CLINICAL STUDY PROTOCOL

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

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Protocol #:	PRO-105
Protocol Version, Date:	Version 2.5, 11 October 2017_FINAL
Development Phase:	II
IND #:	130348
EudraCT #:	2016-003287-39
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PRINCIPAL INVESTIGATOR AGREEMENT AND SIGNATURE

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

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This study will be conducted in compliance with the clinical study protocol (and amendments), International Conference on Harmonisation guidelines for current Good Clinical Practice (ICH-GCP) and applicable regulatory requirements. Compliance with ICH-GCP standards provides assurance that the rights, safety, and wellbeing of study patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

Principal Investigator's signature

Date (dd-Mmm-yyyy)

Principal Investigator's name (printed)

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PROTOCOL SYNOPSIS

Study Title:	A Phase II Open-Label Study of NUC-1031 in Patients with Platinum-Resistant Ovarian Cancer
Protocol #:	PRO-105
IND #:	130348
EudraCT #:	2016-003287-39
Phase:	II
Objectives:	**Primary Objective:** • To assess the anti-tumor activity of NUC-1031 as measured by Objective Response Rate measured by RECIST at the selected dose level (500 mg/m^2 or 750 mg/m^2). Primary assessment will be done by a blinded independent central reviewer (BICR). **Secondary Objectives:** • To assess additional measures of anti-tumor activity, including: o Change from baseline in tumor size. o Duration of Overall Response (per RECIST). o Progression-Free Survival (per RECIST). o Time to Disease Progression (per RECIST). o Disease Control Rate (CR+PR+SD, per RECIST). o Best GCIG Overall Response, combining the change in CA125 from baseline with RECIST assessment (per GCIG criteria). o Overall Survival. • To further assess the safety profile of NUC-1031 administered over multiple cycles. • To explore relationships between NUC-1031 PK, pharmacodynamics and clinical activity. • To describe the effects of NUC-1031 on ovarian cancer symptoms. **Exploratory Objectives:** • To establish the expression of genomic, transcriptomic and proteomic biomarkers in 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 EuroQoL five dimensions, five level (EQ-5D-5L).
Study Design:	This is a randomized, open-label two-part clinical study in up to 64 patients with platinum-resistant ovarian cancer. Patients will be randomized to NUC-1031 500 mg/m^2 or 750 mg/m^2 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 factors (including BRCA mutation status and number of prior lines of chemotherapy) are balanced between the 2 dose levels. 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 enrollment shall continue until a total of 44 evaluable patients are recruited at the selected dose. The study will be deemed complete when all patients have reached the progression free survival endpoint, or 24 months have elapsed since the final patient was enrolled (whichever occurs first).
Study Centers:	This study will be conducted at approximately 30 sites in the United States and Europe.

Endpoints:	**Primary Endpoint** • Objective Response Rate (per RECIST) at the selected dose level (500 mg/m^2 or 750 mg/m^2), assessed by a BICR. **Secondary Endpoints** **Efficacy** • Change from baseline in tumor size. • Duration of Overall Response (per RECIST). • Progression-Free Survival (per RECIST). • Time to Disease Progression (per RECIST). • Disease Control Rate (CR+PR+SD, per RECIST). • Best GCIG Overall Response, combining the change in CA125 from baseline with RECIST assessment (per GCIG criteria). • Overall Survival. • Assessment of ovarian cancer symptoms using the FOSI-18 questionnaire. **Safety** • Treatment-emergent adverse events (per NCI CTCAE v4.03). • Clinically-significant laboratory parameters (per NCI CTCAE v4.03). • Changes in vital signs and serial ECGs. **Pharmacokinetics** PK sampling will be performed at a sub-set of sites specified by NuCana. The PK of single and multiple-dose NUC-1031 will be assessed, including: • Maximum concentration (C_{max}). • Area under the curve (AUC). • Half-life ($T_{1/2}$). • Volume of distribution (V_d). • Clearance (CL). 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. **Exploratory Endpoints** • 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 RRM2. • Assessment of impact of treatment and disease state on health state utility by EuroQoL five dimensions, five level questionnaire (EQ-5D-5L).
Study Population:	Patients with platinum-resistant epithelial cancer of the ovary, fallopian tube or primary peritoneum (here termed 'ovarian cancer'), who have been treated with 3 or more prior chemotherapy regimens.
Study Treatment:	Eligible consenting patients will receive NUC-1031 by intravenous (IV) infusion over 30 minutes at a dose of 500 mg/m^2 or 750 mg/m^2 on days 1, 8 and 15 of a 28-day schedule. Protocol-specific guidelines for dose modifications and discontinuations due to adverse events are provided. Patients will continue to receive NUC-1031 until the occurrence of disease progression using RECIST or unmanageable drug-related adverse events despite dose modification.

