporting more than one medical condition will be counted only once. All surgeries that are not related to the cancer under study will be listed and summarized separately.

Oncology History: For each patient, date and stage of initial diagnosis, primary location of primary tumor, histologic features and grade, and current extent, site of metastatic disease along with other relevant data collected in the eCRF will be listed. A summary table will summarize these disease history characteristics. Patients with prior pancreatectomy and biliary stent will also be summarized.

Cancer mutation: All data collected under “Cancer mutations” form will be listed.

History of tobacco and alcohol use: Patient history of tobacco and alcohol use as noted on the Demographics eCRF during screening will be listed and summarized.

All medical history summaries will be based on ITT population.

9.6 Concomitant Medications and Subsequent Therapies

Any concomitant medication used by patients will be recorded on eCRF. Indication for use, whether taken for medical history or AE, start and end date, ongoing, dose, dose formulation, frequency, and route of administration will be noted. Medications are considered concomitant if exposure occurs during the treatment-emergent period (as defined in Section 7.1). A patient reporting use of the same medication more than once will be counted once in the calculation of the number and percentage of patients who received that medication.

The imputation rules for missing start and end date of a concomitant medication are described in Section 7.5.

Verbatim terms from the eCRF will be mapped to ATC class and Generic drug names using the WHODD Global B3 August 2020 coding dictionary.

A listing will display all entries for medications received by a patient, ordered by "Start date". The listing will display the recorded term from the eCRF and, adjacent to that, the ATC level 2 class (therapeutic subgroup) and the preferred drug name.

A summary table will be organized to display the therapeutic subgroup (2^{nd} level) and preferred drug name. It will include counts and percentages of patients who reported using at least one medication in each therapeutic subgroup.

A data listing will be provided for all concomitant procedures and/or surgeries.

Post-treatment radiotherapy, systemic therapies and subsequent anticancer therapies and surgeries received will be listed and summarized.

All summaries will be based on ITT population.

The duration of treatment on the prior nab-paclitaxel regimen (if applicable) and on the most recent treatment regimen will be calculated and presented in the listing.

9.7 Extent of Exposure and Study Drug Compliance

All recorded information on dosing of relacorilant, including date, time and dose administered (or relevant reason if not administered), actual dose, as well as drug accountability will be presented in a data listing by date of administration.

A separate data listing and summary table will present data collected on nab-paclitaxel administered via an IV infusion. Planned dose level, planned dose, actual dose, whether infusion was interrupted and reason, will be included.

Relacorilant exposure

Following summaries will be provided using relacorilant exposure data.

- Number of cycles of treatment: The number of cycles of treatment will be presented based on the last visit when the patient received treatment.
- Duration of exposure: The duration of exposure for the study drug will be presented in days and calculated as the date of last dose of study drug minus the date of the first dose of study drug, plus one.
- Total dose received: The total dose received for the study drug will be the sum of the actual dose administered for the duration of exposure. For patients where their dose received is either zero or missing, a received dose of zero is included in the total dose received derivation.
- Total dose expected: Expected dose of relacorilant for each patient is set to 100 mg in Cycle 1, 125 mg in Cycle 2 and 150 mg in Cycle 3 irrespective of the actual dose increase. Relacorilant is expected to be taken daily starting at Cycle1 Day 1. A patient

will have expected dose calculations based on all days within a cycle as determined by the earliest start date and the latest end date within a given cycle. For patients where their dose received is either zero or missing, an associated expected dose is included in the total dose expected derivation.

- Relative dose intensity: Relative dose intensity is calculated for the study drug as the total dose received divided by the total dose expected, multiplied by 100.

Nab-Paclitaxel exposure

Following summaries will be presented using nab-paclitaxel exposure data.

