STATISTICAL ANALYSIS PLAN

A Phase II Open-Label Study of NUC-1031 in Patients with Platinum-Resistant Ovarian Cancer

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A Phase II Open-Label Study of NUC-1031 in Patients with Platinum-Resistant Ovarian Cancer

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Approvals

The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan as final. Programming of the tables and listings based upon the specifications within this document can proceed.

Covance Approval

Signature Date

Nicolas Ramon / Principal Biostatistician

NuCana plc:

Signature Date

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Abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
BICR	Blinded Independent Central Reviewer
BMI	Body Mass Index
BOR	Best Overall Response
BPM	Beats Per Minutes
BRCA	Breast Cancer
BRCA 1/2	Breast Cancer (gene) 1/2
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
C1D1	Cycle 1 Day 1
C1D15	Cycle 1 Day 15
C2D15	Cycle 2 Day 15
C3D1	Cycle 3 Day 1
C3D15	Cycle 3 Day 15
CA125	Cancer Antigen 125
CDA	Cytidine DeAminase
CI	Confidence Interval
CR	Complete Response
CS	Clinically Significant
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Event
DBP	Diastolic Blood Pressure
dCK	deoxyCytidine Kinase
DCO	Data Cut Off
DCR	Disease Control Rate
dFdCTP	di-fluoro-deoxyCytidine TriPhosphate
DI	Dose Intensity
DMA	Dimethylacetamide
DOR	Duration of Overall Response
DRM	Data Review Meeting
DSD	Duration of Stable Disease
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram

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ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EFR	Evaluable For Response
EQ-5D-5L	EuroQoL Five Dimensions, Five Levels
EuroQoL	Euro Quality of Life
FACT	Functional Analysis of Cancer Therapy
FAS	Full Analysis Set
FDA	(US) Food and Drug Administration
FOSI-18	FACT/NCCN-Ovarian Symptom Index (containing 18 items)
FOSI-DRS-E	FOSI-Disease Related Symptoms-Emotional
FOSI-DRS-P	FOSI-Disease Related Symptoms-Physical
FOSI-F/WB	FOSI-Function/Well Being
FOSI-TSE	FOSI-Treatment Side Effects
G-CSF	Granulocyte Colony-Stimulating
GCIG	Gynecologic Cancer InterGroup
hENT1	human Equilibrative Nucleoside Transporter 1
INR	International Normalized Ratio
IV	Intravenous
kg	Kilogram
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
m^2	$Meter^2$
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
mmHg	MilliMeters of Mercury
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NCS	Non Clinically Significant
NE	Not Evaluable
ORR	Objective Response Rate
OS	Overall Survival
PARP	Poly ADP Ribose Polymerase
PBMC	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PDI	Planned Dose Intensity
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PFS4	Progression-Free Survival at 4 months

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PFS6	Progression-Free Survival at 6 months
PFS6KM	Progression-Free Survival at 6 months for Kaplan-Meïer analysis
PID	Percent Intended Dose
PIDR	Percentage Intended Doses Received
PK	Pharmacokinetic
PPS	Per Protocol Set
PR	Partial Response
PRO	Patient Reported Outcome
PT/INR	Prothrombin Time/ International Normalized Ratio
RBC	Red Blood Cells
RDI	Relative Dose Intensity
RDR	Relative Doses Received
RECIST v1.1	Response Evaluation Criteria In Solid Tumors version 1.1
RRM1	Ribonucleotide Reductase M1
RRM2	Ribonucleotide Reductase M2
RS	Randomized Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Stable Disease
SDTM	Study Data Tabulation Model
SI	International System
SLD	Sum of Lesion Diameters
SOC	System Organ Class
SS	Safety analysis set
StD	Standard Deviation
TEAE	Treatment Emergent Adverse Event
TTP	Time to Disease Progression
TTR	Time to Response
ULN	Upper Limit of Normal
ULRR	Upper Limit of Response Range
US	United States
VAS	Visual Analogue Scale
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
WBC	White Blood Cell
wk	Week

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1 Introduction

This document presents the statistical analysis plan (SAP) for NuCana plc (NuCana), Protocol No. PRO-105: A Phase II Open-Label Study of NUC-1031 in Patients with Platinum-Resistant Ovarian Cancer.

This analysis plan is based on the final protocol dated 11Oct2017; incorporating amendment no. 1, dated 06Mar2017 and amendment no. 2, dated 20Apr2017

The SAP provides the description of the analysis for the dose selection analysis, primary analysis and a potential efficacy update analysis. Depending on the results of the primary analysis, the study could be expanded. Thus, a possible expansion analysis could be added.

Following a preliminary analysis of the top-line data from Part I, the dose intensity was lower than expected and the decision was made not to proceed with Part II. Therefore, no dose will be selected.

2 Study Objectives

The primary objective is to assess the anti-tumor activity of NUC-1031, as measured by Objective Response Rate (ORR) per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1) criteria at the selected dose level (500 milligrams (mg)/meter² (m²) or 750 mg/m²).

Primary assessment will be done by a Blinded Independent Central Reviewer (BICR).

The secondary objectives are:

- To assess additional measures of anti-tumor activity of NUC-1031 including:
  - Change from baseline in tumor size.
  - Duration of Overall Response (DOR, per RECIST).
  - Progression-Free Survival (PFS, per RECIST).
  - Time to Disease Progression (TTP, per RECIST).
  - Disease Control Rate (DCR) (Complete Response (CR) + Partial Response (PR) + Stable Disease (SD) which lasts at least 6 weeks from baseline, per RECIST).
  - Best Gynecologic Cancer InterGroup (GCIG) Overall Response, combining the change in Cancer Antigen 125 (CA125) from baseline with RECIST assessment (per GCIG criteria).
  - Overall Survival (OS).
- To further assess the safety profile of NUC-1031 administered over multiple cycles.
- To explore relationships between NUC-1031 Pharmacokinetic (PK), pharmacodynamics and clinical activity.
- To describe the effects of NUC-1031 on ovarian cancer symptoms.

The exploratory objectives are:

- To establish the expression of genomic, transcriptomic and proteomic biomarkers in Peripheral Blood Mononuclear Cells (PBMCs) and tissue samples, which may help predict patients who derive additional benefit from NUC-1031.
- To explore the impact of treatment and disease state on health state utility by Euro Quality of Life (EuroQoL) five dimensions, five levels (EQ-5D-5L).

2.1 Primary Endpoint

The primary endpoint of this study is:

- ORR at the selected dose level (500 mg/m² or 750 mg/m²) defined per RECIST v1.1 and assessed by a BICR.

2.2 Secondary Endpoints

The secondary endpoints of this study are:

- Change from baseline in tumor size.
- DOR.

- PFS.
- TTP.
- Time To Response (TTR).
- DCR.
- Best Overall Response (BOR).
- Best GCIG Overall Response, combining the change in Cancer Antigen 125 (CA125) from baseline with RECIST assessment.
- OS.
- Assessment of ovarian cancer symptoms using Functional Analysis of Cancer Therapy (FACT)/ National Comprehensive Cancer Network (NCCN)-Ovarian Symptom Index (containing 18 items) (FOSI-18) questionnaire.
- Time on treatment.

2.3 Safety Endpoints

The safety endpoints of this study are the followings:

- Treatment-emergent adverse events per National Cancer Institute-Common Terminology Criteria for Adverse Event version 4 (NCI CTCAE v4).
- Laboratory parameters
- Changes in vital signs.
- Changes in serial Electrocardiograms (ECG).

2.4 Pharmacokinetic Endpoints

The pharmacokinetic (PK) endpoints of this study are the followings:

- Maximum concentration (C_{max}).
- Area under the curve (AUC).
- Half-life ($T_{1/2}$).
- Volume of distribution (V_d).
- Clearance (CL).

In addition, PK of the following analytes will be measured:

- In plasma/urine: NUC-1031, dFdC and dFdU.
- In PBMCs: NUC-1031, dFdC, dFdCMP, dFdCDP, dFdCTP and dFdU.

PK analyses will not be described in this Statistical Analysis Plan but in a separate document.

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2.5 Exploratory Endpoints

The following exploratory endpoint will be summarized:

- Assessment of the impact of treatment and disease state on health state utility by EuroQoL five dimensions, five level questionnaire.

The following exploratory endpoint will be described separately:

- Assessment of candidate genomic, transcriptomic and proteomic biomarkers of resistance/sensitivity to NUC-1031 in PBMCs and tissue samples. Examples of candidate markers include cytidine deaminase (CDA), deoxycytidine kinase (dCK), human equilibrative nucleoside transporter 1 (hENT1), ribonucleotide reductase M1 (RRM1) and Ribonucleotide Reductase M2 (RRM2).

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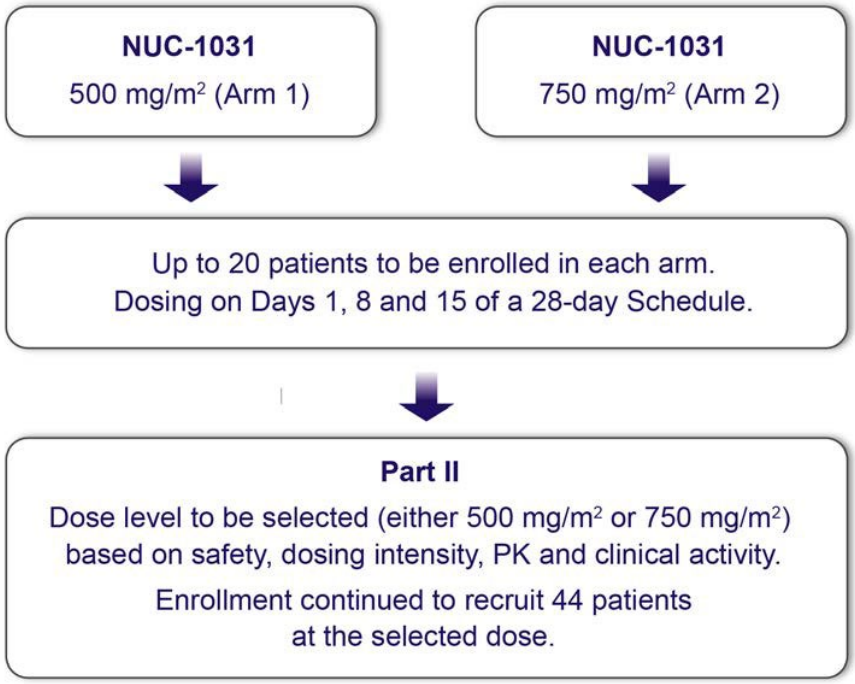
3 Study Design

3.1 Discussion of Study Design

This is a randomized open-label, two-part clinical study of NUC-1031 in up to 64 patients with platinum-resistant ovarian cancer. Patients will be randomized to NUC-1031 500 mg/m² or 750 mg/m² and will be evaluated in two parallel cohorts of up to 20 patients each in Part I of the study. The randomization will be stratified to ensure that key prognostic markers, including Breast Cancer (BRCA) mutation status and number of prior lines of chemotherapy (3 or >3), are balanced between the 2 dose levels. Thus, the stratification factors are BRCA mutation status (Yes/No) and Number of prior lines of chemotherapy (=3/>3).

On the basis of ongoing safety, dosing intensity, PK and clinical activity observed during Part I, one dose level will be selected for further evaluation in Part II of the study, where enrolment shall continue until a total of 44 response evaluable patients are recruited at the selected dose (Figure 1).

Figure 1: Study Design



It is anticipated that up to 64 patients will be enrolled in this study at multiple study centers (24) in the United States (US) (16) and Europe (8). Patients are eligible for the study if all of the inclusion criteria are met and none of the exclusion criteria apply.

The primary analysis of response rate will take place when 44 patients are enrolled at the selected dose and all active patients have undergone the required assessments for assessment of confirmed ORR by RECIST (i.e., approximately 16 weeks after the 44th patient starts treatment). Upon review of the data from Part II by the Data Safety Monitoring Committee (DSMC), the study may be further expanded at the selected dose level, which will be described

in a protocol amendment. A further efficacy update analysis may be performed at a later date to provide more mature efficacy data.

The study will be deemed complete following the efficacy update analysis. If the efficacy update analysis is not required, the study will be considered complete following the Data Cut Off (DCO) for the primary analysis.

Following a preliminary analysis of top-line data in 51 randomised patients from Part I, the dose intensity was lower than expected and the decision was made not to proceed with Part II.

As a consequence, database lock will occur sooner than initially planned and the primary analysis of response rate described above will not be produced.

In addition, the efficacy update analysis described above will not be performed.

3.2 Study Treatment

3.2.1 Study Treatment

In Part I, eligible consenting patients will be randomized to receive Intravenous (IV) NUC-1031 at a dose of either 500 mg/m² or 750 mg/m² on a day 1, 8 and 15 of a 28-day schedule. Up to 20 patients will be enrolled in each arm.

One dose level will be selected for further evaluation in Part II of the study (based on ongoing safety, dosing intensity, PK and clinical activity observed during Part I), where enrolment shall continue until a total of 44 evaluable patients are recruited at the selected dose. The study will be complete when all patients have reached the PFS endpoint or when 24 months have elapsed since the final patient was enrolled (whichever occurs first).

Criteria for inter-cycle and intra-cycle dose delay and dose modification are specified in Section 3.2.4. The reasons for dose delay or dose reduction should be captured as Adverse Events (AE) in the patient medical record and noted on the electronic Case Report Form (eCRF).

3.2.2 NUC-1031 Description

The drug product, NUC-1031 (for injection), is presented as a sterile solution in clear glass vials at a concentration of 250 mg/milliliter (ml) formulated in dimethylacetamide (DMA) and Normal Saline (0.9%) in the ratio of 80:20.

3.2.3 Study Drug Dosage and Administration

NUC-1031 will be administered to each patient based on her Body Surface Area (BSA) at baseline. If a patient's weight increases or decreases by ≥10% during the course of the study, the dose of NUC-1031 should be recalculated. The Dubois & Dubois BSA calculation is the preferred method, however other standard calculations can also be used. Sites should document the method used in the electronic Case Report Form (eCRF).

Dubois & Dubois BSA calculation:

$$BSA(m^2) = 0.007184 \times Height(cm)^{0.725} \times Weight(kg)^{0.425}$$

Patients will receive IV NUC-1031 at an initial dose of 500 mg/m² or 750 mg/m² on Days 1, 8 and 15 of a 28-day schedule. Dose adjustments or dose delays are to be implemented within or between cycles based on drug related toxicities. The dose modification scheme to be employed is detailed in the section below.

3.2.4 Dose Modifications

Adverse events may be managed by dose delays and/or dose reductions according to the clinical situation. Advice on how to modify dosing for hematological and non-hematological toxicities is given below.

Only one dose reduction is permitted within a cycle. This may be a temporary dose reduction, in which case the next cycle can revert to the starting dose of the previous cycle, or it may be a permanent dose reduction which would apply to all subsequent cycles. Over the whole dosing period, each patient may have a maximum of 2 permanent dose reductions, after which treatment will be discontinued. The lowest dose which may be administered is 275 mg/m².

Treatment between cycles can be delayed for up to 14 days in order for patients to meet the re-treatment criteria before starting their next cycle. Patients who do not meet these requirements after this additional time will not be allowed to receive further cycles of NUC-1031 and will be withdrawn from the study.

3.2.4.1 Hematological Toxicity – Dose Adjustment

NUC-1031 administration should be given according to the Absolute Neutrophil Count (ANC) and platelet count on the day of dosing. On Day 1 of each 28-day cycle, if the ANC is $\geq 1.5\times10^9$/l and the platelet count is $\geq 75\times10^9$/l, then NUC-1031 should be given at full dose unless the patient has previously been permanently dose reduced.

On Day 1 of each 28-day cycle, if the ANC is 1.5-1.0$\times10^9$/l and the platelet count is 50-75$\times10^9$/l without evidence of bleeding, then NUC-1031 should be given at a reduced dose unless the patient has received 2 prior dose reductions.

Within a cycle, should patients experience neutropenia or thrombocytopenia, dosing on Day 8 and Day 15 should be adjusted per Table 1 below.

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Table 1. Dose adjustments within a cycle (Days 8 and 15)

ANC		Platelets	Starting dose (750 mg/m²)	Starting dose (500 mg/m²)	Starting dose (375 mg/m²)
$\geq 1.5\times10^9$/l	**AND**	$\geq 75\times10^9$/l	750 mg/m²	500 mg/m²	375 mg/m²
1.5-1.0$\times10^9$/l and afebrile	**AND/OR**	50-75$\times10^9$/l without evidence of bleeding	500 mg/m²	375 mg/m²	275 mg/m²
$<1.0\times10^9$/l, or $<1.5\times10^9$/l with fever	**AND/OR**	$<50\times10^9$/l, or $<100\times10^9$/l with active bleeding	Omit	Omit	Omit

Should both the Day 8 and Day 15 doses be omitted for hematologic toxicity within the same cycle, the dose for all subsequent cycles should be permanently reduced the next dose level.

If a patient starts a treatment cycle at 500 mg/m² and requires further dose reduction on Day 8 or Day 15 of the following cycle due to hematologic toxicity, dose modification should follow the column second from the right of Table 1.

If a patient has her dose permanently reduced to 375 mg/m², and hematologic toxicity persists on any day that a dose is scheduled, dose modification should follow the far right column of Table 1.

For all other hematological toxicities, dose adjustments should be performed according to Table 2.

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Table 2. Dose adjustments for haematological toxicities (excluding toxicities relating to ANC and platelet counts)

NCI CTCAE grade	Dose adjustment
Grade 1 toxicity	If the patient was receiving 750 mg/m^2 then reduce to 500 mg/m^2. If the patient was receiving 500 mg/m^2 then reduce to 375 mg/m^2. If the patient was receiving 375 mg/m^2 then reduce to 275 mg/m^2.
Grade 2, 3 and 4 toxicity	Omit until resolution to ≤Grade 1 if the patient was receiving 750 mg/m^2 then resume at the dose 500 mg/m^2. If the patient was receiving 500 mg/m^2 then resume at the dose 375 mg/m^2. If the patient was receiving 375 mg/m^2 then resume at the dose 275 mg/m^2.

3.2.4.2 Non-Hematological Toxicity – Dose adjustment

Drug adjustment should be performed according to Table 3. If dose omission is required, treatment should be delayed until the toxicity has resolved to ≤ Grade 1. If this occurs, subsequent doses should be permanently reduced, without re-escalation. For significant pulmonary complications (*e.g.* pneumonitis and acute respiratory distress syndrome), study treatment should be stopped.

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Table 3. Dose adjustment for non-hematological toxicities

NCI CTCAE grade	Dose adjustment
Grade 0-2 toxicity or Grade 3 nausea/ vomiting/ alopecia	100% dose (with escalation of anti-emetic prophylaxis for nausea and vomiting)
Grade 3/4 toxicity (except nausea/vomiting/alopecia)	Omit until resolution to ≤ Grade 1 if the patient was receiving 750 mg/m² then resume at the dose 500 mg/m². If the patient was receiving 500 mg/m² then resume at the dose 375 mg/m². If the patient was receiving 375 mg/m² then resume at the dose 275 mg/m².