Sample Size:	Two dose levels of NUC-1031, 500 mg/m^2 and 750 mg/m^2, will be evaluated in parallel cohorts of up to 20 patients each in Part I of the study. 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 enrollment shall continue until a total of 44 evaluable patients are recruited at the selected dose. The primary objective will be assessed in these 44 patients. The study will be considered to have met its primary endpoint if a minimum of 4 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. Data dependent, an efficacy update analysis may also be performed to provide more mature efficacy data, particularly for the longer term efficacy endpoints such as DOR, PFS and OS. The need for such an analysis, and its timing, will be determined by the DSMC following review of the primary analysis results. Upon review of the primary analysis data from Part II by the DSMC, the study may be further expanded at the selected dose level, which will be described in a protocol amendment.
Inclusion Criteria:	1. Provision of signed written informed consent. Patients with easily accessible tumor must also consent to the 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. 2. Original diagnosis and/or histological confirmation of high-grade serous, high-grade endometrioid, epithelial ovarian, fallopian tube or primary peritoneal cancer. 3. Platinum-free interval since last line of platinum of less than 6 months (182 days). 4. Received at least 3 prior chemotherapy-containing regimens. Prior treatment with only non-cytotoxic agents (*e.g.* hormones, antibodies or PARP inhibitors) is permitted, but should not be considered as one of the '3 prior chemotherapy-containing regimens'. Adjuvant chemotherapy should be counted as a prior line of chemotherapy. 5. Age ≥18 years. 6. ECOG performance status of 0 or 1. 7. Measurable disease as defined by RECIST. 8. Adequate bone marrow function as defined by: absolute neutrophil count (ANC) ≥1.5×10^9/l, platelet count ≥100×10^9/l and hemoglobin level ≥10.0 g/dl. 9. Adequate liver function, as defined by: serum total bilirubin ≤1.5×upper limit of normal (ULN), AST and ALT ≤2.5×ULN (or ≤5×ULN if liver metastases are present). 10. Adequate renal function assessed as Cr <1.5×ULN or GFR ≥50 ml/min. 11. Ability to comply with protocol requirements. 12. Patients are assumed to be infertile as a consequence of treatment for their disease, however, in the event they are not, patients must be postmenopausal (12 months of amenorrhea), agree to be abstinent, or they must agree to use two forms of contraception, one of which must be a barrier method and the other must be a highly effective method. These forms of contraception must be used from the time of signing consent, throughout the treatment period, and for 30 days following the last NUC-1031 dose administration. Oral or injectable contraceptive agents cannot be the sole method of contraception. See protocol Section 10.3.1 for more information. Patients of childbearing potential must have a negative serum pregnancy test within 72 hours prior to the first study

	drug administration. This criterion does not apply to patients who have had a previous hysterectomy or bilateral oophorectomy.
Exclusion Criteria:	1. Disease classified as primary platinum refractory (*i.e.* progression while receiving initial line of platinum-based therapy or within 4 weeks of the last platinum dose of the initial regimen). 2. Received fewer than 3 prior chemotherapy-containing regimens. 3. Prior therapy with single-agent gemcitabine (prior gemcitabine plus carboplatin combination treatment is permitted). 4. Prior history of hypersensitivity to gemcitabine. 5. History of allergic reactions attributed to the components of the diluents used with NUC-1031. 6. Mucinous, low-grade serous, low-grade endometrioid, carcinosarcoma, clear cell, or undifferentiated/unclassifiable histology. 7. Symptomatic CNS or leptomeningeal metastases. 8. Prior chemotherapy, radiotherapy (other than short cycle of palliative radiotherapy for bone pain), treatment with a VEGF inhibitor, PARP inhibitor or immunotherapy within 21 days of first receipt of study drug (within 6 weeks for nitrosoureas and mitomycin C); hormone therapy within 14 days of first receipt of study drug; or blood transfusion, or use of hematopoietic growth factors within 28 days of first receipt of study drug. 9. Residual toxicities from chemotherapy or radiotherapy, which have not regressed to Grade ≤1 severity (NCI CTCAE v4.03), except for neuropathy (Grade 2 allowed) or alopecia. 10. Patients who have a history of another malignancy diagnosed within the past 5 years, with the exception of adequately treated non-melanoma skin cancer curatively treated carcinoma *in situ* of the cervix or ductal carcinoma *in situ* (DCIS) of the breast. Patients with previous invasive cancers are eligible if treatment was completed more than 5 years prior to initiating the current study treatment, and the patient has had no evidence of recurrence since then. 11. Presence of an uncontrolled concomitant illness or active infection requiring IV antibiotics. 12. Presence of any serious illnesses, medical conditions, or other medical history, including laboratory results, which, in the Investigator's opinion, would be likely to interfere with the patient's participation in the study, or with the interpretation of the results. 13. Known HIV positive or known active hepatitis B or C. 14. Any condition (*e.g.* known or suspected poor compliance, psychological instability, geographical location, *etc.*) that, in the judgment of the Investigator, may affect the patient's ability to sign the informed consent and undergo study procedures. 15. Currently pregnant, lactating or breastfeeding. 16. QTc interval >450 milliseconds. 17. Concomitant use of drugs known to prolong QT/QTc interval (Appendix 1). 18. History of radiologically confirmed bowel obstruction (including sub-occlusive disease) relating to ovarian cancer within 6 months prior to the first receipt of study drug. 19. Patients who have received a live vaccination within 4 weeks of first planned NUC-1031 dose administration.
Study Duration Per Patient:	Patients will continue to receive NUC-1031 in the absence of disease progression or unmanageable drug-related toxicity.