- Numbder of cycles of treatment: The number of cycles of treatment will be presented based on the last visit when the patient received treatment.
- Number of infusions: The cumulative number of nab-paclitaxel infusions will be presented.
- Duration of exposure: The duration of exposure to the study drug will be presented in days and calculated as the date of last dose of study drug minus the date of the first dose of study drug, plus one.
- Total dose expected: nab-paclitaxel is expected to be taken on Day 1, 8, and 15 of each cycle. The planned nab-paclitaxel dose is calculated from the field "Planned Nab-Paclitaxel dose" of eCRF "Nab-Paclitaxel administration" page. Total dose expected is the sum of planned dose divided by the body surface area (BSA). BSA will be calculated using height and weight value captured in the eCRF nearest and prior to the drug administration date.
- Relative dose intensity: Relative dose intensity is calculated for the study drug as the total dose received divided by the total dose expected, multiplied by 100. The actual Nab-paclitaxel dose is calculated from the field "Actual Nab-Paclitaxel dose administered" of eCRF "Nab-Paclitaxel administration" page. Total dose received is the sum of actual dose divided by BSA.

Data on G-CSF therapy include therapy name, indication, start date, end date, dose level, dose, route and frequency of therapy. A summary table and a listing will be provided for G-CSF therapies.

9.8 Efficacy Analyses

The ITT population as defined in Section 6, will be used to address the primary, secondary and exploratory efficacy objectives of the study. Evaluable population will also be used to provide summaries for all efficacy endpoints. Disease response and progression assessed according to RECIST v1.1 by the Investigator or BICR will provide the basis for efficacy endpoints.

At all scheduled visits, data recorded for target, non-target, and new lesions, and Investigator response assessment will be presented in by-patient listings. Summary tables and figures will be provided for endpoints as described in the following sections.

Response rate endpoints will be summarized by providing the point and interval estimates. Time-to-event variables will be summarized using Kaplan-Meier estimates and plots.

9.8.1 Multiplicity Adjustment for Efficacy Analyses

No multiplicity adjustments were required for efficacy analyses.

9.8.2 Primary Efficacy Endpoint

ORR is defined as the percentage of patients with measurable disease at baseline who achieve confirmed CR or PR per RECIST v1.1, according to BICR. Patients in the ITT Population with no valid post-baseline radiographic tumor assessments will be considered as non-responders.

If patients discontinue earlier than 12 weeks with progressive disease, they will be considered non-responders.

9.8.2.1 Primary Analysis

The primary analysis of ORR per BICR will be performed in the ITT Population. The point estimate and 95% CI will be provided using the Clopper-Pearson method (Clopper and Pearson 1934).

ORR will also be analyzed in the Evaluable Population, as a supportive analysis to the primary endpoint analysis.

9.8.2.2 Sensitivity Analyses

In a sensitivity analysis of the primary endpoint of ORR per Investigator, patients in the ITT population who receive prohibited concomitant medications will be excluded.

9.8.3 Secondary Efficacy Endpoints

Unless stated, all the secondary endpoints will be evaluated in patients treated with relacorilant + nab-paclitaxel.

9.8.3.1 ORR per RECIST v1.1 according to investigator assessments

ORR according to investigator assessments will be summarized similar to primary efficacy endpoint analysis.

9.8.3.2 Best overall response according to BICR

For each patient, BOR will be derived from the date of enrollment across all time points during study observation period, per RECIST v1.1 according to BICR. Patients who have a post-baseline scan that cannot be evaluated because of the quality of the image or other reasons will have “non-evaluable” recorded as their response at that visit. If all post-baseline scans are non-evaluable, the patient will have “non-evaluable” recorded as their best response.

BOR rates will be summarized by the number and percentage of patients within each response category (CR, PR, SD, PD, or non-evaluable).

Waterfall plots will visually illustrate the best percent change in tumor burden (sum of longest diameter for all non-nodal target lesions and shortest diameter for nodal target lesions) measured

on a post-baseline scan. On the y-axis, a positive value represents increase in tumor burden, and a negative value represent maximum decreases in tumor burden. The vertical bars will also indicate (through different colors) the BOR of CR, PR, SD or PD. Waterfall plots will include all patients in the ITT population with measurable disease at baseline and at least one post baseline measurement.