3.2.4.3 Guidance for Dose Omissions

Table 4 outlines the guidance for omission of doses on Day 1, 8 or 15.

Table 4. Dose omission guidance

Day 1 missed dose	Day 8 missed dose	Day 15 missed dose
If the dose omitted was due to be on Day 1 of the next cycle, that cycle will not be considered to start until the day the first dose is actually administered to the patient (i.e. 1-2-3-Rest, X-1-2-3-Rest, etc).	Cycle continues per protocol, with one dose not given (i.e. 1-2-3-Rest, 1-X-3-Rest, 1-2-3-Rest, etc). Day 15 is administered as per cycle calendar if blood results permit.	That week becomes the week of rest. Next dose (if blood results permit) becomes Day 1 of a new cycle, and the patient is considered to have had a 21-Day cycle.

3.3 Study Schedule

3.3.1 Patient Registration and Screening Procedures

All screening activities must be performed within 28 days of randomization. A Screening Log must be kept of all patients considered for the study (*i.e.* all those that are included for screening and any that are subsequently excluded). The reason for exclusion must be recorded on this form. A copy of the Screening Log must be retained on site and provided to the CRO upon request, but without patient identifiers.

In Part I, patient randomization will be stratified according to BRCA mutation status and number of prior lines of chemotherapy (3 or >3). In Part II, sensitivity analyses will be conducted on ORR according to BRCA mutation status and number of prior lines of chemotherapy (see details in Section 4.8.2). Patients known to have germline BRCA mutation(s) prior to randomization can enter the study based on this result. Patients who have

had a tumor BRCA mutation identified in a certified laboratory may also be enrolled on the study based on this result. Patients with unknown BRCA mutation status should undergo local BRCA mutation testing prior to study entry, according to local ethical procedures for genetic testing.

Before entering a patient onto the study, the investigator will confirm eligibility according to the defined inclusion and exclusion criteria. Then, this confirmation is sent to Covance project manager and clinical team leader in a patient registration form and they will confirm that patient may be randomized. Details of the query and outcome of the decision must be documented on the registration/ eligibility checklist. To register a patient to the study, the site must email a completed Registration Form, along with a copy of the blinded histology report, to the patient registration email address supplied. The patient will then be registered to the study. The site will be informed by email and fax of the approval to be treated. Treatment must not start until this registration process is complete and must start no later than 10 days after the day of registration.

3.3.2 Screening Assessments

Standard of care assessments that were completed prior to informed consent but are within the screening window may be used for screening assessments and do not have to be repeated. All protocol required assessments that are not deemed standard of care should not be completed until after informed consent has been signed.

Screening assessments of consented patients will comprise the following:

- Provision of written informed consent.
- Eligibility confirmation, including histological diagnosis of ovarian cancer.
- Patient registration.
- Assessment of medical and surgical history, including prior therapy for ovarian cancer.
- BRCA testing (if BRCA status is unknown).
- ECOG performance status.
- The FOSI-18 and EQ-5D-5L instruments must be completed prior to other scheduled study procedures and dosing (if applicable).
- Routine physical examination, including vital signs.
- Vital signs include measurement of pulse rate, respiratory rate, blood pressure and temperature, after the patient has been seated or in the supine position for 5 minutes.
- Height and weight.
- 12-lead ECG should be performed in triplicate (keeping the leads in place and patient supine during readings) and reviewed by the investigator or a qualified designee for safety and quality. The QTc interval should be calculated for each ECG using the Fridericia formula and averaged. Management of QT/QTc prolongation should be performed in accordance with institutional standard of care at the discretion of the treating physician. Digital and certified paper copies should be stored as part of the study documents in the event they need to be used in a future analysis.
- Recording of demographic data.
- Baseline assessment of symptoms.
- Blood samples drawn for:
    - Hematology: white blood cell (WBC) count, red blood cell (RBC) count,

differential WBC count, including hemoglobin, hematocrit and platelets.
  - Coagulation parameters: prothrombin time (PT)/ international normalized ratio (INR) and activated partial thromboplastin time (aPTT).
  - Chemistry: sodium, potassium, magnesium, urea or Blood Urea Nitrogen (BUN), creatinine, glucose, phosphate, total protein, albumin, adjusted calcium, total bilirubin, bicarbonate, chloride, uric acid, alkaline phosphatase, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) and Lactate dehydrogenase (LDH).
  - Pregnancy testing: For women of childbearing potential serum pregnancy must be performed within 72 hours prior to Cycle 1 Day 1.
  - CA125 (for GCIG response determination).
- Urinalysis: pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilirubin and occult blood. Dipstick testing is acceptable.
- Tumor imaging (Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and/or Positron Emission Tomography (PET)-CT [US only] of thorax, abdomen and pelvis) – performed within 28 days of randomization. Biopsied lesions should not be designated as target lesions for the purposes of RECIST.
- Obtain fresh and archival tumor tissue. For sampling procedures, storage conditions, and shipment instructions, see the Tumor Tissue Laboratory Manual. Patients who do not have easily accessible tumor for biopsy should not be put at undue risk for sample collection and these patients remain eligible for the study. Biopsied lesions should not be designated as target lesions for the purposes of RECIST.
- Recording of concomitant medication.

3.3.3 Re-Screening Patients who fail Inclusion/Exclusion Criteria

If a patient does not meet the inclusion/exclusion criteria upon first assessment, she can be re-screened within 14 days. Patients who fail at re-screening are ineligible and may not be re-screened.

3.3.4 Evaluations to be performed during the study

During treatment, patients will be medically reviewed on dosing days. The following will be assessed:

3.3.4.1 Each Cycle, Day 1

All procedures to be completed prior to dosing except NUC-1031 administration and applicable PK samples. Safety laboratory assessments and weight measurement may be performed up to 3 days prior to Day 1 of each cycle.

- ECOG performance status.
- The FOSI-18 and EQ-5D-5L instruments must be completed prior to other scheduled study procedures and dosing (if applicable).
- Routine physical examination, including vital signs. Vital signs include measurement of pulse rate, respiratory rate, blood pressure and temperature, after the patient has been seated or in the supine position for 5 minutes.
- Weight.

- 12-lead ECGs should be performed pre-infusion. The ECGs should be performed in triplicate (keeping the leads in place and patient supine during readings) and reviewed by the investigator or a qualified designee for safety and quality. The QTc interval should be calculated for each ECG using the Fridericia formula and averaged. Management of QT/QTc prolongation should be performed in accordance with institutional standard of care at the discretion of the treating physician. Digital and certified paper copies should be retained at site and stored as part of the study documents in the event they need to be used in a future analysis.
- At Cycle 1 Day 1 (C1D1) and Cycle 3 Day 1 (C3D1) only the 12-lead ECGs should be performed 30-60 minutes pre-infusion and again 30-60 minutes post-infusion. The ECGs should be performed in triplicate (keeping the leads in place and patient supine during readings) and reviewed by the investigator or a qualified designee for safety and quality. The QTc interval should be calculated for each ECG using the Fridericia formula and averaged. Management of QT/QTc prolongation should be performed in accordance with institutional standard of care at the discretion of the treating physician. Digital and certified paper copies should be retained at site and stored as part of the study documents in the event they need to be used in a future analysis.
- Blood samples drawn for:
    - Hematology: WBC count, RBC count, differential WBC count, including hemoglobin, hematocrit and platelets.
    - Coagulation parameters: PT/INR and aPTT.
    - Chemistry: sodium, potassium, magnesium, urea or BUN, creatinine, glucose, bicarbonate, chloride, uric acid, phosphate, total protein, albumin, adjusted calcium, total bilirubin, alkaline phosphatase, AST, ALT and LDH.
    - CA125.
- Urinalysis: pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilirubin and occult blood. Dipstick testing is acceptable.
- Urine pregnancy test for women of child-bearing potential. If any urine test result is positive, patient dosing will be postponed until the result is confirmed by a serum pregnancy test. Any patient with a positive serum test will not be allowed to receive any study treatment.
- IV administration of NUC-1031.
- AE recording and causality assessment.
- Recording of new or changes to concomitant medication.

3.3.4.2 For sites Collecting Optional Fresh Biopsy: Within 24 Hours of Cycle 1 Day 1

- Obtain fresh tumor biopsy within 24 hours of the end of NUC-1031 infusion on C1D1.. For sampling procedures, storage conditions, and shipment instructions, see the Tumor Tissue Laboratory Manual. Patients who do not have easily accessible tumor for biopsy should not be put at undue risk for sample collection and these patients remain eligible for the study. Biopsied lesions should not be designated as target lesions for the purposes of RECIST.

3.3.4.3 For Sites Participating in PK Sample Collection: Cycles 1 & 3 – Days 1 & 2

- PK: multiple blood samples will be taken on Cycles 1 and 3 on Days 1 and 2, 24 hours after NUC-1031 administration. Optional urine samples may be taken during Cycle 1 on Days 1 and 2..
- AE recording and causality assessment.
- Recording of new or changes to concomitant medication.

3.3.4.4 Each Cycle, Days 8 & 15

All procedures to be completed prior to dosing except NUC-1031 administration and applicable PK samples.

- Routine physical examination, including vital signs. Vital signs include measurement of pulse rate, respiratory rate, blood pressure and temperature, after the patient has been seated or in the supine position for 5 minutes.
- 12-lead ECGs should be performed pre-infusion. The ECGs should be performed in triplicate (keeping the leads in place and patient supine during readings) and reviewed by the investigator or a qualified designee for safety and quality. The QTc interval should be calculated for each ECG using the Fridericia formula and averaged. Management of QT/QTc prolongation should be performed in accordance with institutional standard of care at the discretion of the treating physician. Digital and certified paper copies should be stored as part of the study documents in the event they need to be used in a future analysis.
- At Cycle 1 Day 15 (C1D15) and Cycle 3 Day 15 (C3D15) only the ECGs should be performed 30-60 minutes pre-infusion and again 30-60 minutes post-infusion. The ECGs should be performed in triplicate (keeping the leads in place and patient supine during readings) and reviewed by the investigator or a qualified designee for safety and quality. The QTc interval should be calculated for each ECG using the Fridericia formula and averaged. Management of QT/QTc prolongation should be performed in accordance with institutional standard of care at the discretion of the treating physician. Digital and certified paper copies should be stored as part of the study documents in the event they need to be used in a future analysis.
- Blood samples drawn for:
  - Hematology: WBC count, RBC count, differential WBC count, including hemoglobin, hematocrit and platelets.
  - Chemistry: sodium, potassium, magnesium, urea, creatinine, glucose, bicarbonate, chloride, uric acid, phosphate, total protein, albumin, adjusted calcium, total bilirubin, alkaline phosphatase, AST, ALT and LDH.
- IV administration of NUC-1031.
- AE recording and causality assessment.
- Recording of new or changes to concomitant medications

3.3.4.5 For Sites Participating in PK Sample Collection: Cycle 1 Days 15 & 16

- PK: multiple blood samples will be taken on Cycle 1 Days 15 and 16. Optional urine samples may be taken on Cycle 1 Days 15 and 16.
- AE recording and causality assessment.
- Recording of new or changes to concomitant medication.

3.3.4.6 Every 8 Weeks (± 7 days) from Cycle 1 Day 1 until Disease Progression, Initiation of a New Treatment or Death

- Tumor imaging (CT, MRI and/or PET-CT [US only] of thorax, abdomen and pelvis).
- ECOG performance status should be assessed if the patient has stopped study treatment and is attending a Follow-Up Visit.

3.3.4.7 End of Treatment Visit

The assessments to be performed on discontinuation due to disease progression or early treatment discontinuation for other reasons (*e.g.* withdrawal of consent) are summarized below. The End of Treatment visit should occur within 30 days of the last administration of NUC-1031. The following will be assessed:

- ECOG performance status.
- The FOSI-18 and EQ-5D-5L instruments must be completed prior to other scheduled study procedures.
- Routine physical examination, including vital signs. Vital signs include measurement of pulse rate, respiratory rate, blood pressure and temperature, after the patient has been seated or in the supine position for 5 minutes, and temperature.
- Weight.
- 12-lead ECG should be performed in triplicate (keeping the leads in place and patient supine during readings) and reviewed by the investigator or a qualified designee for safety and quality. The QTc interval should be calculated for each ECG using the Fridericia formula and averaged. Management of QT/QTc prolongation should be performed in accordance with institutional standard of care at the discretion of the treating physician. Digital and certified paper copies should be stored as part of the study documents in the event they need to be used in a future analysis.
- Blood samples drawn for:
    - Hematology: WBC count, RBC count, differential WBC count, including hemoglobin, hematocrit and platelets.
    - Coagulation parameters: PT/INR and aPTT.
    - Chemistry: sodium, potassium, magnesium, urea or BUN, creatinine, glucose, bicarbonate, chloride, uric acid, phosphate, total protein, albumin, adjusted calcium, total bilirubin, alkaline phosphatase, AST, ALT and LDH.
    - Pregnancy testing for women of child-bearing potential.
    - CA125.
- Urinalysis: pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilirubin and occult blood. Dipstick testing is acceptable.
- AE recording and causality assessment.

- Recording of new or changes to concomitant medication.

3.3.4.8 Follow-Up

Patients who stop treatment with no evidence of disease progression as defined by RECIST criteria will continue to receive scans at regular intervals (every 8 weeks [±7 days] from C1D1) until disease progression or death (whichever comes first) in order to determine duration of overall response and progression-free survival.

Patients with evidence of disease progression as defined by RECIST criteria while receiving study medication will discontinue treatment but will enter the follow up period. They will receive a phone call at regular intervals (every 12 weeks [±7 days]) until death, loss to follow-up, or study discontinuation in order to determine duration of Overall Survival.

STATISTICAL ANALYSIS PLAN

Sponsor:	NuCana plc	Protocol Number:	PRO-105

All above information are summarized in the study schedule (see Table 5 below).

Table 5. Summary schedule of events

		Each Cycle				End of Treatment Visit[20]	Follow-up Visit Q8 weeks (±7 days)[2] [1]	Survival Follow-up Q12 weeks (±7 days)
Assessment	**Screening Up to 28 days prior**	**Day 1 (±3)**	**Day 2**	**Days 8 & 15 (±3)**	**Day 16**			
Informed consent	X							
Inclusion/exclusion criteria confirmation	X							
Patient registration	X							
Medical and surgical history, including prior therapy for ovarian cancer[1]	X							
BRCA testing[2]	X							
ECOG performance status	X	X				X	X	
Physical examination, including vital signs[3]	X	X		X		X		
Height and weight[4]	X	X				X		
Pregnancy test	X	X[17]				X		
12-lead ECG[5]	X	X[6]		X[6]		X		
Patient demographics	X							
Baseline symptoms	X							
Hematology[7]	X	X		X		X		
Serum chemistry[8]	X	X		X		X		
Coagulation parameters: PT/INR and aPTT[9]	X	X				X		
Urinanalysis[10]	X	X				X		
Pharmacokinetic sampling[11]		X	X	X	X			
Serum tumor markers (CA125)[12]	X	X				X	X	
Tumor response assessment: CT, MRI and/or PET-CT (US only) scan[13]	Scans performed at Screening then every 8 weeks (±7 days) from C1D1 until disease progression, regardless of treatment cycle. CRs and PRs must be confirmed by repeated images at least 4 weeks after initial documentation.							
Collection of tumor specimen[14]	X	X[19]						
Patient-Reported Outcomes[15]	X	X				X		
NUC-1031 study drug administration[16]		X[18]		X				
Adverse events		X	X	X	X	X	X[22]	
Concomitant medications	X	X	X	X	X	X		
Survival follow-up phone call								X[23]

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STATISTICAL ANALYSIS PLAN

Sponsor:	NuCana plc	Protocol Number:	PRO-105

1. Medical history and prior therapy collected during Screening. Any changes from date of consent should be recorded as Adverse Events.

2. Patients with unknown BRCA mutation status should undergo local BRCA mutation testing prior to study entry, according to local ethical procedures for genetic testing. Results are needed prior to randomization.

3. Vital signs include measurement of pulse rate, respiratory rate, temperature and blood pressure, after the patient has been seated or in the supine position for 5 minutes.

4. Height will be measured at Screening only. If a patient's weight increases or decreases by ≥10% during the course of the study, the dose of NUC-1031 should be recalculated.

5. 12-lead ECG measurements must be obtained at screening, pre-infusion on each treatment day, and at the treatment completion visit. The ECGs should be performed in triplicate (keeping the leads in place and patient supine during readings) and reviewed by the investigator or a qualified designee for safety and quality. The QTc interval should be calculated for each ECG using the Fridericia formula and averaged. Management of QT/QTc prolongation should be performed in accordance with institutional standard of care at the discretion of the treating physician. Digital and/or certified paper copies should be stored as part of the study documents in the event they need to be used in a future analysis.

6. At C1D1, C1D15, C3D1 and C3D15 12-lead ECG measurements should be performed 30-60 minutes pre-infusion and again 30-60 minutes post-infusion. The ECGs should be performed in triplicate (keeping the leads in place and patient supine during readings) and reviewed by the investigator or a qualified designee for safety and quality. The QTc interval should be calculated for each ECG using the Fridericia formula and averaged. Management of QT/QTc prolongation should be performed in accordance with institutional standard of care at the discretion of the treating physician. Digital and/or certified paper copies should be stored as part of the study documents in the event they need to be used in a future analysis.

7. Hematology includes white blood cell (WBC) count, differential WBC count, red blood cell count (RBC), hemoglobin, hematocrit and platelet count.

8. Serum chemistry incudes sodium, potassium, magnesium, urea or blood urea nitrogen, creatinine, glucose, phosphate, total protein, albumin, adjusted calcium, total bilirubin, bicarbonate, chloride, uric acid, alkaline phosphatase, AST, ALT and LDH.

9. Either PT or INR may be measured, depending on institutional standards.

10. Urinalysis includes pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilinogen and occult blood. Dipstick testing is acceptable.

11. Pharmacokinetic sampling (blood and urine) will be performed at a sub-set of sites specified by NuCana. At sites participating in the PK sample collection, blood samples are collected on Cycle 1 (Days 1 and 15), and Cycle 3 (Day 1) at pre-dose (T_0), end of infusion (T_1), T_1 plus 10 minutes (T_2), T_1 plus 30 minutes (T_3), T_1 plus 1 hour (T_4), T_1 plus 2 hours (T_5), T_1 plus 4 hours (T_6), T_1 plus 6 hours (T_7) and T_1 plus 24 hours (T_8). See blood-sampling schedule in the protocol.

Urine samples are collected on Cycle 1 (Days 1 and 15) at 0-6 hours, and 6-24 hours.

12. CA125 to determine GCIG response.

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13. Baseline imaging of the thorax, abdomen, and pelvis is required within 28 days of randomization. CT, MRI and PET-CT (US only) scans are acceptable. In selected situations, combination of CT/MRI is acceptable (*i.e.* CT of chest, MRI of abdomen). The same imaging modalities for each anatomic component be continued throughout the duration of the study. Objective responses using RECIST must be confirmed by repeat assessment performed ≥4 weeks after initial documentation of response. Progressive disease should be confirmed prior to stopping treatment.