SUMMARY SCHEDULE OF EVENTS

Assessment	Screening Up to 28 days prior	Each Cycle: Day 1 (±3)	Each Cycle: Day 2	Each Cycle: Days 8 & 15 (±3)	Each Cycle: Day 16	End of Treatment Visit[20]	Follow-up Visit Q8 weeks (±7 days)[2] [1]	Survival Follow-up Q12 weeks (±7 days)
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]

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.

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.

ABBREVIATIONS

°C	Degrees Centigrade
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable concentration
BICR	Blinded Independent Central Reviewer
BRCA 1/2	Breast cancer (gene) 1/2
BUN	Blood urea nitrogen
CA125	Cancer Antigen 125
CDA	Cytidine deaminase
CL	Apparent clearance
C_{max}	Maximum plasma concentration; peak plasma concentration
CNS	Central Nervous System
CR	Complete Response
CRF	Case report form
CRO	Clinical Research Organization
CSR	Clinical study report
CT	Computed tomography
CTC	Common toxicity criteria
dCK	Deoxycytidine kinase
dFdC	Di-fluoro-deoxycytidine (gemcitabine)
dFdCDP	Di-fluoro-deoxycytidine diphosphate
dFdCMP	Di-fluoro-deoxycytidine monophosphate
dFdCTP	Di-fluoro-deoxycytidine triphosphate
dFdU	Di-fluoro-deoxyuridine
DMA	Dimethylacetamide
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQoL Five Dimensions, Five Level
FDA	(US) Food and Drug Administration
FOSI-18	FACT/NCCN-Ovarian Symptom Index (containing 18 items)
GCIG	Gynecologic Cancer InterGroup
G-CSF	Granulocyte colony stimulating factor
GFR	Glomerular filtration rate
hENT1	Human equilibrative nucleoside transporter 1
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH-GCP	International Conference on Harmonization - Good Clinical Practice
IHC	Immunohistochemistry
IMP	Investigational medicinal product
IND	Investigational New Drug
IRB/EC	Institutional review board/ ethics committee
IV	Intravenous
l	Liter

LDH	Lactate dehydrogenase
LPLV	Last patient last visit
m^2	$Meter^2$
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
µM	Micromolar
ml	Milliliter
mM	Millimolar
MRI	Magnetic Resonance Imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Objective Response Rate
OS	Overall Survival
PARP	Poly ADP ribose polymerase
PBMC	Peripheral blood mononuclear cell
PD	Progressive Disease
PFI	Platinum-Free Interval
PFS	Progression-Free Survival
PK	Pharmacokinetics
PLD	Pegylated liposomal doxorubicin
PR	Partial Response
PRO	Patient-Reported Outcome
PS	Performance Status
RECIST	Response Evaluation Criteria In Solid Tumors (version 1.1)
RRM1	Ribonucleotide reductase M1
RRM2	Ribonucleotide reductase M2
RP2D	Recommended Phase 2 Dose
RSI	Reference Safety Information
SAE	Serious adverse event
SAR	Serious adverse reaction
SD	Stable Disease
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal half-life
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
V_d	Volume of distribution
VEGF	Vascular endothelial growth factor
WBC	White blood cell
WHO DD	World Health Organization Drug Dictionary