9.8.3.3 Best overall response according to Investigator assessment

BOR per RECIST v1.1 according to Investigator assessments will be summarized similar to BOR analysis according to BICR assessment.

9.8.3.4 Duration of Response as determined by the Investigator

DOR is defined as the time from the date that the criteria are met for CR or PR until the first date that PD is objectively documented and determined by the Investigator. Patients who do not experience PD and are alive as of the analysis cutoff date will be censored at the date of last adequate tumor assessment. Censoring rule is described in Table 3.

DOR (months) = (date of progression, death, or censoring – date of first documented objective response + 1)/30.4375

Estimates of median DOR with 95% CIs will be computed using the Kaplan-Meier method. Kaplan-Meier graphs will visually display DOR.

Table 3 Censoring Rules for analysis of DOR

Censoring Categories	Date of Censoring
Patients who did not have documented progression and did not die	Date of the last adequate tumor assessment
Patients who did not have documented progression as determined by the investigator on or before initiation of a new anticancer therapy and did not die on or before the data cutoff date	Date of the last adequate tumor assessment on or before initiation of a new anticancer therapy and on or before the data cutoff date
Patients who had 2 or more consecutive missed scheduled tumor assessments immediately prior to disease progression	Date of the last adequate tumor assessment without evidence of disease progression before the 2 missed tumor assessments
Patients who did not have documented progression and died more than 112 days from most recent tumor assessment.	Date of the last adequate tumor assessment

If a patient meets the criteria for more than 1 censoring rule, the earliest censoring date will be considered.

9.8.3.5 Duration of Response as determined by BICR

DOR per BICR will be assessed as measured from the date of the tumor scan documenting CR or PR until the date of first documented PD or death, whichever comes first.

9.8.3.6 Disease Control Rate

DCR is defined as the percentage of patients who have achieved CR, PR, or SD for ≥18 weeks, as determined by the Investigator and BICR. Patients in the ITT Population with no valid post-baseline radiographic tumor assessment will be considered non-responders.

The point estimate and 95% CI will be calculated using the Clopper-Pearson method.

Summaries will also be presented based on BICR assessments.

Exploratory DCR will be calculated for ≥6 weeks and for ≥12 weeks, respectively.

9.8.3.7 Progression Free Survival

PFS is defined as the time from the date of enrollment to the date the patient experiences unequivocal disease progression per RECIST v1.1, as determined by the Investigator, or death (all causes of mortality), whichever comes first. Both BICR and Investigator assessments will be considered and analyzed separately.

> PFS (months) = (first documented date of progression, death, or censoring – date of enrollment + 1)/30.4375

All events of disease progression or death will be counted regardless of whether the event occurred while the patient was on study drug or had previously discontinued treatment. Patients who do not experience disease progression or death will be censored at the date of last adequate tumor assessment. Censoring rules in Table 4 will be applied.

Table 4 Censoring Rules for the Analysis of PFS

Censoring Categories	Date of Censoring
Patients who did not have baseline or post-baseline tumor assessments and did not die	Enrollment date +1
Patients who did not have unequivocal progression and did not die	Date of the last adequate tumor assessment
Patients who did not have documented progression as determined by the investigator on or before initiation of a new anticancer therapy and did not die on or before the data cutoff date	Date of the last adequate tumor assessment on or before initiation of a new anticancer therapy and on or before the data cutoff date
Patients who had 2 or more consecutive missed scheduled tumor assessments immediately prior to unequivocal disease progression	Date of the last adequate tumor assessment without evidence of unequivocal disease progression before the 2 missed tumor assessments
Patients who did not have documented progression and died more than 112 days from last tumor assessment.	Date of the last adequate tumor assessment

Estimates of median PFS with 95% CIs will be computed using the Kaplan-Meier method. Kaplan-Meier graphs will visually display PFS.

9.8.3.8 Overall Survival

OS is defined as the time from enrollment until the date of death from any cause. If a patient is alive or no known death date, OS will be censored at the date of last contact.