14. Patients must have consented to the submission of archival tumor, if available and collection of fresh biopsy tumor tissue to participate in the study. Patients who do not have easily accessible tumor for biopsy should not be put at undue risk for sample collection and these patients remain eligible for the study. Biopsied lesions should not be designated as target lesions for the purposes of RECIST. Archival tumor tissue, if available may be submitted as paraffin tissue block or at least 10 unstained slides.

15. The FOSI-18 and EQ-5D-5L instruments must be completed prior to other scheduled study procedures and dosing (if applicable) at Screening, on Day 1 of each treatment cycle, at treatment discontinuation, and at the 28-day post-treatment discontinuation follow-up visit for all patients.

16. Patients will receive NUC-1031 on Day 1, 8 and 15 (±3 days) of a 28-day cycle.

17. For women of child-bearing potential, serum pregnancy testing must be performed within 72 hours prior to C1D1 and at End of Treatment visit. In addition, urine pregnancy tests will be performed pre-dose on Day 1 of each cycle. If any urine test result is positive, patient dosing will be postponed until the result is confirmed by a serum pregnancy test. Patients with a positive serum test will be discontinued from the study.

18. Includes insertion of central venous access device, if not already present (if NUC-1031 is centrally administered).

19. Optional fresh biopsy tissue sample collection within 24 hours post administration of C1D1 dose for patients who consent.

20. Includes treatment discontinuation due to disease progression or early treatment discontinuation for other reasons (*e.g.* withdrawal of consent). Progressive disease should be confirmed prior to stopping treatment. Visit to occur within 30 (±7) days of the last dose of NUC-1031.

21. Patients withdrawing from the study with no radiological evidence of disease progression will receive scans every 8 weeks (±7 days) from C1D1 until disease progression, initiation of a new treatment or death in order to determine duration of overall response and PFS.

22. Adverse events should be captured from the time of consent up to 30 days after the last dose of NUC-1031. SAEs deemed definitely, probably or possibly related to NUC-1031 but outside of this window (>30 days from last dose of NUC-1031) should also be captured in the eCRF.

23. Patients with evidence of disease progression as defined by RECIST criteria will receive a phone call at regular intervals (every 12 weeks ±7 days) until death, loss to follow-up, or study discontinuation in order to determine duration of Overall Survival.

3.4 Concomitant Medication

All prescription and non-prescription medications and therapies, including pharmacologic doses of vitamins, herbal medicines, or other non-traditional medicines, taken from 28 days prior to the first dose of NUC-1031 through the End of Treatment Visit must be recorded in the eCRF. All prior anti-cancer therapies from initial diagnosis up until enrolment must be recorded in the eCRF.

3.4.1 Support Medication

Patients may receive standard prophylactic medical treatment for nausea and vomiting. During treatment, patients will be reviewed on a weekly basis during the first cycle and on each day of treatment for subsequent cycles. Additional visits may be arranged at the Investigator's discretion. All support medication must be recorded in the eCRF.

3.4.2 Hematopoietic Growth Factor Support

The prophylactic use of hematopoietic growth factors [e.g. Granulocyte Colony-Stimulating (G-CSF)] is not permitted in cycle 1. However, the Investigator may prescribe G-CSF as treatment for Grade 3 or higher neutropenia according to local protocols and as prophylaxis after the first event of Grade 3 or higher neutropenia or for any febrile neutropenic episode in order to enable the patient to continue on study. All hematopoietic growth factors used from 30 days prior to date of consent until 30 days after administration of last dose of NUC-1031 must be recorded in the eCRF. Any blood or platelet transfusions should also be recorded in the eCRF.

3.4.3 Concomitant Medication and Non-Drug Therapies

Concomitant medication may be given as medically indicated. All concomitant medication and non-drug therapies used from 30 days prior to date of consent until 30 days after administration of last dose of NUC-1031 must be recorded in the eCRF.

3.4.4 Prohibited Therapy and Concomitant Medications

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy
- Radiotherapy
- Immunotherapy including immunosuppressive therapy
- Radioimmunotherapy
- Hormone therapy (other than contraceptives, hormone-replacement therapy, or megestrol acetate)
- Biologic agents intended for the treatment of ovarian cancer (other than hematopoietic growth factors, which are allowed if clinically indicated and used in accordance with instructions provided in the package inserts)
- Any therapies intended for the treatment of ovarian cancer, whether approved by local regulatory authorities or investigational
- Drugs that are known to prolong QTc interval.

3.5 Study Analysis Populations

There will be 5 analysis populations defined for the study analyses:

3.5.1 Randomized Set (RS)

The RS will correspond to all patients who provided informed consent and were randomized into the study in Part I.

It will be used for the dose selection analysis, only for patients in Part I.

3.5.2 Safety Analysis Set (SS)

The SS will correspond to all patients who received at least one dose of study treatment (NUC-1031 500 mg/m² or 750 mg/m²).

This will be the primary analysis set for the assessment of safety parameters. Patients will be analysed according to the dose initially received (the dispensed treatment even if there was randomization error).

3.5.3 Full Analysis Set (FAS)

Based on the intention-to-treat principle, the FAS will be defined as all enrolled patients:

- who received at least one dose of study treatment (NUC-1031 500 mg/m² or 750 mg/m²)

For the purposes of the analyses, patients of part I will be included according to the dose they were randomized to, regardless of any subsequent dose modifications or errors. For part II, patients will be included in the FAS according to the intended dose level, regardless of any dosing errors or subsequent dose modifications.

This will be the primary analysis set for the assessment of PFS and OS, and all quality of life and symptom-related endpoints.

3.5.4 Evaluable For Response Set (EFR)

The EFR will be defined as all patients from the FAS who have measurable disease at baseline based on BICR.

For the purposes of the analyses, patients in Part I will be included according to the dose they were randomized to, regardless of any subsequent dose modifications. For Part II, patients will be included in the EFR according to the intended dose level, regardless of any dosing errors or subsequent dose modifications.

This will be the primary analysis set for the assessment of all efficacy parameters related to response measurements (ORR, DOR, TTP, TTR, DCR, BOR). PFS and OS will also be generated in the EFS set.

3.5.5 GCIG Analysis Set (GCIGAS)

The GCIGAS will correspond to all patients from the FAS with:

- Measurable disease at baseline, as determined by BICR
- A baseline CA125 reading ≥ 2 x the upper reference range (taken within 2 weeks of C1D1)

For the purposes of the analyses, patients in Part I will be included according to the dose they were randomized to, regardless of any subsequent dose modifications or errors. For Part II, patients will be included in the GCIGAS according to the intended dose level, regardless of any dosing errors or subsequent dose modifications.

3.5.6 Other Populations Defined for Tables and Listings

For the purposes of tables and listings (for example, patient disposition) another population is defined:

- Screened population (all screened patients).

3.5.7 Subgroups

For the primary endpoint, the analyses will also be produced in the following subgroups:

- By BRCA mutation status (Yes/ No)
- By number of prior lines of chemotherapy (3/ >3)

Dependent of the results of the primary analysis, additional subgroup explorations will be considered exploratory only and are not covered by this SAP.

Following the decision to stop the study, no subgroup analysis of primary endpoint will be performed.

However, BOR, PFS and OS analyses will be also performed in the following subgroups

- Co-morbidities at baseline (Yes/No)
- Prior gemcitabine intake (Yes/No)
- Time on prior gemcitabine in months (≤ 1/ >1-3/ >3-6/ >6-12/ >12)
- Time to progression from end of last prior platinum-based chemotherapy in months (≤ 1/ >1-3/ >3-6/ >6)
- BRCA mutation status (Yes/No)
- Time to progression from start of last prior therapy (≤ 1/ >1-3/ >3-6/ >6)

3.6 Withdrawn Patients

Patients will continue to receive NUC-1031 until the occurrence of disease progression by RECIST or unmanageable drug-related adverse events despite dose modification. Patients may also decline treatment at any time for any reason, or they may meet any of the other reasons for treatment withdrawal. Reasons for treatment discontinuation must be captured in the patient medical record and on the Treatment Discontinuation page of the eCRF.
Should a patient discontinue treatment without radiological evidence of disease progression, the patient should continue to undergo tumor assessment every 8 weeks from C1D1 until such time as progression can be documented or new treatment is initiated.

3.6.1 End of Treatment

Treatment with NUC-1031 is to be continued until one of the following occurs:

- PD as defined by RECIST criteria. Patients should not discontinue NUC-1031 because of raised CA125 or other clinical signs of PD until PD has been confirmed by RECIST.
- Unmanageable toxicity defined as an AE that is considered by the Investigator to warrant permanent discontinuation of NUC-1031 including the following:
    - AE resulting in a dosing delay of more than 14 days in starting the next cycle, unless the patient is receiving clinical benefit.
    - Clinically significant drug-related AE that recurs despite dose reduction in two consecutive cycles. Patients may continue to receive treatment if the Principal Investigator and Medical Monitor agree that the patient is receiving a clinical benefit and the toxicity is manageable, reversible or transient.
- Lack of further clinical benefit or unfavorable risk/benefit profile as judged by the Investigator.
- Inter-current illness that prevents further administration of NUC-1031.
- Patient withdraws consent from further treatment or for further data collection.
    - If the patient withdraws consent for further treatment, follow-up visits should continue.
    - If the patient withdraws consent for further treatment and data collection, then no additional study visits or data collection should occur.
- Patient requires use of a prohibited concomitant medication or therapy.
- Pregnancy.
- Changes in the patient's condition, which in the opinion of the Investigator, make the patient unsuitable for further treatment with NUC-1031.
- Patient non-compliance.
- Lost to follow-up.
- Patient withdrawal of consent.
- Sponsor request.

All study procedures outlined for the End of Treatment visit are to be completed within 30 days (±7 days) of the last dose of study drug. The primary reason for study drug discontinuation is to be recorded in the eCRF.

3.6.2 Follow-Up after Treatment Discontinuation

Patients who have documented disease progression defined by RECIST criteria while receiving study medication will discontinue treatment but will enter the follow up period. Patients should not discontinue NUC-1031 because of raised CA125 or other clinical signs of PD until PD has been confirmed by RECIST.
Patients who stop treatment with no evidence of disease progression will enter the follow-up period and should attend clinic every 8 weeks (±7 days) from C1D1 for follow-up scans and assessments. This should continue until disease progression, initiation of a new treatment or death.

3.6.3 Consent Withdrawal

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care.

Consent withdrawal means that a patient has expressed a wish to withdraw from the study altogether. Under these circumstances, the site personnel should document all relevant discussions in the patient notes and mark all future electronic Case Report Form (eCRF) pages as not applicable. Under these conditions, Investigators are still responsible to follow up any Serious Adverse Events (SAE) until resolution.

3.6.4 Study Completion

The study is considered complete when 44 response evaluable patients have been treated at the selected dose and all patients have reached the PFS endpoint or 24 months have elapsed since the final patient was enrolled (whichever occurs first).

Adverse events present at the time of study withdrawal should continue to be assessed for a minimum of 30 days following the last dose of study drug or until resolution to baseline values, whichever occurs first. This should ensure that sufficient information is available to enable assessment of the primary endpoint and other critical secondary endpoints including safety. In the weeks subsequent to a determination that sufficient information is available for these assessments, a date for database lock will be assigned, and any outstanding inquiries concerning data elements will be resolved.

The data cut-off for the primary analysis will be performed 16 weeks after the 44th patient is enrolled at the selected dose. All endpoints will be reported at the time of the primary analysis. Data dependent, a further efficacy update analysis may be performed at a later date, to provide more mature efficacy data for PFS, OS and DOR data. ORR may also be updated at this time point. The timing of this analysis, if required, will be determined upon review of the primary analysis.

Following a preliminary analysis of top-line data in 51 randomised patients from Part I, the dose intensity was lower than expected and the decision was made not to proceed with Part II.

As a consequence, database lock will happen sooner than initially planned and the primary analysis mentioned above won't be produced.

In addition, the efficacy update analysis described above will not be performed.

3.7 Randomization

For Part I of the study, patients will be randomized to NUC-1031 500 mg/m² or 750 mg/m² and will be evaluated in two parallel cohorts of up to 20 patients each. The randomization with a ratio 1:1 will be stratified on BRCA mutation status (Yes/No) and number of prior lines of chemotherapy (=3/>3). The randomization will be conducted centrally using RAVE module in Medidata system and will have 4 separate randomisation sequences.

After the dose selection (based on ongoing safety, dosing intensity, PK and clinical activity observed during Part I), in Part II, patients will be enrolled to the selected dose without randomization in order to recruit 44 evaluable patients, as required for the main analysis.

3.8 Blinding

This is an open label study.

3.9 Sample Size

The primary analysis of response rate will take place when 44 patients at the selected dose have undergone the required assessments for assessment of confirmed ORR by RECIST. The study will be considered to have met its primary endpoint if a minimum of 4 confirmed responses (CR or PR) are observed. Based on 44 patients, if the true ORR is 15%, there is greater than an 80% probability of observing 4 or more responses. Furthermore, if the true response rate were only 5%, there would be less than a 7% probability of observing 4 or more responses out of 44 patients.

4 Statistical Methodology

4.1 Planned Analyses

Demographic analyses will be carried out using the randomised set, the safety analysis set, or full analysis set,. Some of them will also be performed in the randomized set for dose selection analysis.

The efficacy analyses will be carried out on the FAS and the EFR (for response assessments). GCIG criteria will be analysed with the GCIG Analysis Set.

Unless otherwise stated, summary statistics will be presented for continuous variables, by way of n, mean, standard deviation (StD), median, minimum and maximum and by way of group frequencies and percentages for categories of categorical variables. Percentages will be calculated using the total patients per dose group, and overall.

The primary endpoint, ORR, will be summarised to show the number and percentage of responders, along with the corresponding 80% and 95% Clopper-Pearson (exact) and Mid-p confidence intervals. In addition, the number and percentage of patients achieving individual best response criteria of CR, PR, SD, PD, or NE will be described. Due to the decision not to continue the study, this analysis of ORR with a dedicated table will not be produced. Only the number and percentages of responder/ non responder patients will be provided in the table of BOR.

DCR will be summarized as described above for ORR. Due to the decision not to continue the study, this analysis will not be produced.

Kaplan-Meier (KM) plot of PFS, OS, DOR, TTR and TTP will be produced (for DOR and TTR, these will only include the subset of patients defined as responders by the BICR). Descriptive statistics (median, 25th percentile, 75th percentile, minimum and maximum) will also be produced based on the KM estimates. Due to the decision not to continue the study, DOR, TTR and TTP will not be analysed.

Percentage changes from baseline to each visit of the Sum of Lesion Diameters (SLD) (mm) as well as best percentage change will be summarized. In addition, waterfall plots will be provided for sum of lesion diameters at week 8, week 16 and for the best percentage change. In addition, descriptive statistics will be summarized by dose groups at the same timepoints.

For CA125, percentage changes from baseline to each visit (Cycle X Day 1) and best percentage change from baseline will be summarized and presented with a waterfall plot (Cycle 3 Day 1 – Baseline and Cycle 5 Day1 – Baseline only). Different bar types will be used to distinguish between the two dose levels.

Exploratory endpoints will be summarised using the FAS. Due to the decision not to continue the study, this analysis will not be produced.

Safety endpoints will be presented using descriptive statistics based on the Safety Analysis Set.

No baseline testing will be performed.

Statistics will be displayed for the following:

- NUC-1031 500 mg/m²
- NUC-1031 750 mg/m²

Notes:

- Where a percentage change, a relative change or a change from baseline is presented, results for baseline are the most recent assessments prior to the first day of NUC-1031 (500 mg/m² or 750 mg/m²) infusion (or pre-dose on C1D1 if applicable).
- All data will be listed.

4.2 Interim Analyses

Interim analyses are planned to aid the dose selection for Part I of the study. There may be up to 3 dose selection analysis timepoints (see Section 4.2.1).

Data from the dose selection analyses will be reviewed by a DSMC. Members of DSMC will include:

- Chief Investigators from US and Europe
- Selected Principal Investigators from participating sites
- Covance Medical Monitors
- NuCana Medical Director
- Study management staff from NuCana.

Except PK analyses, all other analyses will be provided by the statistician and described in this document.

For each dose selection analysis, according to the Data Management Plan, 15 business days prior to the DSMC meeting, data management will send a raw data extract to the statistical team (lead statistician and lead statistical programmer) in order to produce and send the results to the DSMC members 5 business days prior the DSMC meeting. No database lock will be performed, but a defined data cut-off date will be determined based on study enrolment and DSMC member availability. The raw data will be "as clean as possible": all queries closed, 100% medical coding complete, all critical data Source Data Verified and Data Management Review completed.

This extract will be stored by the statistical team and used to develop CDISC (SDTM and ADaM datasets).

An update efficacy analysis may also be performed after the primary analysis, to provide more mature efficacy data. The same process as described above for dose selection analysis will be followed.

Thus, different data cut-offs will be used to correspond to the different protocol objectives:

- dose selection
- primary analysis

- efficacy update analysis.

It will let us show and present the data that was available at the time of the analysis (dose selection, primary analysis or efficacy update analysis, if necessary) and use those different results for the Clinical Study Report.

4.2.1 Dose Selection Analysis

Two dose levels of NUC-1031, 500 mg/m² and 750 mg/m², will be evaluated in parallel cohorts of up to 20 patients in each in Part I of the study. One dose level will be selected for further evaluation in Part II of the study (based of ongoing safety, dosing intensity, PK and clinical activity observed during Part I), where enrolment shall continue until a total of 44 evaluable patients are recruited at the selected dose.

The decision to determine the Part II dose (500 mg/m² or 750 mg/m²) will be made by the DSMC after review of all required data as outlined below. This analysis could be performed once, twice or three times depending on whether a decision can be made at the time of the initial analysis:

- once 10 patients are enrolled in each arm and have undergone at least one post treatment scan
- once 15 patients are enrolled in each arm and have undergone at least one post treatment scan
- at the end of the randomization: once 20 patients are enrolled in each arm and have undergone at least one post treatment scan

The DSMC will review the safety, dosing intensity, pharmacokinetic and clinical activity data from Part I of the study to decide on which dose should be used in Part II.

The following analyses will be provided for all patients randomized in Part I:

- Patient disposition
- Baseline and Demographic Characteristics
- Ovarian Cancer History
- Prior Ovarian Cancer Therapies
- Exposure
- Prior and Concomitant Medications (only listed)
- Best Overall Response according to RECIST v1.1 assessment based on BICR as well as based on Investigator-Recorded Assessment (including unconfirmed responses)
- Percentage change from baseline in tumor size at week 8 and at week 16 and best percentage change from baseline
- Percentage change of CA125 at Cycle 3 Day 1 and Cycle 5 Day 1 and best percentage change from baseline
- Best GCIG Overall Response, combining the change CA125 from baseline with RECIST assessment (only listed).
- Adverse Events
- Laboratory Findings
- Physical Examination (only listed)

- Vital Signs (only listed)
- ECG
- ECOG Performance Status (only listed)

Only descriptive statistics without inferential (no statistical test) will be provided.

4.2.2 Efficacy Update Analysis

An efficacy update analysis may be performed after the primary analysis, to provide more mature efficacy data.

The same process as described for dose selection analysis regarding extract of the data and output delivery will be followed.