1 INTRODUCTION AND STUDY RATIONALE

1.1 Treatment Options for Recurrent Ovarian Cancer

Ovarian cancer is the most common cause of gynecologic cancer death and the fifth leading cause of death from cancer in women (Siegel *et al*, 2014). The majority of women present with advanced stage disease which is treated initially with optimal surgical debulking followed by systemic treatment with a platinum plus taxane chemotherapy regimen. Although complete response (CR) following this initial treatment is observed in 70% of patients, the majority will relapse generally within 2 years. As a result, the 5-year survival rate for women with ovarian cancer is only 30% (American Cancer Society, Cancer Facts and Figures, 2015).

The selection of treatment for recurrent disease is governed by the period from cessation of primary platinum-based chemotherapy to disease recurrence or progression, known as the platinum-free interval (PFI; Friedlander *et al*, 2011). Patients with disease progression while receiving platinum-based therapy or within 4 weeks of last platinum dose are defined as having platinum-refractory disease; those with a PFI of more than 1 month and less than 6 months have platinum-resistant disease. For such patients, single-agent chemotherapy with or without bevacizumab is standard therapy. Patients with a PFI of 6-12 months have partial platinum resistance; and those with PFI more than 12 months have platinum-sensitive recurrence. For these patients, re-treatment with platinum-containing chemotherapy doublets is standard therapy.

1.2 Treatment for Platinum-Resistant Ovarian Cancer

There are no highly effective treatments for patients with platinum-resistant ovarian cancer. A number of chemotherapeutic agents have demonstrated modest anti-tumor activity in these patients with response rates generally in the range of 10-20% and median times to progression of 3-4 months (Markman & Bookman, 2000). Standard treatment for patients with platinum-resistant disease generally involves the sequential use of single-agent chemotherapy including, agents such as paclitaxel, topotecan, pegylated liposomal doxorubicin, and gemcitabine. Paclitaxel, topotecan, and pegylated liposomal doxorubicin (PLD) have been approved by global regulatory authorities in this population of patients, while gemcitabine is only approved for use in combination with carboplatin for patients with platinum-sensitive relapsed disease.

Recent clinical data have demonstrated that the addition of bevacizumab to single-agent chemotherapy (either PLD, topotecan or weekly paclitaxel) in patients with platinum-resistant disease, who had received no more than 2 prior chemotherapy regimens, results in an improved outcome compared to chemotherapy alone. In this study, median progression-free survival (PFS) increased from 3.4 months to 6.7 months (HR=0.48, 95 % CI: 0.38 to 0.60, $p<0.001$), in patients treated with bevacizumab plus chemotherapy compared to chemotherapy alone (Pujade-Lauraine *et al*, 2014).

The histologic subtype of ovarian cancer is a factor known to influence outcome and response to treatment. Mucinous, clear cell, and low-grade serous carcinomas are distinct entities, are less responsive to chemotherapy in both the primary and recurrent settings and have differing natural histories (Groen *et al,* 2015).

BRCA1/2 mutation status has a significant impact on response to treatment (Yang *et al,* 2011). In the recurrent setting, ovarian cancer patients with a somatic or germline BRCA1/2 mutation are highly responsive to platinum and other DNA-damaging chemotherapy regimens. Recurrent ovarian cancer patients with BRCA1/2 mutations are also generally more responsive to other chemotherapy agents that induce direct DNA damage and specifically to targeted agents, such as PARP inhibitors.

PLD gives an enhanced time to treatment failure and improved overall survival to second and third-line treatments in recurrent ovarian cancer patients with a BRCA1/2 mutation (Safra *et al*, 2011; Kaye *et al*, 2012). An overall response rate of 31% was achieved with the PARP inhibitor olaparib in 193 recurrent ovarian cancer patients with a known deleterious germline BRCA1/2 mutation (Kaufman *et al*, 2015).

Ovarian cancer patients are often currently managed with multiple sequential therapeutic regimens. The number of prior therapies might influence outcome. Also, it has been noted recently that 'the designation of platinum-sensitive vs platinum-resistant on the basis of a time line in the patient with recurrent ovarian cancer beyond the third line of therapy may be less precise or important' (Alvarez *et al*, 2016).

In summary, while there are multiple chemotherapeutic options for patients with platinum-resistant, recurrent ovarian cancer, there remains a clear unmet need for more effective agents to treat this population of women.