OS (months) = (date of death or censoring – date of enrollment + 1)/30.4375

Median, 25th and 75th percentiles of OS, in months, with 95% CIs will be summarized and plotted graphically using the Kaplan-Meier estimates.

9.8.3.9 PFS rate at 3, 6, and 12 months

The proportion of patients who are progression-free (as defined above) at 3, 6 and 12 months will be summarized using Kaplan-Meier estimates.

9.8.3.10 OS rate at 3, 6 and 12 months

The proportion of patients surviving (as defined above) at 3, 6 and 12 months will be summarized using Kaplan-Meier estimates.

9.8.3.11 Change in CA19-9 from baseline at 8 and 16 weeks

Change in CA19-9 from baseline in patients who have elevated CA19-9 at baseline (baseline CA19-9 >ULN) will be reported. Descriptive statistics will be provided at each of the time points during the observation period.

9.8.3.12 CA19-9 response at 8 and 16 weeks

CA19-9 response is defined as the percentage of patients with elevated CA19-9 at baseline (baseline CA19-9 >ULN) who have ≥50% reduction in CA19-9. CA19-9 response rate at 8 weeks and 16 weeks will be reported. The point estimate and the 95% CI using the Clopper-Pearson method will be presented.

9.8.3.13 Tumor response assessed by FDG-PET at 6 weeks per EORTC criteria, according to BICR

FDG-PET tumor response will be summarized at 6 weeks. FDG-PET response will be reported as the number and percentages of patients achieving complete metabolic response, partial metabolic response, stable metabolic disease, and progressive metabolic disease according to BICR assessment of changes in standardized uptake values (SUVs) from the baseline FDG-PET scan to the post-baseline (6-week) scan using EORTC criteria (Young et al. 1999). The SUVs obtained from FDG-PET scans will be summarized by visit in a table and presented graphically in waterfall plots.

9.8.3.14 Time to progression on study treatment, as determined by the Investigator

TTP is defined as the time from enrollment to disease progression per RECIST v1.1 as determined by the Investigator. TTP will be analyzed using Kaplan-Meier estimates. Censoring rules in Table 4 will be applied as well.

9.8.4 Exploratory Efficacy Endpoints

Presence of sarcopenia by CT/MRI scans of body composition (i.e., skeletal muscle mass)

The percent change in skeletal muscle mass from baseline will be summarized. Summary statistics will be provided at each of the post-baseline time points during the observation period.

Change in CEA and CA-125 from baseline in patients who do not have elevated CA19-9 at baseline: Change in CEA and CA-125 from baseline, in patients who do not have elevated CA19-9 at baseline, will be reported for each time point using summary statistics during the observation period.

The percentage of patients with elevated CEA (≥2.5 ng/mL) who have ≥50% reduction in CEA, at 8 weeks and 16 weeks, will be reported for ITT and evaluable populations, respectively. Point estimates and 95% CIs using Clopper-Pearson method will be provided.

The percentage of patients with elevated CA-125(>35 U/mL) who have ≥50% reduction in CA-125, at 8 weeks and 16 weeks, will be reported for ITT and evaluable populations, respectively. Point estimates and 95% CIs using the Clopper-Pearson method will be provided.

Change from baseline in KPS score: KPS score will be assessed by two observers. If the values obtained by each observer are discrepant, the one with the lowest assessment will be considered. Summary statistics will be provided for KPS score at screening, baseline and at each of the post-baseline time points during the observation period. The changes of KPS score from baseline will be summarized by post-baseline visits. Patient data will be listed.

Pharmacodynamic Analysis

Analyses of pharmacodynamic parameters will be described in a separate document.

Patient Reported Outcomes and Quality of Life Assessment

PRO and QoL will be assessed in this study using the NFHSI-18 questionnaire (Butt et al. 2012), PROMIS (Cella et al. 2007) short form, EQ-5D-5L/VASc (Herdman et al. 2011), and a questionnaire for healthcare service utilization.

NFHSI-18 questionnaire data will be listed and summarized.