The following analyses will be provided:

- ORR based on BICR
- BOR
- DCR
- PFS
- OS
- DOR
- TTP
- TTR
- Best GCIG Overall Response, combining the change CA125 from baseline with RECIST assessment (per GCIG criteria).

Due to the decision not to proceed with Part II, the study will be stopped and no efficacy update analysis will be produced.

4.3 Disposition of Patients

The number of patients receiving study treatment, in each analysis population, who continued treatment, who continued into follow-up, who continued into Survival Follow-up, who died and the primary reasons for ending treatment and the primary reasons for ending study participation will be presented by dose group.

In addition, the number of patients in each analysis set with reasons for exclusion will be described.

Moreover, the number and percentages of patients with each major protocol violation will be summarized too.

These analyses will be produced for the dose selection analysis and the primary analysis in all screened patients for patient disposition and major protocol violations, and in patients from the Safety Analysis Set for the description of analysis sets.

Patient disposition, Inclusion/ Exclusion criteria descriptions, patients' eligibility, and protocol violations/ deviations will be presented in data listings.

Due to the decision not to proceed with Part II, the patient eligibility listing will not be provided.

4.4 Baseline and Demographic Characteristics

4.4.1 Baseline and Demographic Characteristics

All baseline and demographic characteristics will be summarised by treatment group. This will include:

- gender,
- race,
- ethnicity,
- age group (<55, 55-<66, 66-75, >75),
- ECOG performance status,
- BRCA mutation status,
- number of prior lines of chemotherapy,
- time to progression from start of last chemotherapy in months (≤3/>3),
- time to progression from start of last platinum based chemotherapy in months (≤1/>1-3/>3-6/>6),
- time to progression from end of last platinum based chemotherapy in months (≤1/>1-3/>3-6/>6),
- patients who received prior gemcitabine,
- patients who received prior gemcitabine and had a best response of PD,
- patients who had gemcitabine intake as last prior chemotherapy,
- Time on prior gemcitabine in months (≤1/>1-3/>3-6/>6-12/>12)
- patients with a co-morbidity at baseline,
- time to progression from start of last prior therapy in months (≤1/>1-3/>3-6/>6).

In addition, all co-morbidities at baseline will be described.

All demographic data and baseline characteristics will be summarized in output tables by treatment groups and presented in data listings for the dose selection analysis and the primary analysis in all patients from the Randomized Set.

Notes:

- Age groups are defined as: <55, 55-<66, 66-75, >75 years of age. If birth date is partially missing, substituting rules defined in Section 4.13.5 will be applied.

- Listing will also present women with childbearing potential, age, weight (kilograms (kg)), BSA (m^2), Body Mass Index (BMI) (kg/m^2).
- BMI will be calculated as weight(kg)/height^2(m)
- BSA at screening will be calculated as (Dubois & Dubois BSA calculation)

$$BSA(m^2) = 0.007184 \times Height(cm)^{0.725} \times Weight(kg)^{0.425}$$

- Time to Progression from start of last chemotherapy (defined as the one received immediately before coming on study) (months) = (Progression date – Start date of last chemotherapy + 1)/30.4375

- Time to Progression from start of last platinum-based chemotherapy (defined as the one received immediately before coming on study) (months) = (Progression date – Start date of last platinum based chemotherapy + 1)/30.4375

- Time to Progression from end of last platinum-based chemotherapy (defined as the one received immediately before coming on study) (months) = (Progression date – Last intake date of last platinum-based chemotherapy + 1)/30.4375

- Time on prior gemcitabine (months) = (Last intake date of last prior gemcitabine – First intake date of last prior gemcitabine + 1)/30.4375

- Time to Progression from start of last prior therapy (defined as the one received immediately before coming on study) (months)= (Progression date – First intake date of last prior therapy + 1)/30.4375

- A co-morbidity at baseline is defined as at least one LLT present at the time of first intake among the LLT list below extracted from medical history:
    - Anorexia
    - Arthralgia
    - Arthritis
    - Asthma
    - Atrial fibrillation
    - Chronic kidney disease
    - Chronic kidney disease stage 3
    - Chronic renal insufficiency
    - Diabetes
    - Hypertension
    - Hypotension
    - Myalgia
    - Neuropathy
    - Neuropathy peripheral
    - Osteoarthritis
    - Osteoporosis

- Peripheral sensory neuropathy
- Pleural effusion
- Polymyalgia
- Polymyalgia rheumatica
- Pulmonary embolism
- Rheumatoid arthritis
- Sensory neuropathy
- Tachycardia
- Type II diabetes mellitus
- Ureteral stent insertion
- Urinary tract infection
- UTI
- Vaginal haemorrhage
- Venous thrombosis

4.4.2 Medical/ Surgical History

Medical history will be presented in a data listing with System Organ Class (SOC) and Preferred Term for the primary analysis in patients from the Safety Analysis set.

Notes:

- Medical history will be coded (System Organ Class (SOC) and Preferred Term) according to MedDRA version 18.1 or higher.

4.4.3 Ovarian Cancer History

Ovarian Cancer History will be summarized by treatment groups for the dose selection analysis as well as the primary analysis in patients from the randomized set.

The following criteria will be described:

- Time since initial diagnosis (days) defined as Screening date – Diagnosis date + 1
- Original diagnosis (Ovarian/ Fallopian Tube/ Primary Peritoneal/ Other)
- Histology (High Grade Serous/ High Grade Endometrioid/ Undifferentiated Epithelial/ Unclassifiable Epithelial/ Mixed Epithelial/ Other)
- Stage at initial diagnosis (Stage I (IA/ IB/ IC) / Stage II (IIA/ IIB) / Stage III (IIIA1/ IIIA2/ IIIB/ IIIC) / Stage IV (IVA/ IVB) / Unknown)
- Current stage at screening visit (Stage I (IA/ IB/ IC) / Stage II (IIA/ IIB) / Stage III (IIIA1/ IIIA2/ IIIB/ IIIC) / Stage IV (IVA/ IVB) / Unknown)
- Documented deleterious BRCA mutation? (Yes/ No)
- Type of BRCA mutation, if BRCA mutation=Yes (BRCA 1/ BRCA 2/ BRCA 1/2)
- Any current known metastatic disease sites (Yes/ No)
- Metastatic disease sites (Abdomen/ Adrenals/ Bone Marrow/…/Other)

Ovarian Cancer History will also be listed.

Note:

- In case of missing initial diagnosis date, substituting rules defined in Section 4.13.3 will be applied.

4.4.4 Prior Ovarian Cancer Therapy

Prior Ovarian Cancer Therapy will be summarized by treatment group.

The following descriptive statistics will be provided for the dose selection analysis (Randomized set) as well as the primary analysis (Safety analysis set):

- Number of prior lines of therapy for Ovarian Cancer:
  - Number and percentage of patients in each category: < 3, 3, 4, 5, 6, 7, 8, > 8
  - Quantitative description: n, Mean (SD), Median, Min, Max
- Number and percentage of patients who have received a prior gemcitabine-containing regimen (Yes/ No)
- Number and percentage of patients who have shown resistance to prior Gemcitabine-containing regimens (i.e., who have had a documented best response of PD) (Yes/ No),
- Time to Progression post starting last platinum-containing regimen (months) in classes (≤ 6, >6-9, >9-12, > 12) defined as (Progression date – Start date of last platinum containing regimen + 1) / 30.4375
- Time to Progression post completion of last platinum-containing regimen (months) in classes (≤ 1, >1-6, > 6) defined as (Progression date – Last date of last platinum containing regimen + 1) / 30.4375
- Time to Progression post starting most recent chemotherapy (regardless of agent) (months) in classes (≤ 1, >1-6, >6-9, >9-12, > 12) defined as (Progression date – Start date of most recent chemotherapy + 1) / 30.4375. It corresponds to the one received immediately before coming on study
- Treatment-Free Interval from completion of most recent chemotherapy treatment (months) in classes (≤ 1, >1-3, >3-6, >6-9, > 9) defined as (First study treatment intake date – Last date of last prior treatment regimen + 1) / 30.4375

They will also be listed.

In addition, descriptive statistics of each agent name as prior therapies will be performed for the dose selection analysis as well as the primary analysis (Safety analysis set).

Moreover, the following items will be listed for the primary analysis:

- Any prior systemic cancer therapy (Yes/ No)
- Agent Type (Chemotherapy/ Radiotherapy/ Hormonal Therapy/ Immunotherapy/ PARP Inhibitor/ Vascular Endothelial Growth Factor (VEGF) or Vascular Endothelial Growth Factor Receptor (VEGFR)/ Other)

- For each Agent Type:
  - Reason for Administration (Radio Sensitizing/ Radiation Indicated/ Neoadjuvant/ Adjuvant/ Other)
  - Number of Cycles
  - Best Response
  - Reason for Discontinuation (Progressive or Relapse Disease/ Unmanageable Toxicity/ Completed Treatment/ Lack of Efficacy/ Other)
  - Time to Progression/ Relapse defined as Progression/ Relapse date – Start Date of regimen + 1
- If Agent Type=Radiotherapy:
  - Field of radiation (site) (Abdomen/ Chest/ GI tract/ Kidney/ Liver/ Lung/ Lymph Nodes/ Spleen/ Other)
  - Estimated total dose of radiation

However, following the decision not to proceed to Part II, those listings won't be produced.

Note:

- In case of partially missing first or last intake dates of prior ovarian cancer therapies or in case of partially missing PD dates of prior ovarian cancer therapies for patients whose discontinuation reason is "Progressive/ Relapse Disease" in the CRF, substituting rules defined in Section 4.13.4 will be applied.

- If PD date or first intake date of the last platinum-containing regimen is completely missing (so not substituted), "Time to Progression post starting last platinum-containing regimen (months)" will not be derived, and patient will be counted as missing in the table.

- If PD date or last intake date of the last platinum-containing regimen is completely missing (so not substituted), "Time to Progression post completion of last platinum-containing regimen (months)" will not be derived, and patient will be counted as missing in the table.

- If PD date or first intake date of the most recent chemotherapy is completely missing (so not substituted), "Time to Progression post starting most recent chemotherapy (regardless of agent) (months)" will not be derived, and patient will be counted as missing in the table.

- If last intake date of the most recent chemotherapy is completely missing (so not substituted), "Treatment-Free Interval from completion of most recent chemotherapy treatment (months)" will not be derived, and patient will be counted as missing in the table.

- Platinum-containing regimen corresponds to treatments include in the following list:
  - Carboplatin (ATC Code = L01XA01)
  - Cisplatin (ATC Code = L01XA02)
  - Oxaliplatin (ATC Code = L01XA03)
  - Satraplatin (ATC Code = L01XA04)
  - Polyplatillen (ATC Code = L01XA05)

4.5 Exposure

Exposure will be described by treatment group and presented in a data listing for the dose selection analysis as well as the primary analysis in patients from the Full Analysis Set.

4.5.1 Study Drug Administration

The following endpoints will be described:

- Number of NUC-1031 doses received throughout study as a continuous variable #
- Total dose received: overall and by cycle #
- Number of cycles by patients #
- Number of patients by cycle*
- Dose reduction*: overall and by cycle
- Missing Dose * (visit without administration according to schedule): overall and by cycle
- Duration of exposure (in days)* to NUC-1031 as a continuous variable. This will be calculated as the date of last administration - date of first administration + 1 day throughout study.

According to table 4 (see Section 3.2.4.3 Guidance for Dose Omissions), the following rules will be applied for the description of missing dose:

- Day 1 missed dose *(If day 1 is missed but day 8 is given then the day 8 dose is considered to be the day 1 dose for the new cycle)*: no missed dose to be considered for Day 1 as in the cycle patient will be dosed 3 times
- Day 8 missed dose: to be considered as a missing dose
- Day 15 missed dose *(If day 15 is missed then this is considered the week off and the next dose becomes day 1 of a new cycle and the previous cycle is abbreviated to 3 weeks)*: the patient will only be dosed twice in the cycle. So a missing dose will be considered for this cycle (corresponding to day 15 dose).

Note:

- For dose selection analysis, only endpoints flagged with a star (*) will be described.
- Due to the decision not to proceed with Part II, endpoints flagged with a # will not be described.

4.5.2 Relative Dose Intensity (RDI) and Percent Intended Dose (PID)

The RDI is defined as:

RDI at cycle i = (d at cycle i/D at cycle i)*100

where:

- where d is the actual cumulative dose (in mg/m²) delivered **up to the earlier of progression** (or a censoring event) **or the actual last day of dosing,**
- D is the intended cumulative dose (in mg/m²) **up to the earlier of progression** (or a censoring event) **or the actual last day of dosing**.

Dose intensity (DI) (mg/m²/week (wk)) and RDI (%) will be calculated by cycle. Descriptive statistics will be provided.

The actual cumulative dose received (mg/m²) at cycle i is equal to the actual dose received (mg) at cycle i divided by the BSA at the beginning of the cycle i.

Actual dose intensity by cycle i is defined as follows

$$\text{Actual DI at cycle i} = \frac{\text{Actual dose received (mg/m}^2\text{) at cycle i}}{\text{Actual duration of cycle i (wks)}}$$

With

Actual duration of cycle i (wks) = [(Course date at cycle i+1) − (Course date at cycle i)]/7

If cycle i is the last cycle, then the time is taken to be 28.

The percentage of RDI at cycle i is the ratio of the actual dose intensity (mg/m^2/wk) at cycle i to the Planned Dose Intensity (PDI) (mg/m^2/wk), that is to say:

RDI at cycle i = ((Actual DI at cycle i)/ PDI)*100

With PDI=Planned dose (mg/m²)/4

RDI will be calculated with one decimal.

The same analyses will be performed for the PID. It will be defined as:

PID at cycle i = (d at cycle i/D at cycle i)*100

where:

- d is the actual cumulative dose (in mg/m²) delivered **up to progression** (or a censoring event),
- D is the intended cumulative dose **up to progression** (or a censoring event). D is the total dose (in mg/m²) that would be delivered, if there were no modification to dose or schedule.

Notes:

- If a patient records an early termination visit, the early termination date is used as the end date of that last visit interval.
- For Dose Selection Analysis, these parameters will be described at different timepoints:
  - For all patients for a fixed planned 2 cycles
  - For a fixed planned 3 cycles only in patients who completed them
  - For a fixed planned 4 cycles only in patients who completed them
  - **Rule:** If there are fewer than 3 patients in an arm who completed a cycle (3 or 4 for the 2 previous analyses), then the corresponding analysis won't be performed.
- For the Primary Analysis, these analyses will be performed twice:
  - once for a fixed planned 4 cycles in all patients
  - once for all cycles up to progression in all patients
- Following a preliminary analysis of top-line data in 51 randomised patients from Part I, the dose intensity was lower than expected and the decision was made not to proceed to Part II . Consequently, the same analyses as those performed at the time of Dose Selection Analysis will be performed for the primary analysis. Nevertheless, analyses for all patients for a fixed planned 2 cycles will be repeated in patients with at least one co-morbidity at baseline and in patients with no co-morbidity at baseline.

4.5.3 Relative Doses Received (RDR) and Percentage Intended Doses Received (PIDR)

Same calculations will be performed for the RDR and the PIDR. Instead of the cumulative doses, the number of doses will be considered.

RDR will be defined as

$$RDR = 100 * d/D,$$

where

- d is the number of doses actually received **up to the earliest of progression** (or censoring event) **or last dose,**
- D is the number of doses that should have been received if there were no interruptions or delays in treatment, **up to the earliest of progression** (or censoring event) **or last dose.**

PIDR will be defined as

$$PIDR = 100 * d/D,$$

where

- d is the number of doses actually received **up to progression** (or censoring event),
- D is the number of doses that should have been received if there were no interruptions or delays in treatment, **up to progression** (or censoring event).

Notes:

- If a patient records an early termination visit, the early termination date is used as the end date of that last visit interval.
- For Dose selection analysis, those two parameters won't be described.
- For the Primary Analysis, these analyses will be performed twice:
  - once for a fixed planned 4 cycles in all patients
  - once for all cycles up to progression
- Following the decision not to proceed to Part II, the same analyses as those performed at the time of Dose Selection Analysis will be performed for the primary analysis; that means that RDR and PIDR will only be listed.

4.5.4 Treatment Delays

Deviations from treatment visit intervals (Treatment delay) will also be described:

- The number of cycles delayed will be presented by cycle number and overall at Day 1 of each cycle.
- The number of patients with one or more treatment delays in each cycle will be summarized

A treatment delay is defined as a delay > 3 days from the target interval of 28 days.

The delay will be categorized as (3-7 days], (7-14 days], (14-21 days], > 21 days.

According to Table 4 (see Section 3.2.4.3 Guidance for Dose Omissions), the following rules will be applied for the description of treatment delay:

- Day 1 missed dose *(If day 1 is missed but day 8 is given then the day 8 dose is considered to be the day 1 dose for the new cycle)*: a treatment delay will be calculated since a cycle is planned to last 28 days
- Day 15 missed dose *(If day 15 is missed then this is considered the week off and the next dose becomes day 1 of a new cycle and the previous cycle is abbreviated to 3 weeks)*: no treatment delay.

Note:

- For Cycle 1 Day1, as stated in the protocol, the visit has to be performed within 28 days after screening visit.

4.6 Prior and Concomitant Medication

Incidence of concomitant medication will be presented by treatment groups, WHO DD anatomical, therapeutic and chemical class (Anatomical Therapeutic Classification (ATC)

levels 1,2 and 4) and preferred drug name for the primary analysis in patients from the safety analysis set.

Number of events/medications will be presented too.

Prior medication will be listed only.

Prior medications are those that started and stopped before exposure to study medication; concomitant medications are all medications taken during the study period, including those started before but on going at first dose.

Where a medication start date is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant.

Prior and concomitant medications will also be listed for dose selection analysis as well as primary analysis.

Note:

Medications are coded using World Health Organization Drug dictionary.

4.7 Concomitant Procedures/ Surgeries/ Therapies

Concomitant Procedures/ Surgeries/ Therapies will be listed by treatment groups at the time of the primary analysis. The following criteria will be listed:

- Procedure, surgery or therapy date
- Procedure, surgery or therapy description
- Indication (Medical History/ AE/ Other)
- If indication is an AE, AE selected
- If indication is a Medical History, Medical History selected
- If indication is other, specify
- Study drug suspended for this procedure? (Yes/ No)

4.8 Efficacy / Primary and Secondary Analysis

All efficacy analyses will be performed in patients from either the EFR (for response assessments) or the FAS.

4.8.1 Primary Endpoint

The primary efficacy endpoint of this study is the ORR at the selected dose level (500 mg/m^2 or 750 mg/m^2) per RECIST criteria and assessed by a BICR.

ORR is defined as the proportion of patients achieving a confirmed response: CR or PR.

4.8.1.1 Normality Assumption Checking

Not applicable

4.8.1.2 Closed Testing Procedure for Primary Analysis

The primary analysis will be performed when all 44 patients at the selected dose have completed at least 16 weeks of treatment. A further efficacy update analysis may be performed at a later timepoint to provide more mature efficacy data. As the primary endpoint is ORR, and 4 confirmed responses are required to declare that the study has met its primary endpoint, no adjustment for multiplicity is planned to account for the primary and update analyses, because once 4 responses have been achieved, the threshold will have been met and further analyses will not inflate the false positive risk.