1.3 Gemcitabine in Ovarian Cancer

Gemcitabine in combination with a platinum agent (cisplatin or carboplatin) is approved globally for women with platinum-sensitive recurrent ovarian cancer. In the AGO-OVAR study, 356 patients with platinum-sensitive recurrent ovarian cancer were assigned to either single-agent carboplatin AUC5 or carboplatin AUC4 in combination with gemcitabine 1,000 mg/m^2 on days 1 and 8 every 3 weeks (Pfisterer *et al*, 2006).

After a median follow-up of 17 months, a median PFS of 8.6 months was observed for gemcitabine plus carboplatin, compared with 5.8 months for single-agent carboplatin (p=0.0031). An Objective Response Rate (ORR) of 47.2% was recorded for gemcitabine plus carboplatin compared with 30.9% for single-agent carboplatin (p=0.0016). In view of the improved response rate and duration of response, gemcitabine is usually given alongside carboplatin in the relapsed, platinum-sensitive setting. For these patients in the relapsed setting, the choice of gemcitabine is seen as advantageous over paclitaxel as gemcitabine does not cause hair loss or neurotoxicity.

In patients with platinum-resistant recurrence, gemcitabine given in combination with carboplatin was shown in one study to have an ORR of 47% (Ledermann *et al*, 2010). However, in view of the likely resistance to carboplatin and relatively poor cellular uptake of gemcitabine in these patients, other non-platinum regimens are generally favored over carboplatin and gemcitabine.

1.3.1 Gemcitabine Resistance

Gemcitabine is associated with key cancer resistance mechanisms (Slusarczyk *et al*, 2014), which may result in limited efficacy in ovarian cancer patients. These resistance mechanisms include:

- Inefficient uptake into cells requiring active membrane transporters, which limits the ability of the drugs to reach their site of action (Achiwa *et al*, 2004);
- Poor intracellular conversion via intracellular kinases to the active di- and tri-phosphates forms (Kroep *et al*, 1998);
- Metabolism via deamination, thus rendering them inactive (Kroep *et al*, 1998).

1.4 NUC-1031

NUC-1031 (Acelarin®) is a new chemical entity resulting from the phosphoramidate transformation of gemcitabine. NUC-1031 is synthesized as a pre-activated molecule bearing one protected phosphate group, termed the phosphoramidate motif, imparting several potential advantages over gemcitabine:

- NUC-1031 is more efficiently taken up by cells as it does not rely on nucleoside transporters to cross the cellular membrane;
- NUC-1031 presents the cell with an already partially activated (monophosphate) form of the nucleoside, thereby obviating the need for the rate limiting initial kinase activation;
- NUC-1031 is protected from enzymatic breakdown (especially by deaminases and phosphorylases) resulting in greater stability and a reduction in the generation of major metabolites.

1.4.1 Nonclinical Data

NUC-1031 has shown *in vitro* efficacy against a range of cancer cell lines including: pancreatic, bladder, prostate, breast, NSCL and colon. The *in vitro* studies showed a consistent increase in cytotoxicity of NUC-1031 compared to gemcitabine controls (EC_{50} values for NUC-1031 showed 1.3 to 343-fold improvement over gemcitabine).

In vivo, NUC-1031 has also demonstrated greater efficacy across a range of xenograft studies compared to gemcitabine. In all of the studies reported, NUC-1031 was more effective than gemcitabine at an equimolar dose. The increased effectiveness was in some cases related to improved tolerance to NUC-1031 allowing a higher dose to be administered. Where equivalent doses were tolerated, NUC-1031 showed a higher reduction in tumor growth over gemcitabine.

Toxicology findings for NUC-1031 are consistent with the cytotoxic mechanism of action and are qualitatively similar to those reported for gemcitabine. Dose range finding and four-week toxicity studies have shown that NUC-1031 could be administered at a dose equivalent to four-times the reported gemcitabine maximum tolerated dose in dog. The main findings included evidence of gastrointestinal mucosal irritation, suppression of the hematopoietic system, lymphoid atrophy and thymic atrophy. Data from genotoxicity studies suggest that NUC-1031 is only weakly genotoxic and significantly less so than gemcitabine. Further nonclinical data can be found in the Investigator's Brochure.

1.4.2 Clinical Data

The Phase I, first-in-human (FIH) dose escalation study of NUC-1031 as a single-agent has been completed in patients with advanced solid tumors (PRO-001). The Investigator-sponsored study enrolled a total of 68 patients with advanced solid tumors between October 2012 and October 2014. The dose range tested was from 500-1,000 mg/m^2 in monthly cycles of administration, using a schedule derived from that used for gemcitabine (Day 1, 8 and 15 every 28 days).