Baseline PRO and QoL assessments will be collected at Screening prior to the first dose of study treatment. Post-baseline assessments will be collected every cycle starting with Cycle 2 Day 1, at the End-of-Treatment Visit, and at the 30-Day Post-Treatment Follow-Up Visit.

PROMIS Physical Function: Self-reported measure of physical capability, including functioning of upper extremities (dexterity), lower extremities (walking or mobility), central regions (neck,

back), as well as instrumental activities of daily living such as running errands, will be obtained at scheduled visits.

EQ-5D-SL/VASc: The five dimensions of this instrument, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, along with a visual analog score for overall health will be assessed at designated visits. The same will be listed and summarized.

PRO and QoL will be analyzed in the ITT Population and summarized for patients experiencing clinical benefit (response and/or disease control ≥18 weeks). Summary statistics will be provided for baseline and observed values at all post-baseline timepoints during the observation period. Data collected using the PRO instruments and QoL assessments will be listed.

Data from healthcare utilization form will be summarized and listed including data on urgent care visits, emergency department visits and use of inpatient hospital services.

9.8.5 Subgroup Analyses

BOR and DCR per Investigator assessment will be analyzed for the following subgroups of the ITT and Evaluable Populations:

- Prior lines of therapy (2 vs. ≥3)
- KPS score (≥70 to <90 vs. ≥90 to 100, 70 vs 80+)
- Site of metastatic disease (lung and lymph nodes only vs. liver vs. diffuse disease)
- Time since diagnosis of pancreatic ductal adenocarcinoma to time of informed consent (<=12 months vs. > 12 months)
- Duration of last treatment
- Duration of last prior nab-paclitaxel
- Prior systemic therapy

Forest plot of DCR for SD ≥6 Weeks and SD ≥12 Weeks will be generated for age (<65, ≥65), sex, KPS, prior lines of therapy (2, 3, 4), metastatic disease at baseline, CA19-9 at baseline and prior nab-paclitaxel for ITT and evaluable populations respectively.

9.9 Pharmacokinetic Analyses

The PK of relacorilant and nab-paclitaxel will be assessed in the PK population. Intensive PK sampling will occur on Cycle 1 Day 15 and will consist of a total of 7 samples collected at the following time points: pre-dose (0 hour), 0.5, 0.75, 1, 2, 4, and 6 hours post-dose. Where possible, the following PK parameters will be calculated:

- $AUC_{0\text{-}6h}$: AUC values from time 0 to 6 hours post-dose.
- $AUC_{0\text{-}24h}$: AUC values from time 0 to 24 hours post-dose.
- AUC_{last}: AUC values from time 0 to time of last measurable concentration.
- C_{max}: Maximum concentration.
- C_{last}: Minimum concentration from time 0 to time of last measurable concentration.
- T_{max}: Time to maximum concentration.
- T_{last}: Time after dosing of the last quantifiable concentration.

- λ_z: Apparent terminal rate constant.

PK parameters will be listed and summarized using descriptive statistics.

9.10 Safety Analyses

All safety analyses will be performed on the safety analysis population. Data collected on study drug exposure, adverse events, deaths, clinical lab assessments, concomitant medications and therapies, physical examination, vital signs, 12-lead ECG will be presented in data listings and summary tables.

9.10.1 Adverse Events

AEs will be collected immediately following signing of informed consent and will continue until 30 days after the last dose of relacorilant or nab-paclitaxel, whichever is latest. An abnormal laboratory value that leads to a dose modification/interruption, treatment discontinuation, or patient withdrawal from the study will be recorded as an AE. Adverse events reported more than 30 days after the last dose of study treatment will be considered post-treatment AEs.