Following a preliminary analysis of top-line data in 51 randomised patients from Part I, the dose intensity was lower than expected and the decision was made not to proceed with Part II Consequently, the primary analysis described above as well as the efficacy update analysis will not be performed.

4.8.2 Method of Analysis for Primary Outcome

All patients included in the study must be assessed for response to treatment, even if there is a major protocol treatment deviation or if they are ineligible, or not followed/re-evaluated. Each patient will be assigned one of the following categories: CR, PR, SD, PD, Not Evaluable (NE).

Patients' response will also be classified as "unknown" if insufficient data were collected to allow evaluation per these criteria.

According to RECIST v1.1, the following table provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline:

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Sponsor:	NuCana plc	Protocol Number:	PRO-105

Table 6: Integration of target, non-target and new lesions into response assessment

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires
Patients with target lesions ± non-target lesions				
CR	CR	No	CR	Normalization of tumor markers All tumor nodes <10 mm Documented on 2 successive or more post-baseline scans with at least 4 weeks interval
CR	Non-CR/Non-PD	No	PR	Documented on 2 successive or more post-baseline scans with at least 4 weeks interval
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression (or evidence of unequivocal disease progression) at that time should be reported as "*symptomatic deterioration"*. This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.				

The overall response will be determined for all protocol specified assessments, ie scheduled assessments (with or without missing information) and also for all unscheduled assessments with non-missing information.

If a scheduled assessment is completely missing (target, non-target, new lesion), the overall response will be NE.

The BOR according to RECIST v1.1 is defined as the best response recorded from the initiation of treatment until disease progression.

When SD is believed to be the BOR, it needs to be assessed a minimum of 6 weeks after randomization (Part I) or start of treatment (Part II). Otherwise, the BOR will be NE, unless any PD was further documented, in which case BOR will be PD.

If a patient progressed before this first assessment, he will be considered as 'early progressive'. If this event occurs, the overall response of the patient will be presumed as progression.

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Sponsor:	NuCana plc	Protocol Number:	PRO-105

Confirmation of CR and PR (assessed a minimum of 4 weeks after the first assessment of CR or PR) is needed to deem either one the BOR.

Complete response [CR] and partial response [PR] would be confirmed 4 weeks later at a subsequent time point.

Table 7: BOR when confirmation of CR and PR required

Response: First Time Point	Subsequent Time Point	BOR	Also Requires
CR	CR	CR	Normalization of tumor markers. All tumor nodes <10 mm.
CR	PR	SD, PD or PR (see comment*)	
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE	
PR	CR	PR	
PR	PR	PR	
PR	SD	SD	
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE	
NE	NE	NE	
* may consider PR providing initial "CR" likely PR on subsequent review – then original CR should be corrected. Recurrence of lesion after true CR should result in the subsequent assessment being classified as a PD rather than a PR. The BOR would then be SD provided the initial CR were observed at least 6 weeks after start of treatment, or PD otherwise.			

Patients for whom response is not confirmed will be classified as "NE", unless they meet the criteria for stable disease (or the criteria for partial response in case of an unconfirmed complete response).

ORR is defined as the number of patients achieving a confirmed CR or PR as the BOR.

Number and percentage of patients achieving a response according to BICR will be presented along with its two-sided 80% and 95% Clopper-Pearson and Mid-p CI.

In addition, two sensitivity analyses will be performed for ORR:

- A sensitivity analysis will be performed using investigator-recorded assessment of response instead of BICR (based on the subset of the FAS deemed to have measurable disease by the investigators)

- A sensitivity analysis of ORR based on BICR using the PPS, to investigate the impact of major deviations on the primary endpoint.

These analyses will be performed in patients from the Evaluable For Response Set and Per Protocol Set at the time of Primary Analysis.

ORR based on BICR may also be updated at the time of the efficacy update analysis (if performed).

Following the decision not to proceed to Part II, the analysis of ORR mentioned above will not be performed. However, descriptive statistics of responder/non responder patients will be provided in the same table as BOR.

4.8.3 Secondary Endpoints

The secondary endpoints of this study are:

- BOR according to RECIST v1.1 assessment.
- DCR.
- PFS.
- OS.
- DOR.
- TTP.
- TTR.
- Change from baseline in tumor size.
- Best GCIG Overall Response, combining the change CA125 from baseline with RECIST assessment (per GCIG criteria).
- Relative Change of CA125.
- Time on treatment.
- FOSI-18 questionnaire.

4.8.4 Methods of Analysis for Secondary Outcomes

All tables by weeks or listings based on BICR will apply the following rules:
- Cycle 2 will correspond to week 8
- Cycle 4 will correspond to week 16
- Cycle 6 will correspond to week 24
- Cycle 8 will correspond to week 32
- Cycle 10 will correspond to week 40
- Cycle 12 will correspond to week 48
- Unscheduled assessments will be considered as unscheduled

- Follow-up assessments will be considered as Follow-up

In addition, all tables by weeks or listings based on investigator recorded assessment will apply the following rules:

- A scan will be considered as week 8 scan if the tumor assessment date is in the windows of Cycle 1 Day 1 date + 49 days and Cycle 1 Day 1 date + 63 days.
- A scan will be considered as week 16 scan if the tumor assessment date is in the windows of Cycle 1 Day 1 date + 105 days and Cycle 1 Day 1 date + 119 days.
- A scan will be considered as week 24 scan if the tumor assessment date is in the windows of Cycle 1 Day 1 date + 161 days and Cycle 1 Day 1 date + 175 days.
- A scan will be considered as week 32 scan if the tumor assessment date is in the windows of Cycle 1 Day 1 date + 217 days and Cycle 1 Day 1 date + 231 days.
- A scan will be considered as week 40 scan if the tumor assessment date is in the windows of Cycle 1 Day 1 date + 273 days and Cycle 1 Day 1 date + 287 days.
- A scan will be considered as week 48 scan if the tumor assessment date is in the windows of Cycle 1 Day 1 date + 329 days and Cycle 1 Day 1 date + 343 days.

4.8.4.1 BOR according to RECIST v1.1 Assessment

The BOR will be assessed by providing number and percentage of patients achieving each individual best response criteria (CR, PR, SD, PD, or NE).

The BOR will be assessed for both BICR and Investigator assessed responses.

This analysis will be performed in patients from the Evaluable For Response Set at the time of dose selection analysis and primary analysis.

Following the decision not to proceed to Part II, the BOR primary analysis will be performed in the same way as the dose selection analysis without confirmation rule of CR and PR responses.

Moreover, same BOR analyses will be performed in the following subgroups:

- Co-morbidities at baseline (Yes/No)
- Prior gemcitabine intake (Yes/No)
- Time on prior gemcitabine in months (≤ 1/ >1-3/ >3-6/ >6-12/ >12)
- Time to progression from end of last prior platinum-based chemotherapy in months (≤ 1/ >1-3/ >3-6/ >6)
- BRCA mutation status (Yes/No)
- Time to progression from start of last prior therapy (≤ 1/ >1-3/ >3-6/ >6)

4.8.4.2 DCR

DCR is defined as the proportion of patients achieving as BOR a confirmed response (CR or PR) or SD whose SD duration from baseline lasts at least of 6 weeks based on BICR.

Summary statistics showing the number and percentage of patients with disease control will be presented. The presentation will show the overall disease control figures, along with the category of disease control achieved (CR, PR, SD ≥ 6 weeks (-5 days), SD < 6 weeks (-5 days).

DCR will be evaluated in patients from the Evaluable For Response Set at the time of primary analysis.

Same analysis with DCR based on Investigator-Recorded Assessment will also be provided.

Following the decision not to proceed to Part II, this endpoint will not be described but only listed.

4.8.4.3 PFS

PFS is defined as the time from the date of study treatment initiation (start of treatment) or randomization (if randomized) to the first date of objectively determined PD or death from any cause (in the absence of progression) based on BICR.
Event dates are assigned to:

- The first time when confirmed progressive disease was noted, or
- Date of death.

In case of progressive disease followed by death, the first event will be considered in the analysis.

The progressive disease date is assigned to the first time at which progressive disease can be declared.

For patients who are still alive at the time of the data cut-off date and without evidence of tumor progression, PFS will be censored at the date of the most recent objective progression-free observation (last tumor assessment date).

For patients who receive subsequent anticancer therapy prior to objective disease progression or death, PFS will be censored at the date of the last objective progression-free observation (last tumor assessment date) prior to the date of subsequent therapy.

For patients without any scan and without death, PFS will be censored at the day after the first treatment intake date.

When tumor assessment visits are completely missing, FDA Guidance “Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics” [4] states that "events occurring after two or more missed radiological assessments will be censored in the analysis at the last adequate assessment’.

This will be implemented as follows:

PD occurring after two or more missed radiological assessments will be censored in the analysis at the last adequate assessment before the missing assessments.

If a patient has one missed radiological assessment before a PD, the PD event will be analyzed as an event.

The PFS time will be calculated as the time from first administration of NUC-1031 (for Part II patients) or randomization (for Part I patients) to either progressive disease or death as follows:

PFS (months) = [(Date of event – date of randomization/ first administration) + 1]/30.4375

The number of overall censored patients, number of patients with events and Kaplan-Meier estimates median time will be provided with 25th percentile and 75th percentile. In addition, the results will be presented graphically in Kaplan-Meier plots including count for numbers of patients at risk.

Moreover, same PFS analyses will be performed in the following subgroups:

- Co-morbidities at baseline (Yes/No)
- Prior gemcitabine intake (Yes/No)
- Time on prior gemcitabine in months (≤ 1/ >1-3/ >3-6/ >6-12/ >12)
- Time to progression from end of last prior platinum-based chemotherapy in months (≤ 1/ >1-3/ >3-6/ >6)
- BRCA mutation status (Yes/No)
- Time to progression from start of last prior therapy (≤ 1/ >1-3/ >3-6/ >6)

In addition, analysis of PFS with a cut-off date at 6 months using the KM method (PFS6KM) will also be carried out on all patients in the analysis population, but only considering data between first treatment intake date and first treatment intake date + 183 days (6 months).

For the analysis of PFS6KM, the following censoring rules will be applied:

- If the patient doesn't miss any visit and has not died before 6 months or has not documented progression before 6 months, he will be censored at the 6 months date.
- If the patient misses a visit and has not died before 6 months or has not documented progression before 6 months, he will be censored at the last non-missing tumor assessment date.
- For patients who receive subsequent anticancer therapy prior to objective disease progression or death in the 6 month period, PFS will be censored at the date of the last objective progression-free observation (last tumor assessment date) prior to the date of subsequent therapy.
- For patients without any scan and without death in the 6 month period, PFS will be censored at the day after the first treatment intake date.

These analyses will be produced in patients from the FAS at the time of the primary analysis.

Moreover, number and percentage of patients with PFS at 4 months as binary data (Yes/ No/ Missing, where "Yes" corresponds to not progressing) will be presented in patients from the FAS, EFR at the time of the primary analysis. The same analysis will be performed for PFS at 6 months only in patients randomized/included prior to the last 6 months of the trial.

For PFS4 and PFS6 considered as binary variables, the following rules will be applied:

- If the patient receives any other anti-cancer treatment prior to 4/6 months then he will be counted as a "No" (i.e., counted as being a progressing).

- If the patient is missing his last scheduled tumor assessment (and he has not died before 4/6 months, nor has documented progression before 4/6 months) then he will be counted as "missing".
- For patients not randomized in the last 6 months of the trial, PFS6 will be displayed as Not Applicable (NA) in the listing.

Due to the decision not to proceed to Part II, only classic PFS with Kaplan-Meier based on BICR will be performed. However, KM plots of PFS will. not be displayed.

Analysis based on Investigator Recorded assessment will not be produced. Only listings will be produced for Investigator Recorded assessments as well as for PFS4, PFS6 and PF6KM endpoints.

Note:

- PFS will be calculated with one decimal.

➔ Methodology of Kaplan-Meier estimator $\hat{S}_t$

The survival function is defined as $S_t = P[T > t] = 1 - F(t), t \geq 0$

Assume 2 timepoints t_i and t_{i+1} $(t_{i+1} > t_i)$ then,

$$S(t_{i+1}) = P[T > t_{i+1}] = P[T > t_{i+1} \text{ and } T > t_i]$$

With conditional probability theorem we obtain:

$$P[T > t_{i+1}] = P[T > T_{i+1} / T > T_i] \times P[T > t_i]$$

With:

- $P[T > T_{i+1} / T > T_i]$ can be estimated by $1 - d_{t_{i+1}} / n_{t_{i+1}}$ where $d_{t_{i+1}}$ is the number of patients with the events at t_{i+1} and $n_{t_{i+1}}$ is the number of patients at risk at t_{i+1}.
- $P[T > t_i] = S(t_i)$ by definition

Thus we obtain $\hat{S}(t_{i+1}) = \left(1 - \frac{d_{t_{i+1}}}{n_{t_{i+1}}}\right) \times \hat{S}(t_i)$

Knowing that $\hat{S}_0 = 1$, we obtain the Kaplan-Meier estimator $\hat{S}(t)$:

$$\hat{S(t)}_{KM} = \prod_{i/t_i \le t}\left(1 - \frac{d_i}{n_i}\right)$$

4.8.4.4 OS

OS is defined as the time from first administration of NUC-1031 or randomization (if randomized) until death from any cause. All deaths will be included, whether they occur during the study or following treatment discontinuation.

For patients who have not died, overall survival will be censored at the date of last contact (date the patient was last known to be alive).

OS time (in months) = [(date of death/ date patient last known to be alive - date of randomization/ first administration) + 1]/30.4375.

The OS will be analysed as described for PFS.

The number of overall censored patients, number of patients with events and Kaplan-Meier estimates median time will be provided with 25th percentile, 75th percentile. In addition, the results will be presented graphically in Kaplan-Meier plots.

OS analysis will be produced in patients from the FAS at the time of the primary analysis.

Moreover, same PFS analyses will be performed in the following subgroups:

- Co-morbidities at baseline (Yes/No)
- Prior gemcitabine intake (Yes/No)
- Time on prior gemcitabine in months (≤ 1/ >1-3/ >3-6/ >6-12/ >12)
- Time to progression from end of last prior platinum-based chemotherapy in months (≤ 1/ >1-3/ >3-6/ >6)
- BRCA mutation status (Yes/No)
- Time to progression from start of last prior therapy (≤ 1/ >1-3/ >3-6/ >6)

Due to the decision not to proceed to Part II, KM plots will not be displayed.

4.8.4.5 DOR

DOR will be evaluated for the subset of patients categorized as responders for the assessment of ORR (Section 4.8.1).

DOR is defined as the period from the date of initial confirmed PR or CR (whichever occurs first) until the date of PD or death from any cause (whichever occurs first).

Only responses that were later confirmed, will be considered when calculating the DOR.

DOR will be calculated as follows:

DOR (months) = ((Date of PD or death – Date of first confirmed PR or CR) + 1) /30.4375

For patients who were lost to follow-up without progression or reached the time point of analysis without a known record of death or progression, the duration of response will be censored at the date of last tumor assessment.

For patients who receive subsequent anticancer therapy prior to objective disease progression, DOR will be censored at the date of the last tumor assessment date prior to the date of subsequent therapy.

Only patients with BOR of CR or PR (i.e., responders) will be included in the analysis of DOR.

The analysis and presentation of DOR will be described as for PFS, at the time of the primary analysis and will be based on the subset of the Evaluable For Response Set categorized as responders for ORR based on BICR.

The number of overall censored patients, number of patients with events and Kaplan-Meier estimates median time will be provided with 25th percentile and 75th percentile. In addition, the results will be presented graphically in Kaplan-Meier plots.

Same analysis with DOR based on Investigator-Recorded Assessment will also be provided.

Due to the decision not to proceed to Part II, DOR will only be listed.

4.8.4.6 TTP

TTP is measured with the Duration of Stable Disease (DSD), from the randomization date (Part I patients) or start of the treatment (Part II patients) until the criteria for progression are first met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

TTP (months) = ((Date of progression of disease – Randomization date/ Time from first dose) + 1) /30.4375

For patients who were lost to follow-up without progression or reached the time point of analysis without a known record of progression, the time to progression will be censored at the date of last tumor assessment.

For patients who died without documented progression, the time to progression will be censored at the date of last tumor assessment.

For patients who receive subsequent anticancer therapy prior to objective disease progression, TTP will be censored at the date of the last tumor assessment date prior to the date of subsequent therapy

The analysis and presentation of TTP will be as described for PFS in patients from the EFR and PPS at the time of primary analysis.

The number of overall censored patients, number of patients with events and Kaplan-Meier estimates median time will be provided with 25th percentile and 75th percentile. The results will also be presented graphically in Kaplan-Meier plots.

Due to the decision not to proceed to Part II, TTP will only be listed.

4.8.4.7 TTR

TTR will be evaluated for the subset of patients categorized as responders for the assessment of ORR (Section 4.8.1).

TTR is measured from the randomization date (Part I patients) or start of the treatment (Part II patients) until the first documentation of confirmed PR or CR (whichever occurs first).

TTR (months) = ((Date of first confirmed response - time from randomization/ first dose) + 1) /30.4375

The analysis and presentation of TTR will be described as for PFS in responder patients from the Evaluable for Response Set at the time of the primary analysis.

Kaplan-Meier estimates median time to response, 25th and 75th percentiles and the range (min-max) will be provided with 25th percentile and 75th percentile. The results will also be presented graphically in Kaplan-Meier plots.

Due to sponsor decision after dose selection analysis to stop the study, DOR will only be listed.

4.8.4.8 Percentage Change from Baseline in Tumor Size

Percentage changes from baseline to each visit of the Sum of Lesion Diameters (SLD) (mm) as well as best percentage change will be summarized by dose group in patients from the Evaluable for Response Set at the time of the dose selection analysis as well as the primary analysis.

In addition, the following waterfall plots of percentage change from baseline of SLD will be presented:

- Percentage change from baseline to week 8,
- Percentage change from baseline to week 16
- Best percentage change from baseline

4.8.4.9 Best GCIG Overall Response, combining the Change CA125 from Baseline with RECIST Assessment (per GCIG criteria)

The GCIG recommends that for trials of relapsed ovarian cancer the following definition for response according to CA125 be used in addition to the standard RECIST response criteria.

Definition of response according to CA125.

A response according to CA125 has occurred if there is at least a 50% reduction in CA125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA125 only if they have a pretreatment sample that is at least twice the Upper Limit of Normal (ULN) and within 2 weeks prior to starting treatment.

To calculate CA125 responses accurately, the following rules apply:

- intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.
- variations within the normal range of CA125 levels will not interfere with the response definition.
- For each patient, the same assay method must be used and the assay must be tested in a quality-control scheme.
- Patients are not evaluable by CA125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by Human Anti-Mouse Antibody (HAMA)) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days. If assessing therapy that includes two treatment modalities for relapse (e.g., surgery and chemotherapy), any CA125 response results from both treatments modalities. CA125 cannot distinguish between the effects of the two treatments.

The date when the CA125 level is first reduced by 50% is the date of the CA125 response.