Incidence of AEs will be listed and summarized using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 by system organ class and preferred term. A hierarchical listing will display the MedDRA system organ classes represented in the data, and within each system organ class, the listing will display each unique preferred term ordered alphabetically. Adverse event listings will show missing relationship as missing. Tabular summaries with numbers and percentages of patients that have the following adverse events will be provided:

- Overview of TEAEs
- Summary of TEAEs:
  - by SOC and PT
  - by decreasing incidence of PT
  - by SOC, PT, and maximum severity
- Summary of TEAEs related to relacorilant by investigator assessment:
  - by decreasing incidence of PT
- Summary of TEAEs related to nab-paclitaxel by investigator assessment:
  - by decreasing incidence of PT
- Summary of treatment-emergent serious adverse events:
  - by SOC and PT
  - by decreasing incidence of PT
  - by SOC, PT, and maximum severity
  - Related to relacorilant per investigator by SOC and PT
  - Related to nab-paclitaxel per investigator by SOC and PT
- Summary of TEAEs with action taken of permanent discontinuation of relacorilant:
  - by decreasing incidence of PT
- Summary of TEAEs with action taken of permanent discontinuation of nab-paclitaxel:

  - by decreasing incidence of PT
- TEAEs by SOC and PT occurring in at least 10% of the Safety Population
  - Related to relacorilant per investigator by SOC and PT
  - Related to nab-paclitaxel per investigator by SOC and PT
- TEAEs with fatal outcome
  - by SOC and PT
  - by decreasing incidence of PT
  - Related to relacorilant per investigator by SOC and PT
  - Related to relacorilant per investigator by decreasing frequency of PT
  - Related to nab-paclitaxel per investigator by SOC and PT
  - Related to nab-paclitaxel per investigator by decreasing frequency of PT
- Grade 3 or higher TEAE by SOC and PT
  - by SOC and PT
  - by decreasing incidence of PT
- Grade 3 or higher TEAEs related to relacorilant by investigator assessment
  - by SOC and PT
  - by decreasing incidence of PT
- Grade 3 or higher TEAEs related to nab-paclitaxel by investigator assessment
  - by SOC and PT
  - by decreasing incidence of PT
- TEAEs leading to dose reductions for relacorilant
  - by SOC and PT
  - by decreasing incidence of PT
- TEAEs leading to dose interruptions for relacorilant
  - by SOC and PT
  - by decreasing incidence of PT
- TEAEs leading to dose reductions for nab-paclitaxel
  - by SOC and PT
  - by decreasing incidence of PT
- TEAEs leading to dose interruptions for nab-paclitaxel
  - by SOC and PT
  - by decreasing incidence of PT
- TEAEs reported due to COVID-19 by SOC and PT
- TE Neutropenia by decreasing incidence of PT

At each level of summarization (e.g., any AE, SOC, and PT), patients experiencing more than one AE will be counted only once within each dose level or follow-up period. In the summary of TEAEs by severity grade, patients will be counted once at the highest severity reported at each

level of summarization; in the summary of TEAEs by relationship, patients will be counted once at the closest relationship to study drug.

Adverse events that are associated with infections due to SARS-CoV-2, including adverse events reported as COVID-19, will be summarized to assess the impact of the 2020 pandemic on the results.

9.10.1.1 Identified Risks and General Safety Topics

Neutropenia incidence and severity will be examined as described in Section 9.10.1:
TE Neutropenia by decreasing incidence of PT

In addition, following combined categories of TEAEs will be analyzed (Table 5).

Table 5 Selected TEAEs

Selected TEAEs	Preferred Terms
Neutropenia-1	neutropenia, neutrophil count decreased
Neutropenia-2	neutropenia, neutrophil count decreased, leukopenia, white blood cell count decreased
Neutropenia-3	neutropenia, neutrophil count decreased, leukopenia, white blood cell count decreased and febrile neutropenia
Anemia	anemia, hemoglobin decreased
Thrombocytopenia	thrombocytopenia, platelet count decreased
Pancytopenia	pancytopenia, neutropenia, neutrophil count decreased, leukopenia, white blood cell count decreased, febrile neutropenia, anemia, hemoglobin decreased, thrombocytopenia, platelet count decreased
Abdominal pain	abdominal pain, abdominal pain upper, abdominal lower
Fatigue	asthenia, fatigue
Peripheral neuropathy	peripheral sensory neuropathy, peripheral neuropathy, neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, neurotoxicity, hypoesthesia, dysesthesia

9.10.2 Deaths

All deaths, date and primary cause, whether they occurred during treatment or after 30-day follow-up, and whether an autopsy report is available will be listed and summarized.

9.10.3 Clinical Laboratory Tests

Screening Hepatitis B and C serologies and HIV, and other clinical laboratory tests for safety (hematology, chemistry, coagulation, urinalysis) will be performed according to the study schedule, data processed by local laboratories, and entered directly into the electronic data capture by site users. The table below lists all laboratory variables evaluated during the study. All results, along with abnormal values where relevant, and normal ranges will be presented in

data listings. If there are several measurements performed within the single visit window period, the measurement nearest to the planned visit date will be considered.

Table 6 Clinical Laboratory Variables Evaluated During the Study

Hematology	Serum Chemistry	Urinalysis (dipstick)
Red blood cell count	Sodium	Bacteria
Hemoglobin	Potassium	Blood
Hematocrit	Calcium	Urobilinogen
Platelet count	Chloride	Nitrites
White blood cell count (WBC)	Phosphorus [a]	Color
WBC with 5-part differential:	Magnesium [a]	Clarity
Neutrophils	Serum creatinine	pH
Lymphocytes	Total bilirubin	Specific gravity
Monocytes	Albumin	Ketones
Eosinophils	Alkaline phosphatase	Protein
Basophils	Lactate dehydrogenase	Glucose
Coagulation	(at Screening only)	Bilirubin
International normalized ratio	Aspartate aminotransferase	Leukocyte esterase
Activated partial thromboplastin time	Alanine aminotransferase	**Hormone**
Prothrombin time	Glucose, document whether fasting	Serum or urine human chorionic
Tumor Markers	or non-fasting	gonadotropin, if applicable
CA19-9	Blood urea nitrogen	**Other [b]**
CA-125 [c]	Uric acid	HIV immunoassay [d]
CEA [c]	Bicarbonate	Hepatitis B/C serology [e]
	Total protein	

[a] Magnesium and phosphorus at Screening and Day 1 of each cycle only.
[b] Must be confirmed as negative prior to randomization and first dose of study drug.
[c] CA-125 and CEA will only be measured in those patients who do not have elevated CA19-9 at Screening.
[d] 4th generation immunoassay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen.
[e] Serologic assays for hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), antibody to hepatitis B surface antigen (anti-HBs), and anti-hepatitis C antibodies.

For safety lab panels, summaries of actual values and change from baseline will be presented at each assessment time point. Change from baseline will be calculated as the post-baseline minus the baseline measurement. If either value is missing, the observation will not be included in the summary statistics.

For parameters that can be graded using NCI-CTCAE v5.0, shift tables that summarize counts and percentages of patients by severity grade at baseline and worst post-baseline result will also be constructed.

Results from a serum or urine pregnancy test for patients of childbearing potential, performed prior to start of study treatment and subsequently every 12 weeks, will be listed.

9.10.4 Vital Signs and Weight

At designated visits, vital signs will be recorded and will include weight, systolic and diastolic blood pressure, resting heart rate, body temperature, and respiratory rate. A listing of all vital signs will be provided. Additionally, data will be summarized using descriptive statistics at baseline, each study evaluation, and change from baseline to evaluation. Change from baseline will be calculated as the post-baseline minus the baseline measurement. If either value is missing, the observation will not be included in the summary statistics.

9.10.5 Electrocardiograms

At Screening and End of Treatment visits, 12-lead ECG data, obtained in triplicate, will be classified as normal, abnormal but not clinically significant, or abnormal and clinically significant by the Investigator or qualified designee. All recorded results will be included in a listing, and results averaging the triplicate reading at screening and end of study will be summarized as an absolute value and change from baseline.

9.10.6 Physical Examination

Any abnormalities observed during physical examination are captured as AEs or Medical History as appropriate.

10 REFERENCES

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11 APPENDIX