In addition, those patients who have both a CA125 response and whose CA125 level falls to within the normal range, can be classified as CA125 complete responders. Patients who have a fall of CA125 to within the normal range but whose initial CA125 was less than twice the upper limit of normal, have not had a CA125 response and cannot therefore be classified as a CA125 complete responder.

Definition of Progression on first line therapy and Recurrence after first line therapy according to CA125.

Progression is defined according to RECIST but can also be based upon serum CA125 (defined below) but tumor measurements should take precedence over CA125.

If measurable disease is shrinking during treatment, but the CA125 indicates progression (as defined below) the patient should continue to receive protocol treatment. If measurable disease shows stable disease but CA125 indicates progression after a minimum of 3 courses of chemotherapy, protocol treatment should be changed.

If the GCIG definition based on CA125 is used to define progression after relapse therapy it should be noted that it has not been validated.

Evaluation of progression according to CA125

Progression or Recurrence based on serum CA125 levels will be defined on the basis of a progressive serial elevation of serum CA125, according to the following criteria and table 8:

A) Patients with elevated CA-125 pretreatment and normalization of CA125 must show evidence of CA125 greater than, or equal to, two times the upper limit of the reference range on two occasions at least one week apart

or

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B) Patients with elevated CA125 before treatment, which never normalizes must show evidence of CA125 greater than, or equal to, two times the nadir value on two occasions at least one week apart

or

C) Patients with CA125 in the reference range before treatment must show evidence of CA125 greater than, or equal to, two times the upper limit of the reference range on two occasions at least one week apart.

Elevated values must be confirmed by two separate measurements obtained at least one week apart. CA125 Progression will be assigned the date of the first measurement that meets the criteria as noted. Patients are not evaluable by CA125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by HAMA) or if there has been medical and/or surgical interference with their peritoneum or pleura (eg, paracentesis) during the previous 28 days.

A patient may be declared to have progressive disease on the basis of either the objective RECIST 1.1 criteria or the CA125 criteria. The date of progression will be the date of the earlier of the two events if both are documented.

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Table 8: Definition of progression after first-line therapy in ovarian cancer as proposed by GCIG

GCIG subcategorized group	RECIST Measurable/ Non-measurable disease		CA125
A	Compared to baseline (or lowest sum while on study if less than baseline), a 20% increase in sum of longest diameters (RECIST definition) Or Any new lesions (measurable or non-measurable) Or Unequivocal increase in non target disease PD date: date of documentation of increase or new lesions	AND /	CA125 ≥ 2 x Upper Limit of Response Range (ULRR) documented on two occasions # PD date: first date of the CA125 elevation to ≥ 2 x ULRR
B	As for A	OR	CA 125 ≥ 2 x nadir value on 2 occasions #
C	As for A		As for A
GCIG groups A, B & C defined above # Repeat CA125 any time, but normally not less than 1 week after the first elevated CA125 level. CA125 levels sampled after patients received mouse antibodies (unless the assay used has been shown not to be influenced by HAMA) or if there has been medical and /or surgical interference with their peritoneum or pleura during the previous 28 days, should not be taken into account.			

Evaluation of BOR in patients with initial measurable disease and who are also evaluable by CA125

A report that combines both CA125 and RECIST criteria, is likely to include patients that are measurable by one or both of the criteria, who may have events at different time points. In patients that are measurable by both criteria the date of response will be the earlier date of the two events.

The following rules apply when determining the BOR:

- If patients have PD according to RECIST within 28 days of CA125 response they are classified as PD.
- If the PD according to RECIST is > 28 days after the CA125 response they are classified as PR.
- Patients whose best response according to RECIST is SD but who have a CA125 response are classified as CA125 responders.

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The following table presents the BOR combining RECIST and CA125.

Table 9: BOR in patients with initial measurable disease and who are also evaluable by CA125, combining both criteria

Target Lesions ~	Non-Target Lesions #	New Lesions	CA125	BOR	
CR	CR	No	Normal	**CR**	**Best RECIST response for this category also requires it to be confirmed and maintained for at least 28 days**
CR	Non-CR/Non-PD	No	Not PD	**PR**	
CR	CR	No	PR not normal	**PR**	
CR	NE	No	PR	**PR**	
PR	Non-PD or Not All Evaluated	No	Not PD	**PR**	
Not All Evaluated	Non-PD	No	PR	**PR**	
(PD or New) > 28 days from CA125 PR *			PR	**PR**	
SD	Non-PD	No	PR	**PR**	
SD	Non-PD or Not All Evaluated	No	Not PR and not PD	**SD**	
(PD or New) ≤ 28 days from CA125 PR *			PR	**PD**	
PD	Any	Yes or No	Any	**PD**	
NE or Any	PD	Yes or No	Any	**PD**	
NE or Any	Any	Yes	Any	**PD**	
NE or Any	Any	Yes or No	PD	**PD**	

Notes:
~ target lesions include up to 5 measurable lesions (2 per organ) as defined by RECIST 1.1
# non-target lesions include ascites and peritoneal thickening which are not measurable according to RECIST 1.1
* patients who have a CA125 response that occurs more than 28 days from PD according to RECIST 1.1 are considered as PR according to best response, but PD if the RECIST 1.1 PD is within 28 days of CA125 response

Best GCIG Overall Response, combining the change CA125 from baseline with RECIST assessment (per GCIG criteria) will be summarized in patients from the GCIG Analysis Set at the time of primary.

It will also be presented in a data listing for the dose selection analysis and primary analysis.

Due to the decision not to proceed to Part II, Best GCIG Overall Response will not be summarized and will only be listed.

4.8.4.10 Percentage Change of CA125

Percentage changes from baseline to each visit of CA125 value (U/mL) will be summarized in patients from the GCIG Analysis Set at the time of the dose selection analysis as well as the primary analysis.

In addition, waterfall plots of relative change of CA125 value in patients with measurable CA125 value at baseline will be presented at each visit and for the best percentage change from baseline. Percentage changes from baseline to Cycle 3 Day 1 and to Cycle 5 Day 1 will be of special interest in order to be able to compare the results with percentage changes of tumor size (SLD) from baseline to Week 8 and to Week 16.

4.8.4.11 Time on Treatment

A Swimmer plot of time on Treatment by Response Category will be presented at the time of the primary analysis for the 2 following evaluations:

- BOR according to RECIST v1.1 based on BICR in patients from the Evaluable for Response Set
- Best GCIG Overall Response combining the change CA125 from baseline with RECIST assessment (per GCIG criteria) in patients from the GCIG Analysis Set

Time on treatment will be calculated as the date of last administration - date of first administration + 1 day throughout study.

Due to sponsor decision after dose selection analysis to stop the study, these figures won't be displayed.

4.8.4.12 FOSI-18 Questionnaire

The FOSI-18 questionnaire will be filled by the patient at screening visit, days 1 of each cycle, end of treatment visit and follow-up visits (every 8 weeks).

The following endpoints will be evaluated:

- Lack of energy (coded as GP1)
- Pain (coded as GP4)
- Ill (coded as GP6)
- Cramps in stomach area (coded as O3)

- Fatigue (coded as HI7)
- Bothered by constipation (coded as Cx6)
- Swelling in stomach area (coded as O1)
- Control of bowels (coded as C3)
- Sleeping well (coded as GF5)
- Worries about conditions (coded as GE6)
- Nausea (coded as GP2)
- Bothered by hair loss (coded as B5)
- Bothered by side effects of treatment (coded as GP5)
- Vomiting (coded as O2)
- Bothered by skin problems (coded as BMT15)
- Ability to get around by herself (coded as BMT5)
- Ability to enjoy life (coded as GF3)
- Content with the quality of life right now (coded as GF7)

The possible evaluations are Not at all, A little bit, Somewhat, Quite a bit, Very much.

Number and percentage of patients with each response category at each visit will be summarized from the Full Analysis Set at the time of primary analysis.

In addition, 5 scores can be developed based on the FOSI-18 item questionnaire: one scale on the overall questionnaire named FOSI-18 Total (score range: 0-72) and 4 subscales named:

- FOSI-Disease Related Symptoms-Physical (FOSI-DRS-P) (score range: 0-36) composed of
    - GP1
    - GP4
    - GP6
    - O3
    - HI7
    - Cx6
    - O1
    - C3
    - GF5
- FOSI-Disease Related Symptoms-Emotional (FOSI-DRS-E) (score range: 0-4) corresponding to GE6 item,

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- FOSI-Treatment Side Effects (FOSI-TSE) (score range: 0-20) composed of
    - GP2
    - B5
    - GP5
    - O2
    - BMT15
- FOSI-Function/Well Being (FOSI-F/WB) (score range: 0-12) composed of
    - BMT5
    - GF3
    - GF7.

For the calculation of the scores, responses to items GP1, GP4, GP6, O3, HI7, Cx6, O1, GE6, GP2, B5, GP5, O2, BMT15 are coded as follows:

- Not at all = 4
- A little bit = 3
- Somewhat = 2
- Quite a bit = 1
- Very much = 0

Conversely, responses to items C3, GF5, BMT5, GF3, and GF7 are coded as follows:

- Not at all = 0
- A little bit = 1
- Somewhat = 2
- Quite a bit = 3
- Very much = 4

The following formulas describe the calculation of each score:

- FOSI-18 Total Score

FOSI-18 Total Score = 18 * (Sum of all individual item scores) / (Number of items answered)

- FOSI-DRS-P Score

FOSI-DRS-P Score = 9 * (Sum of individual item scores) / (Number of items answered)

- FOSI-DRS-E Score

FOSI-DRS-E Score = GE6 Score

- FOSI-TSE Score

FOSI-TSE Score = 5 * (Sum of individual item scores) / (Number of items answered)

- FOSI-F/WB Score

FOSI-F/WB Score = 3 * (Sum of individual item scores) / (Number of items answered)

Thus, a high score is good. Therefore, a score of "0" is a severely symptomatic patient and the highest possible score is an asymptomatic patient.

Each Score will be described at each visit in patients and graphically represented in patients from the Full Analysis Set at the time of primary analysis.

In addition, changes from baseline to each visit of each score will be provided in patients from the Full Analysis Set at the time of primary analysis.

FOSI-18 questionnaire will be listed too.

Due to the decision not to proceed to Part II, FOSI-18 questionnaire will not be described, nor listed.

4.9 Exploratory Endpoints

4.9.1 EQ-5D-5L Questionnaire

The EQ-5D-5L questionnaire will be filled by the patient at screening visit, days 1 of each cycle, end of treatment visit and follow-up visits (every 8 weeks).

The following endpoints will be evaluated:

- Dimensions
    - Mobility (No problems/ Slight problems/ Moderate problems/ Severe problems/ Unable)
    - Self-Care (No problems/ Slight problems/ Moderate problems/ Severe problems/ Unable)
    - Usual Activities (No problems/ Slight problems/ Moderate problems/ Severe problems/ Unable)
    - Pain/ Discomfort (No problems/ Slight problems/ Moderate problems/ Severe problems/ Unable)
    - Anxiety/ Depression (No problems/ Slight problems/ Moderate problems/ Severe problems/ Unable)
- Visual Analogue Scale (VAS)

Notes:

- There should be only one response for each dimension

- For dimensions, ambiguous values (e.g, several boxes are ticked for a single dimension) should be treated as missing values

The following analyses will be performed in patients from the Full Analysis Set at the time of primary analysis.

EQ-5D-5L endpoints will also be presented in a data listing.

4.9.1.1 Analysis of Dimensions (Health profiles)

The number and percentage of patients in each level of each dimension will be provided at each visit by treatment group in patients from the Full Analysis Set.

It will also be graphically represented using bar charts.

4.9.1.2 EQ VAS

VAS will be described at each visit by treatment group in patients from the Full Analysis Set. It will also be graphically represented using line charts.

4.9.1.3 EQ-5D-5L Index Value

For each patient, a 5L profile will be derived with 5 digits (one digit by dimension). For each dimension, the following code will be computed:

- No problems=1
- Slight problems=2
- Moderate problems=3
- Severe problems=4
- Unable=5

Then using the "EQ-5D-5L Crosswalk Index Value Calculator" downloaded from the EuroQol website, an index value for the patient will be calculated according to his country.

Once these index values are calculated, descriptive statistics at each visit will be provided as well as changes from baseline.

Mean values will also be graphically represented at each visit.

Notes:

- If a patient has a missing value for one dimension, her 5 L profile won't be derived.

- The *Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets*. *Q-5D-5L Index Value Calculator developed by the EuroQol Group* document developed by Van Hout B, Janssen MF, et al (EuroQol Group) has index values calculated for Denmark, France, Germany, Netherlands, Spain and United Kingdom. If one other European country is included in the study, index values for US patients will be used for all patients of the study.

- Due to the decision not to proceed to part II, EQ-5D-5L questionnaire will not be described or listed.

4.10 Safety Analysis

Safety data will include AE, Clinical Laboratory Evaluations (chemistry, hematology, urine and coagulation), Physical Examinations, Vital Signs, ECG and ECOG.

All safety analyses will be presented by treatment group in patients from the safety analysis set for dose selection analysis as well as the primary analysis.

4.10.1 Adverse Events

All AE will be recorded and graded by investigators using the National Cancer Institute-Common Terminology Criteria for Adverse Event (NCI-CTCAE) classification (Version 4.0) and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1 or higher, and will be classified by MedDRA Preferred Term and SOC.

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

4.10.1.1 Definition

For FDA regulated studies the FDA defines an adverse event as the following:

"*Adverse event means any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related.*"

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study drug. Patients or their legally authorized representatives will be instructed to contact the Investigator or Sub-Investigator at any time after signing the ICF if any symptoms develop.

A Treatment Emergent Adverse Event (TEAE**)** is defined as:

- any event not present before exposure to study drug, thus occurring between first study drug dose intake date and last study dose drug intake date + 30 days
- or any event already present that worsens in either intensity or frequency after exposure to study drug; thus worsening between first study drug dose intake date and last study dose drug intake date + 30 days

AE are classified as serious or non-serious. A SAE is defined as any event that:

- Results in death,
- Is immediately life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect,

- Significant medical event in the investigator's judgment (*e.g.,* may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

PD and disease-related death will not be considered as an AE or SAE.

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

4.10.1.2 Reporting

At every study visit, patients will be asked nondirective questions to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over the counter medications). In addition to patient observations, AEs will be documented from any data collected on the eCRF or other documents that are relevant to patient safety. Any allergic reaction to the agents administered as study drug treatment must be reported as an AE.

All AEs that occur from date of consent through 30 days after the last dose of study drug must be reported in detail on the AE eCRF. Disease progression in the medical opinion of the physician and/or disease-related morbidity and mortality as a study endpoint will not be considered an AE or SAE but should be captured on the Death eCRF. Information to be collected for each AE includes onset date, type of event, etiology, Investigator specified assessment of severity and relationship to study drug, seriousness, any required treatment or evaluations, outcome and date of resolution. AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed for 30 days after the patient's last dose, or until resolution, whichever comes first.

Preexisting conditions (present before the start of the AE collection period) are considered concurrent medical conditions and should not be recorded as AEs. However, if the patient experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded as an AE. Pre-existing AEs that worsen should be followed until 30 days after the patient's last dose or resolution to the AE level present at study entry. Investigators should ensure that the AE term recorded captures the change in the condition (e.g. "worsening of [condition]").

Insufficient clinical response, efficacy, or pharmacological action should NOT be recorded as an AE. The Investigator must make the distinction between exacerbation of preexisting illness and lack of therapeutic efficacy. PD is NOT an AE; however, some sequelae of PD (i.e. pain, neurologic impairment) may be reported as AEs (generally not related to NUC-1031).

Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy or further diagnosis beyond

repeat testing for confirmation, or (if not associated with clinical signs or symptoms) they remain at levels consistent with severe abnormalities despite appropriate medical intervention. It is requested that when reporting AEs for which potentially redundant NCI CTCAE terms exist, the Investigator utilizes the more clinically-oriented terminology (for example, 'anemia' is preferable to 'hemoglobin decreased').

It is also requested that in the setting of an allergic reaction or suspected allergic reaction considered by the Investigator to be related to NUC-1031, that the Investigator reports both the specific symptoms associated with the reaction (i.e. 'urticaria', 'dyspnea') and also report the appropriate term indicating the allergic reaction ('allergic reaction' or 'anaphylaxis' if appropriate [Immune System Disorders; CTCAE v4]).

4.10.1.3 Assessment of Causality

The Investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship of an AE to NUC-1031 should be classified using the following guidelines:

Related: A temporal relationship exists between the event onset and administration of NUC-1031. It cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. This includes events that are considered possibly, probably, or definitely related to NUC-1031.

Not Related: Evidence exists that the AE has an etiology other than the study drug (*e.g.* pre-existing condition, underlying disease, intercurrent illness, or concomitant medication). This includes events that are considered probably not or not related to NUC-1031. It should be emphasized that ineffective study drug treatment should not be considered as causally related in the context of AE reporting (in other words, PD is not considered an AE; however some sequelae of PD may be reported as AEs and should generally be reported as AEs not related to NUC-1031).

4.10.1.4 Assessment of Severity

The severity of each AE is to be assessed by the Investigator according to NCI CTCAE, v4. If the AE is not included in the NCI CTCAE, then the Investigator is to determine the intensity of the AE according to the following criteria:

Mild (Grade 1):	AE that disappears or is easily tolerated on continuation of study drug
Moderate (Grade 2):	AE sufficiently discomforting to cause interference with usual work activities.
Severe (Grade 3):	AE that is incapacitating, with inability to work or perform daily
Life-Threatening (Grade 4):	AE that is *potentially* life-threatening*

Death (Grade 5): Death related to AE

*If a life-threatening (Grade 4) AE is *immediately* life-threatening, the event is, by definition, serious and is to be reported.

4.10.1.5 Description of Analyses

Missing severity, relationship or outcome will be classed as unknown.

A patient with more than one occurrence of the same adverse event in a particular system organ class will be counted only once in the total of those experiencing adverse events in that particular system organ class.

If a patient experiences the same adverse event at more than one severity, or with more than one relationship to study drug, the most severe rating or the stronger causal relationship to study drug will be given precedence.

Any missing severity, causality, or outcome will not be imputed and classed as unknown.

Summaries classifying events according to severity and relationship will be presented.

The denominator used to calculate incidence percentages consists of patients in the Safety analysis set.

AEs will be grouped by System Organ Class and Preferred Term and sorted in descending frequency in the overall group.

For tables by NCI-CTCAE grade, if a patient has more than one AE the worst grade will be summarized.

Hence, the following summaries will be presented by dose for the safety analysis set:

- Summary of Adverse Events*: number of AEs, number of TEAEs, number of TEAEs related to study drug, number of Infusion Reaction TEAEs (or a component of one), number of serious TEAEs, number of TEAEs leading to dose modification (reduction or increase or drug interrupted or drug withdrawn), number of TEAEs leading to treatment discontinuation, number of TEAEs with grade 3 or higher, TEAEs by severity grade, TEAEs by relationship to study treatment (related/ not related), TEAE last outcome, TEAE last action taken with study drug.
- Summary of Deaths*: number of deaths, number of deaths within 30 days of starting treatment, number of deaths with Progressive Disease as the Primary Cause, number of AEs whose outcome=Death.

Table of summary of Adverse Events will also be produced in the following subgroups:
- Patients with at least one co-morbidity at baseline
- Patients with no co-morbidity at baseline

The following description of Adverse Events will also be provided (incidence of) with number and percentage of patients and the number of events:

- Treatment Emergent Adverse Events by System Organ Class and Preferred Term*
- Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term*
- Most frequent (≥10% of patients) Treatment Emergent Adverse Events by Preferred Term in Order of Frequency
- Most frequent (≥10% of patients) Serious Treatment Emergent Adverse Events by Preferred Term in Order of Frequency
- Treatment Emergent Adverse Events Leading to Treatment Discontinuation by Preferred Term in Order of Frequency *
- Treatment Emergent Adverse Events Leading to Death by Preferred Term in Order of Frequency *
- Treatment Emergent Adverse Events Leading to Dose Modification (Action Taken = "Dose reduced" or "Dose increased" or "Drug interrupted" or "Drug withdrawn") by Preferred Term in Order of Frequency
- Treatment Emergent Adverse Events by System Organ Class and Preferred Term and Worst NCI-CTCAE Grade
- Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term and Worst NCI-CTCAE Grade*
- Treatment Related Emergent Adverse Events by System Organ Class and Preferred Term and Worst NCI-CTCAE Grade
- Serious Treatment Related Emergent Adverse Events by System Organ Class and Preferred Term and Worst NCI-CTCAE Grade
- Treatment Emergent Adverse Events with a Grade Greater Than or Equal to 3 by System Organ Class and Preferred Term and Worst NCI-CTCAE Grade
- Deaths* will be listed with time interval between date of death and first/last study dose drug intake date (in days) = death date – first/last study dose drug intake date + 1

Related events will be defined as events that are ticked as "related" in the eCRF.

All other information collected (e.g. action taken) will be listed as appropriate.

Only treatment emergent adverse events will be included in the adverse event and serious adverse event tables. Non-treatment emergent events (starting prior first study drug dose intake date) will be included in the patient listings and flagged but not included in the above summaries.

Where an AE start date is partially or fully missing, and it is unclear as to whether the AE is treatment emergent, it will be assumed that it is.

All AE safety analyses will be presented by dose group in patients from the safety analysis set at the time of primary analysis. Those flagged with a * will also be provided for the dose selection analysis.

Listings will be presented and sorted by treatment group, patient and AE number for all adverse events recorded during the study.

The following listings will be provided:

- Adverse events*,
- Grade 3 or 4 adverse events*,
- Adverse events leading to dose modifications (Action Taken = "Dose reduced" or "Dose increased" or "Drug interrupted" or "Drug withdrawn"),
- Adverse events leading to treatment discontinuation*,
- Adverse Events leading to death*,

Those flagged with a * will also be provided for the dose selection analysis.

Due to the decision not to proceed to Part II, only tables and listings already produced for dose selection analysis will be edited for the primary analysis, with the addition of the following tables:

- Summary table of AE in patients with at least one co-morbidity at baseline
- Summary table of AE in patients with no co-morbidity at baseline
- Treatment Related Emergent Adverse Events by System Organ Class and Preferred Term
- Treatment Related Emergent Adverse Events by System Organ Class and Preferred Term and Worst NCI-CTCAE Grade

4.10.2 Laboratory Findings

The following laboratory parameters will be studied:

Hematology:

- RBC,
- Hemoglobin,
- Hematocrit,
- Platelet count,
- WBC,
- Neutrophils (Absolute and/or Differentials),
- Lymphocytes (Absolute and/or Differentials),
- Monocytes (Absolute and/or Differentials),
- Eosinophils (Absolute and/or Differentials),
- Basophils (Absolute and/or Differentials).

Biochemistry:

- Sodium,

- Potassium,
- Magnesium,
- Urea or BUN,
- Creatinine,
- Glucose,
- Phosphate,
- Total Protein,
- Albumin,
- Adjusted Calcium,
- Total Bilirubin,
- Bicarbonate,
- Chloride,
- Uric Acid,
- Alkaline Phosphatase (ALP),
- AST,
- ALT,
- LDH.

Hematology and Biochemistry parameters will be collected at the following visits: screening visit, Days 1 of each cycle, Days 8 of each cycle, Days 15 of each cycle and at end of treatment visit.

Urine:

- pH,
- Specific gravity,
- Ketones,
- Leukocytes,
- Protein,
- Glucose,
- Bilirubin,
- Urobilinogen
- Occult blood.

Coagulation

- Prothrombin Time
- INR
- aPTT

Urine and Coagulation parameters will be collected at screening visit, Days 1 of each cycle, and at end of treatment visit.

Categorical and numeric variables will be presented separately.

All laboratory parameters (hematology, chemistry, urinary and coagulation) will be also listed.

The following analyses will be performed in patients of the safety analysis set for the dose selection analysis and the primary analysis.

Notes:

Distribution: *Original:* *Copy:*

- For analyses of changes from baseline to worst value according to the NCI CTCAE grade, all emergent (on treatment values with grade > baseline grade) values will be considered (repeat results within a visit or unscheduled visit). In case of several values with the same worst grade, the first one will be taken into account
- For shift table analyses from baseline to worst/ last value, repeat laboratory results within a visit or unscheduled visit will be taken into account.
- Unscheduled and repeat results will also be listed.
- All results outside predefined normal ranges will be flagged in the data listings.
- Any other laboratory results will be listed only.
- If a laboratory result is missing, the observation will not be taken into account and will not be listed.
- All laboratory values will be converted to International System (SI) of units.
- All laboratory parameters will be graded using SI values and the NCI-CTCAE classification Version 4.0 (or higher). Laboratory results not corresponding to an NCI CTCAE term will not be graded. For some parameters, grade can be derived for low values and high values. In that situation, the shift table will be produced for the 2 cases (high grade and low grade).
- Some Blood Urea Nitrogen (BUN) values may be filled for Urea in the eCRF. So for Urea analyses, the following conversion rules will be applied:
    - BUN [mmol/L] = BUN [mg/dL] * 0.3571 (to get the SI value of BUN) and BUN [mmol/L]= urea [mmol/L]
    - Urea [mmol/L] = BUN [mg/dL of nitrogen] x 10 [dL/L] / 14x2 [mg N/mmol urea] (the mass of nitrogen within urea is used)
    - To convert BUN to urea in mg/dL by using following formula: Urea [mg/dL]= BUN [mg/dL] * 2.14
    - Essentially:
        - BUN (mg/dL) = Urea (mg/dL) / 2.1428
        - Urea (mmol/L) = BUN (mg/dL) * 0.357

4.10.2.1 Hematology and Biochemistry

Shift tables presenting worst post baseline grade according to baseline grade will also be displayed for the following parameters:

- Haematology

- Hemoglobin (Low)
- Hemoglobin (High)
- Leukocytes (Low)
- Leukocytes (High)
- Neutrophils (Low)
- Platelets (Low)
- Lymphocytes (Low)
- Lymphocyte (High)

- Biochemistry
  - Phosphate (Low)
  - Alanine Aminotransferase (High)
  - Albumin (Low)
  - Alkaline Phosphatase (High)
  - Aspartate Aminotransferase (High)
  - Bilirubin (High)
  - Calcium Corrected (Low)
  - Calcium Corrected (High)
  - Creatinine (High)
  - Glucose (Low)
  - Glucose (High)
  - Magnesium (Low)
  - Magnesium (High)
  - Potassium (Low)
  - Potassium (High)
  - Sodium (Low)
  - Sodium (High)

Box plots over time will be produced for all Hematology and Biochemistry parameters.

In addition, for all Hematology and Biochemistry parameters, scatter plots displaying the mean within-patient percentage change from baseline over the study (one data point per patient) according to the dose received will be presented.

Scatter plots of maximum Total Bilirubin by maximum ALT (respectively AST) by patient will also be provided, where ALT, AST and Total Bilirubin will be presented in multiples of the ULN, with reference lines at 3xULN for ALT (and AST) and 2xULN for Total Bilirubin.

In addition, for patients with Potential Hy's law, values of ALT, AST, ALP and Bilirubin according to ULN (Value/ULN) will be graphically represented over time by patient, presenting all 4 liver function test on the same plot.

The following laboratory abnormalities define potential Hy's law cases:

- Post-baseline AST and/or ALT elevations that are > 3 × ULN

And

- Elevation of Total Bilirubin > 2 × ULN (or clinical jaundice if total bilirubin measures are not available), regardless of whether this occurs at the same time as the ALT/ AST elevation

Due to the decision not to proceed to Part II, only shift tables produced for dose selection analysis will be repeated for primary analysis. No box plot, scatter plot or Hy's law plot will be displayed.

4.10.2.2 Urinalysis

Urinary parameters will be listed only.

4.10.2.3 Coagulation

Coagulation parameters will be listed only.

4.10.3 Physical Examinations

Physical examination will be performed at screening, Day 1 of each cycle, Day 8 of each cycle, Day 15 of each cycle as well as at end of treatment visit.

The following endpoints will be listed:

- Physical Examination performed? (Yes/ No)
- General appearance (Normal/ Abnormal, Non Clinically Significant (NCS)/ Abnormal Clinically Significant (CS)/ Not Evaluated)
- Head and Neck (including Eyes, Ears and Throat) (Normal/ Abnormal, NCS/ Abnormal CS/ Not Evaluated)
- Cardiovascular (Normal/ Abnormal, NCS/ Abnormal CS/ Not Evaluated)
- Respiratory (Normal/ Abnormal, NCS/ Abnormal CS/ Not Evaluated)
- Abdomen or Gastrointestinal (Normal/ Abnormal, NCS/ Abnormal CS/ Not Evaluated)
- Musculoskeletal Extremities (Normal/ Abnormal, NCS/ Abnormal CS/ Not Evaluated)
- Lymph Nodes (Normal/ Abnormal, NCS/ Abnormal CS/ Not Evaluated)
- Neurological Systems (Normal/ Abnormal, NCS/ Abnormal CS/ Not Evaluated)
- Skin (Normal/ Abnormal, NCS/ Abnormal CS/ Not Evaluated)
- Other (Normal/ Abnormal, NCS/ Abnormal CS/ Not Evaluated)

Physical examination will be presented in a data listing in patients from the safety analysis set for the dose selection analysis as well as the primary analysis.

4.10.4 Vital Signs

Vital signs will be evaluated at screening, Day 1 of each cycle, Day 8 of each cycle, Day 15 of each cycle as well as at end of treatment visit.

The following criteria will be presented with box plots over time:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (beats per minutes (bpm))
- Weight (kg)

Box plots will be produced at each visit by treatment group and all vital sign parameters will be listed in patients from the safety analysis set for the primary analysis.

Then, scatter plots displaying by parameter the mean percentage change from baseline over the study by patient according to the dose received will be presented at the time of the primary analysis.

Vital sign parameters will also be presented in a data listing at the time of dose selection analysis.

Due to the decision not to proceed to Part II, only the listings produced for dose selection analysis will be edited for primary analysis. No box plot or scatter plot will be displayed.

4.10.5 ECG

ECG parameters will be evaluated at screening, Day 1 of each cycle, Day 8 of each cycle, Day 15 of each cycle as well as at end of treatment visit.

The following endpoints will be summarized by visit.

- QTc Average (msec)
- QTc Average (Derived) (msec)

The following endpoints will only be listed:

- Investigator's overall assessment (Nomal/ Abnormal Clinically Significant/ Abnormal Not Clinically Significant/ Incomplete Analysis/ Un-interpretable/ Not Done)
- Heart Rate (beats/ min)
- PR Interval (msec)
- RR Interval (sec)
- QRS Interval (msec)

- QT Interval (msec)

ECG parameters will be described at each visit by treatment group and listed in patients from the safety analysis set for the dose selection analysis as well as the primary analysis.

In addition, Box Plots for QTc Average and QTc Average (Derived) values over time will be presented for the primary analysis.

Then, scatter plots displaying for QTc Average and QTc Average (Derived) values, the mean percentage change from baseline over the study by patient according to the dose received will be presented for the primary analysis.

Moreover, profile plots for QTc Average and QTc Average (Derived) changes pre and post dose at Cycle 1 Day 1, Cycle 1 Day 15, Cycle 3 Day 1 and Cycle 3 Day 15 will be displayed at the time of the dose selection analysis as well as the primary analysis.

Due to the decision not to proceed to Part II, the table, the listing and the profile plot produced for dose selection analysis will be performed for primary analysis. No box plot or scatter plot will be displayed.

4.10.6 ECOG

ECOG performance status is measured at Screening and on Day 1 of each cycle and at End of Study visit.

ECOG performance status will be presented in a data listing at the time of dose selection analysis and primary analysis.

4.11 Adjustment for Covariates

Not applicable.

4.11.1 Center Effects

This study will be conducted in up to 24 sites: approximately 16 sites in the US and approximately 8 in Europe. The randomization of the study was not stratified by site. No center effect is expected.

4.12 Protocol Violations or Deviations

A Data Review Meeting (DRM) will be held prior to database lock before the primary analysis. The primary purpose of this meeting will be to identify important deviations from the protocol and discuss any data cleaning or statistical analysis issues. Detailed definitions of important deviations and how they are to be identified will be documented in a separate specifications document which will be approved prior to the DRM. Deviations will be classified as minor or major.

Where possible, deviations from the protocol are to be identified programmatically.

The major protocol deviations will be fully defined and documented.

A list of patients with important deviations from the observational plan will be agreed upon during the DRM and will be documented in the "Analysis Set Specifications" document.

If protocol violations do occur as outlined in the criteria below, then the data from complete individual patients, individual visits or individual evaluations will be excluded from this analysis. The finalisation of protocol violations and excluded data will be made prior to the database lock.

4.12.1 Violation Criteria

Patients who meet any of the following criteria will be listed and presented in the study report:

- Non-compliance with inclusion criteria
- Non-compliance with exclusion criteria
- Non-compliance with study treatment;
- Treatment administration deviation;
- Unauthorised concomitant therapy
- Other, e.g. consent not signed

Note: Other reasons for violation may be added to this list, but will be done so prior to database lock of the study.

4.12.2 Protocol Deviations

Deviations from the protocol, as defined in the protocol, will be documented on an ongoing basis by the study monitors and project manager throughout the study period.

At the time of database lock, while the protocol violations are being reviewed, the project manager will forward all relevant documentation highlighting protocol deviations to the study statistician. These deviations will be included in the protocol violation document for agreement and will be listed with the protocol violations in the Clinical Study Report (CSR).

4.13 Missing Values – Missing Visits

For partially missing dates for efficacy endpoints, the following imputation rules will be used: if the day of the month is missing, but month and year are known (UN-MMM-YYYY), it will be imputed by the 1st of the month (01-MMM-YYYY). If this implementation rule produces a date before start of treatment, then the date of start of treatment is used.

4.13.1 Adverse Events

In case of missing information for AEs, this will be treated as described in section 4.8.1.

STATISTICAL ANALYSIS PLAN

Sponsor:	NuCana plc	Protocol Number:	PRO-105

For missing or partially missing start/stop dates of AE, the following rules will be applied:

Table 10: Substituting rules for (partially) missing AE start/stop dates

Missing start or stop date	**Substituted start date**	**Substituted stop date (recovery date if AE outcome is "Resolved without sequelae" or "Resolved with sequelae" or if AE is not ongoing)**
.. /mmm/yyyy (= missing day)	If same month and year than first administration date, then: **First administration date + 1** Else: **01/mmm/yyyy**	If same month and year than last visit date, then: **Last visit date** Else: **Last day of the month /mmm/yyyy**
../…/yyyy (= missing day and month)	If same year than first administration date, then: **First administration date + 1** Else: **01/JAN/yyyy**	If same year than last visit date, then: **Last visit date** Else: **31/DEC/yyyy**
.. /… /…. (= completely missing date)	**First administration date + 1**	**Last visit date**

4.13.2 Concomitant medication

In case of missing or partially missing dates for concomitant medication, the following rules will be applied:

Table 11: Substituting rules for concomitant medication with (partially) missing dates

Missing start or stop date	Substituted start date	Substituted stop date
../mmm/yyyy (= missing day)	If same month and year than first administration date then: **First administration date + 1** Else: **01/mmm/yyyy**	- **the completion/withdrawal date** if the patient is completed/withdrawn the same month and year otherwise - **the last day of the month (28-29-30-31/mmm/yyyy)**
../…/yyyy (= missing day and month)	If same year than first administration date, then: **First administration date + 1** Else: **01/JAN/yyyy**	- **the completion/withdrawal date** if the patient is completed/withdrawn the same year otherwise - **the last day of the year : 31/DEC/yyyy otherwise.**
../.../…. (= completely missing date)	**First administration date + 1**	- **No substitution** (i.e., treatment considered as still ongoing)

4.13.3 Initial Diagnosis Date

In case of missing or partially missing dates for initial diagnosis, the following rules will be applied:

- If initial diagnosis date=../mmm/yyyy (= missing day), then it will be substituted by **01/mmm/yyyy**
- If initial diagnosis date=.../.../yyyy (= missing day and month), then it will be substituted by **01/JAN/yyyy**
- If initial diagnosis date=.../.../…. (= completely missing), then it won't be substituted.

4.13.4 Treatment Intake dates and PD dates for prior ovarian cancer therapies

In case of missing or partially missing dates for first or last intake dates of prior ovarian cancer therapies, the following rules will be applied:

STATISTICAL ANALYSIS PLAN

Sponsor:	NuCana plc	Protocol Number:	PRO-105

Table 12: Substituting rules for partially missing first/ last intake dates of prior ovarian cancer therapies

Missing first or last intake date	Substituted first intake date	Substituted last intake date
.. /mmm/yyyy (= missing day)	**01/mmm/yyyy**	**Last day of the month mmm/yyyy**
../…/yyyy (= missing day and month)	**01/JAN/yyyy**	**31/DEC/yyyy**
.. /… /…. (= completely missing date)	**No substitution**	**No substitution**

In case of missing or partially missing PD dates of prior ovarian cancer therapies for patients whose discontinuation reason is "Progressive/ Relapse Disease" in the CRF, the following rules will be applied:

Table 13: Substituting rules for prior ovarian cancer therapies with (partially) missing PD dates

Missing PD date	Substituted PD date
../mmm/yyyy (= missing day)	If same month and year than first intake date of the corresponding prior ovarian cancer therapy then: **First prior ovarian cancer therapy intake date + 1** Else: **01/mmm/yyyy**
../…/yyyy (= missing day and month)	If same year than first intake date of the corresponding prior ovarian cancer therapy, then: **First prior ovarian cancer therapy intake date + 1** Else: **01/JAN/yyyy**
../.../…. (= completely missing date)	**No substitution**

4.13.5 Birth Date

In case of partially missing birth dates, the following rules will be applied:

- If birth date=../mmm/yyyy (= missing day), then it will be substituted by **01/mmm/yyyy**
- If birth date=.../.../yyyy (= missing day and month), then it will be substituted by **01/JAN/yyyy**

- If birth date=.../.../…. (= completely missing), then it won't be substituted.

4.14 Deviations from SAP

Any deviations from the original statistical plan will be described and justified in the final CSR, whether written post dose selection or primary analysis.

4.15 Changes in Conduct or Planned Analyses from the Protocol

⇨ Vital Signs

Abnormal values of vital signs won't be tabulated although it was planned in the protocol because it was not deemed useful.

Due to the decision to stop the study, this SAP has been updated in order to reflect what will really be provided after database lock for an abbreviated clinical study report.

Below are the list of updates following this decision:

- No dose selection was performed and part II will not take place;
- No efficacy update analysis will be performed;
- No PPS will be developed, 5 analysis populations will be defined instead of 6;
- No subgroup will be defined for ORR but BOR, PFS and OS analyses will be performed in 6 subgroups ;
- DSMC analyses will be repeated for primary analysis in addition to some other outputs;
- Patients eligibility listing will not be provided;
- Demographic and baseline characteristics outputs will not be displayed in the SS, FAS, EFR Set and GCIG set;
- Ovarian Cancer history results will not be displayed in the SS;
- For study drug administration, some items will not be described (see section 4.5.1);
- RDR and PIDR endpoints will not be studied and will only be listed; but RDI and PID will also be described in co-morbidity subgroups;
- No ORR analysis will be displayed in a specific table. Only a description of responder/non responder patients will be provided in the BOR table;
- BOR will not be described with the confirmatory rule for CR and PR responses. Same analysis as Dose selection analysis will be done;

- DCR, DOR, TTP and TTR endpoints will only be listed;
- PFS based on BICR will not be analysed in EFR. PFS based on Investigator Recorded assessment won't be produced as well as PFS4, PFS6 and PF6KM endpoint analyses. In addition, no KM plot will be displayed;
- OS analyses will not be performed in EFR and no KM plot will be displayed;
- Best GCIG Overall Response will only be listed;
- Swimmer plot of time of Treatment will not be edited;
- FOSI-18 and EQ-5D-5L questionnaires will not be described, nor listed;
- AE analyses will be the same as those provided for dose selection analysis but summary table of adverse events will be repeated in co-morbidity subgroups;
- No box plot, scatter plot or Hy's law plot will be displayed for laboratory parameters;
- No box plot or scatter plot will be displayed for vital signs or ECG;

4.16 Algorithms/SAS Codes

- **Tables that need descriptive statistics – continuous variables:**

```
PROC UNIVARIATE DATA=dset NOPRINT;
    VAR var1 var2 var3 …varn;
    BY byvar; (optional)
    OUTPUT OUT=outname
    N=n MEAN=mean MIN=min MAX=max MEDIAN=median STD=std;
RUN;
```

- **Tables that need frequency counts:**

```
PROC FREQ DATA=dset NOPRINT;
    BY byvar; (optional)
    TABLES var1*var2;
    OUTPUT OUT=outname;
RUN;
```

- **Tables that need 95% CIs within group for binomial proportions:**

```
PROC FREQ DATA=dset;
    BY byvar; (optional)
    TABLES var1;
    EXACT BINOMIAL;
RUN;
```

- **Tables that need number of events/censored and probabilities of failure/survival at cut off times:**

```
PROC LIFETEST DATA=dset OUTSURV=LIFE METHOD=LT INTERVALS=12, 24,;
```

*TIME duration*censor (0 or 1);*
ID patient;
STRATA treatment;
RUN;

- **Tables that need life table with estimates of survival, with CIs and log rank test:**
PROC LIFETEST DATA=dset OUTSURV=LIFE METHOD=KM;
*TIME duration*censor (0 or 1);*
ID patient;
STRATA treatment;
RUN;

- **Tables that need 95% CIs within group for continuous variables:**
DATA outdata;
SET outname;
LCL=mean-(TINV(0.975,n-1)(std/SQRT(n)));*
UCL=mean+(TINV(0.975,n-1)(std/SQRT(n)));*
RUN;

5 Tables and Listings

5.1 Table Format

All output will be produced using SAS version 9.2 or a later version.

In the top left portion of each table/listing, a *table/listing number* followed by the *title* of the table/listing will be presented. After the title line, optional *sub-title* or *population* information can be presented. Horizontal lines will appear before and after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page.

The *sponsor name*, *protocol number,* programmers User ID, status of the table/listing (i.e. draft or final) and *SAS program name* will appear bottom left in a string and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of table/listing will appear bottom left under the sponsor name. The source listing number will appear bottom left.

A *landscape layout* is proposed for both table and listing presentations.

The *left* and *right margins* of all tables and listings will be a minimum of 2.1 cm from the left and 1.9cm from the right. The *top and bottom margins* will be a minimum 2.92cm. *Header and footer* will be both 1.27 cm.

There is no special requirement of *font type* and *size*, but an *8-point* font size for tables and *7*or *8-point* for listings is proposed using *Courier New* font. A maximum SAS line size=141 and page size=44 for *8-point* font size, and line size=161 and page size=50 for *7-point* will be used so as to fit on both UK and US paper sizes.

In a listing, in the case that a patient's record has been continued to the next page, an appropriate identification (e.g., the patient ID number) must be presented at the beginning of that page.

5.2 Conventions

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data. Wherever possible data will be decimal aligned.

Unless otherwise specified frequency tabulations will be presented by number and percentage, where the percentage is presented in brackets to 1 decimal place.

P-values, if applicable, will be presented to 3 decimal places. If a p-value is less than 0.05 but is greater than or equal to 0.01, then an asterisk (*) will be added next to this value. If a p-value is less than 0.01 but is greater than or equal to 0.001, then two asterisks (**) will be added next to this value. Finally, if the p-value is less than 0.001 then three asterisks (***) will be added next to this value and it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999. Any date information in the listing will use the *date9.* format, for example, 07MAY2002. In the listing, a unit associated with a variable will be presented only

once within parentheses either below or next to that variable in the heading portion. If a parameter has multiple units, each unit will be displayed only once, as applicable.

All tables will have their source listing referenced in a footnote. Listings should be sorted by treatment group, patient and visit and have the Study Data Tabulation Model (SDTM) data referenced in a footnote. All tables, listings and figures will be converted into Microsoft Word documents and collated into three complete documents.

5.3 Tables

Tables flagged with a * will be also produced for the Dose Selection Analysis. Those flagged with a # will be also produced for the Efficacy Update Analysis (if performed).

Due to the decision not to proceed to Part II, no efficacy update analysis will be performed and several analyses scheduled for primary analysis will not be produced.

5.3.1 Section 14.1: Demographic and Baseline

Table 14.1.1.1	Patient Disposition (All screened patients)*
Table 14.1.1.2	Analysis Sets (All screened patients) *
Table 14.1.1.3	Major Protocol Violations (All screened Patients)
Table 14.1.2.1	Demographics and Baseline Characteristics (Randomized Set) *
Table 14.1.2.2	Baseline co-morbidities (Randomized Set)
Table 14.1.3	Ovarian Cancer History (Randomized Set) *
Table 14.1.4.1	Prior Ovarian Cancer Therapy – Agent Names (Randomized Set) *
Table 14.1.4.2	Prior Ovarian Cancer Therapy – Baseline Characteristics Details (Randomized Set) *
Table 14.1.5.1.1	Exposure and Study Drug Administration (Full Analysis Set) *
Table 14.1.5.2.1	Exposure and Dose Intensity (Full Analysis Set) *
Table 14.1.5.2.2	Exposure and Dose Intensity in patients with at least one co-morbidity at baseline (Full Analysis Set)
Table 14.1.5.2.3	Exposure and Dose Intensity in patients with no co-morbidity at baseline (Full Analysis Set)
Table 14.1.5.3.1	Exposure and Treatment Delay Intervals (Full Analysis Set) *
Table 14.1.6.1	Concomitant Medications (Safety Analysis set)

5.3.2 Section 14.2: Primary

Following the decision not to proceed to Part II, the analysis of primary endpoint will not be performed. However, descriptive statistics of responder/non responder patients will be provided in the same table as BOR.

STATISTICAL ANALYSIS PLAN

Sponsor:	NuCana plc	Protocol Number:	PRO-105

5.3.3 Section 14.2: Secondary

Table 14.2.2.1	Best Overall Response according to RECIST v1.1 based on BICR (Evaluable For Response Set) *
Table 14.2.2.2	Best Overall Response according to RECIST v1.1 based on Investigator-Recorded Assessment (Evaluable For Response Set) *
Table 14.2.2.3	Best Overall Response according to RECIST v1.1 based on BICR according to co-morbidities at baseline (Evaluable for Response Set)
Table 14.2.2.4	Best Overall Response according to RECIST v1.1 based on BICR according to prior gemcitabine intake (Evaluable for Response Set)
Table 14.2.2.5	Best Overall Response according to RECIST v1.1 based on BICR according to time on prior gemcitabine (Evaluable for Response Set)
Table 14.2.2.6	Best Overall Response according to RECIST v1.1 based on BICR according to time to progression from end of last prior platinum based chemotherapy (Evaluable for Response Set)
Table 14.2.2.7	Best Overall Response according to RECIST v1.1 based on BICR according to BRCA mutation status (Evaluable for Response Set)
Table 14.2.2.8	Best Overall Response according to RECIST v1.1 based on BICR according to time to progression from start of last prior therapy (Evaluable for Response Set)
Table 14.2.4.1	Progression Free Survival based on BICR (Full Analysis Set)
Table 14.2.4.2	Progression Free Survival based on BICR according to co-morbidities at baseline (Full Analysis Set)
Table 14.2.4.3	Progression Free Survival based on BICR according to prior gemcitabine intake (Full Analysis Set)
Table 14.2.4.4	Progression Free Survival based on BICR according to time on prior gemcitabine (Full Analysis Set)
Table 14.2.4.5	Progression Free Survival based on BICR according to time to progression from end of last prior platinum based chemotherapy (Full Analysis Set)
Table 14.2.4.6	Progression Free Survival based on BICR according to BRCA mutation status (Full Analysis Set)
Table 14.2.4.7	Progression Free Survival based on BICR according to time to progression from start of last prior therapy (Full Analysis Set)
Table 14.2.5.1	Overall Survival (Full Analysis Set)
Table 14.2.5.2	Overall Survival according to co-morbidities at baseline (Full Analysis Set)
Table 14.2.5.3	Overall Survival according to prior gemcitabine intake (Full Analysis Set)
Table 14.2.5.4	Overall Survival according to time on prior gemcitabine (Full Analysis Set)
Table 14.2.5.5	Overall Survival according to time to progression from end of last prior platinum based chemotherapy (Full Analysis Set)
Table 14.2.5.6	Overall Survival according to BRCA mutation status (Full Analysis Set)

Table 14.2.5.7	Overall Survival according to time to progression from start of last prior therapy (Full Analysis Set)
Table 14.2.9.1	Sum of Lesion Diameters – Percentage Change from Baseline based on BICR (Evaluable for Response Set) *
Table 14.2.11.1	CA125 – Percentage Change from Baseline (GCIG Analysis Set) *

5.3.4 Section 14.2: Exploratory – EQ-5D-5L

Not Applicable, following the decision not to proceed to Part II.

5.3.5 Section 14.3: Safety

5.3.5.1 Adverse Events

Table 14.3.1.1	Summary of Adverse Events*
Table 14.3.1.1.1	Summary of Adverse Events in patients with at least one co-morbidity at baseline
Table 14.3.1.1.2	Summary of Adverse Events in patients with no co-morbidity at baseline
Table 14.3.1.2	Summary of Deaths*
Table 14.3.1.3.1	Treatment Emergent Adverse Events by System Organ Class and Preferred Term *
Table 14.3.1.3.2	Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term *
Table 14.3.1.3.3	Treatment Related Emergent Adverse Events by System Organ Class and Preferred Term
Table 14.3.1.5.1	Treatment Emergent Adverse Events Leading to Treatment Discontinuation by Preferred Term in Order of Frequency *
Table 14.3.1.5.2	Treatment Emergent Adverse Events Leading to Death by Preferred Term in Order of Frequency *
Table 14.3.1.6.2	Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term and Worst NCI-CTCAE Grade *
Table 14.3.1.6.3	Treatment Related Emergent Adverse Events by System Organ Class and Preferred Term and Worst NCI-CTCAE Grade

5.3.5.2 Laboratory Results

Table 14.3.5.1.1	Laboratory results – Hematology – Shift Table of Worst Post Baseline Grade according to Baseline Grade *
Table 14.3.5.2.1	Laboratory Results – Biochemistry – Shift Table of Worst Post Baseline Grade according to Baseline Grade *

5.3.5.3 Electrocardiogram

Table 14.3.6 Electrocardiogram *

All safety tables will be produced using the Safety Analysis Set.

5.4 Listings

Listings flagged with a * will also be produced for the Dose Selection Analysis. Those flagged with a # will also be produced for the Efficacy Update Analysis (if performed).

Due to the decision not to proceed to Part II, no efficacy update analysis will be performed and several analyses scheduled for primary analysis will not be produced.

Listing 14.3.2	Listing of Deaths (Safety Analysis Set) *
Listing 16.1.7	Randomization (Randomized Patients) *
Listing 16.2.1.1	Patient Disposition (Safety Analysis Set) *
Listing 16.2.1.2	Inclusion/Exclusion Criteria Descriptions (All screened Patients)
Listing 16.2.2.1	Protocol Violations (Safety Analysis Set)
Listing 16.2.4.1	Demographics and Baseline Characteristics (Safety Analysis Set) *
Listing 16.2.4.2	Medical/ Surgical History, including reported and coded terms (Safety Analysis Set)
Listing 16.2.4.3	Ovarian Cancer History (Randomized Set)*
Listing 16.2.4.4.1	Prior Ovarian Cancer Therapy – Baseline Details (Randomized Set) *
Listing 16.2.4.5	Prior & Concomitant Medications including reported and coded terms (Safety Analysis Set) *
Listing 16.2.4.6	Concomitant Procedures/ Surgeries/ Therapies (Safety Analysis Set)
Listing 16.2.5.1	Study Treatment Administration (Safety Analysis Set) *
Listing 16.2.5.2	Extent of Exposure (Safety Analysis Set) *
Listing 16.2.6.1.1	Tumor Assessment – Target Lesions according to BICR (Full Analysis Set)
Listing 16.2.6.1.2	Tumor Assessment – Target Lesions according to Investigator-Recorded Assessment (Full Analysis Set)
Listing 16.2.6.2.1	Tumor Assessment – Non-Target Lesions according to BICR (Full Analysis Set)
Listing 16.2.6.2.2	Tumor Assessment – Non-Target Lesions according to Investigator-Recorded Assessment (Full Analysis Set)
Listing 16.2.6.3.1	Tumor Assessment – New Lesions according to BICR (Full Analysis Set)
Listing 16.2.6.3.2	Tumor Assessment – New Lesions according to Investigator-Recorded Assessment (Full Analysis Set)
Listing 16.2.6.4	Assessment of Anti-Tumor Activity based on BICR (RECIST criteria) (Full Analysis Set) * #
Listing 16.2.6.5	Assessment of Anti-Tumor Activity based on Investigator-Recorded Assessment (RECIST criteria) (Full Analysis Set) *
Listing 16.2.6.6.1	Assessment of Anti-Tumor Activity – Derived Efficacy Endpoints based on BICR (RECIST criteria) (Full Analysis Set) * #
Listing 16.2.6.6.2	Assessment of Anti-Tumor Activity – Derived Efficacy Endpoints based on Investigator-Recorded Assessment (RECIST criteria) (Full Analysis Set) * #

Listing 16.2.6.7	Best GCIG Overall Response, combining the Change CA125 from Baseline with RECIST Assessment (per GCIG criteria) (GCIG Analysis Set) * #
Listing 16.2.7.1	Adverse Events (Safety Analysis Set) *
Listing 16.2.7.2	Adverse Events Leading to Treatment Discontinuation (Safety Analysis Set) *
Listing 16.2.7.3	Adverse Events Leading to Death (Safety Analysis Set) *
Listing 16.2.7.4	Grade 3 or 4 Adverse Events (Safety Analysis Set) *
Listing 16.2.8.1	Laboratory Results: Hematology (Safety Analysis Set) *
Listing 16.2.8.2	Laboratory Results: Biochemistry (Safety Analysis Set) *
Listing 16.2.8.3	Laboratory Results: Urinalysis (Safety Analysis Set) *
Listing 16.2.8.4	Laboratory Results: Coagulation (Safety Analysis Set) *
Listing 16.2.9	Physical Examination (Safety Analysis Set) *
Listing 16.2.10	Vital Signs (Safety Analysis Set) *
Listing 16.2.11	Electrocardiogram (Safety Analysis Set) *
Listing 16.2.12	ECOG Performance Status (Safety Analysis Set) *

5.5 Figures

Figures flagged with a * will also be produced for the Dose Selection Analysis. Those flagged with a # will also be produced for the Efficacy Update Analysis (if performed).

Due to the decision not to proceed to Part II, no efficacy update analysis will be performed and several analyses scheduled for primary analysis will not be produced.

Figure 14.2.8.1	Waterfall Plots of Percentage Changes from Baseline of SLD (Evaluable For Response Set) *
Figure 14.2.10.1	Waterfall Plots of Percentage Changes from Baseline of CA125 (GCIG Analysis Set) *
Figure 14.3.9.3	Electrocardiogram – Profile Plots of QTc Changes Pre and Post Dose (Safety Analysis Set) *

Tables, Listings, and Figures will follow the format of: PRO-105_NuCana_35679_shell_Final_26May2020.doc

5.6 Appendices

The following appendices are for internal use only and not for inclusion into the CSR. {**Note**: ALL analyses will require raw SAS output}.

Due to the decision not to proceed to Part II, only 14 tables with inferential statistics will be produced. Thus, only 14 corresponding appendices will be needed.

Appendix 14.2.4.1	Progression Free Survival based on BICR (Full Analysis Set)
Appendix 14.2.4.2	Progression Free Survival based on BICR according to co-morbidities at baseline (Full Analysis Set)

Appendix 14.2.4.3	Progression Free Survival based on BICR according to prior gemcitabine intake (Full Analysis Set)
Appendix 14.2.4.4	Progression Free Survival based on BICR according to time on prior gemcitabine (Full Analysis Set)
Appendix 14.2.4.5	Progression Free Survival based on BICR according to time to progression from end of last prior platinum based chemotherapy (Full Analysis Set)
Appendix 14.2.4.6	Progression Free Survival based on BICR according to BRCA mutation status (Full Analysis Set)
Appendix 14.2.4.7	Progression Free Survival based on BICR according to time to progression from start of last prior therapy (Full Analysis Set)
Appendix 14.2.5.1	Overall Survival (Full Analysis Set)
Appendix 14.2.5.2	Overall Survival according to co-morbidities at baseline (Full Analysis Set)
Appendix 14.2.5.3	Overall Survival according to prior gemcitabine intake (Full Analysis Set)
Appendix 14.2.5.4	Overall Survival according to time on prior gemcitabine (Full Analysis Set)
Appendix 14.2.5.5	Overall Survival according to time to progression from end of last prior platinum based chemotherapy (Full Analysis Set)
Appendix 14.2.5.6	Overall Survival according to BRCA mutation status (Full Analysis Set)
Appendix 14.2.5.7	Overall Survival according to time to progression from start of last prior therapy (Full Analysis Set)

5.7 References

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