The 68 patients treated on the study included 22 males and 46 females. The mean age of the patients was 56.3 years (range 20.3 to 83.5 years). The common cancer histories (>10%) included ovarian cancer (14.7%), pancreatic cancer (13.2%) and colorectal carcinoma (10.3%). The largest primary tumor (>30%) category was categorized as 'other', which included one patient with papillary serous carcinoma later classified as ovarian cancer. All the patients had been previously treated with chemotherapy with a mean (standard deviation) number of prior

chemotherapy regimens of 3.0 (1.77). A total of 34/68 patients (50.0%) received prior gemcitabine therapy. Across the range of doses tested on the study, the median number of NUC-1031 cycles received was 3 (range 0.3 to 19). A total of 14 patients received 6 or more cycles of treatment.

NUC-1031 was generally well tolerated. Although treatment emergent adverse events were reported in all patients, the majority were Grade 1 or 2 in severity, were reversible, and were considered unrelated to the study drug. Likewise, the majority of Grade 3 or 4 adverse events were considered unrelated to the study drug and resolved without sequelae.

The most commonly occurring treatment emergent and treatment related adverse events were laboratory abnormalities, specifically decreased blood cell counts (neutropenia, lymphopenia and thrombocytopenia), as well as elevations in liver function enzymes (alanine aminotransferase and aspartate aminotransferase). The most commonly occurring treatment related clinical adverse events were fatigue, nausea and vomiting and disturbance in taste (dysguesia). Within each cycle of therapy, these laboratory and clinical abnormalities were managed by withholding or delaying treatment. In addition, dose reductions were implemented in subsequent cycles of treatment for patients continuing on the protocol.

Dose-limiting toxicities were observed at doses of 725 mg/m^2 and above and occurred in 4 patients. Reversible Grade 4 thrombocytopenia occurred in 1 patient at 750 mg/m^2. Reversible Grade 4 thrombocytopenia and neutropenia occurred in 1 patient at 1,000 mg/m^2. Reversible Grade 3 transaminase elevation occurred in 2 patients (1 at 725 mg/m^2 and 1 at 1,000 mg/m^2).

NUC-1031 demonstrated substantive anti-tumor activity at doses of 500 mg/m^2 and above. Efficacy was evaluable in 49 of 68 patients (72%) who received two or more cycles of NUC-1031 and were evaluated radiographically using RECIST criteria. PRs were reported in five patients (10%). The five patients achieving PRs included 3/7 patients (42.9%) from the 750 mg/m^2 group, 1/4 patients (25.0%) from the 1,000 mg/m^2 group and 1/2 patients (50.0%) from the 625 mg/m^2 treatment group. Confirmatory scans were not available for three patients (1 each in the 1,000 mg/m^2, 750 mg/m^2 and 625/m^2 mg treatment groups). The two patients who received a confirmatory scan had durable responses of 7.5 months and 14.5 months. An additional 32 patients (65%) achieved Stable Disease, resulting in an overall Disease Control Rate (DCR) of 76% (37/49). In the efficacy evaluable patients, the duration of PFS ranged from 0.5 to 18.7 months and the median PFS duration ranged from 1.8 to 9.2 months. Further clinical data can be found in the Investigator's Brochure.

1.4.3 Pharmacokinetics

The disposition of NUC-1031 and its metabolites in plasma, peripheral blood mononuclear cells (PBMCs), and urine following IV administration of NUC-1031 was investigated in the PRO-001 study.

Overall, plasma exposures of NUC-1031, di-fluoro-deoxycytidine (dFdC; gemcitabine) and the potentially toxic metabolite di-fluoro-deoxyuridine (dFdU) differed substantially. Median plasma $AUC_{0\text{-}t}$ values ranged from 22.3–272, 0.31–2.19, and 6.61–115 µg*h/mL, respectively. Median C_{max} values ranged from 74.4–718, 0.18–2.49, and 0.36–5.81 µg/mL, respectively.

Intracellular exposures were low for all analytes with the exception of the primary anti-cancer metabolite, dFdCTP. Median intracellular dFdCTP $AUC_{0\text{-}t}$ and C_{max} estimates ranged from 13.9– 87.8 µg*h/mL and 3.31–13.4 µg/mL, respectively.

In urine, dFdU constituted the largest percentage of drug excretion; 21.7% and 27.3% of the NUC-1031 dose was excreted as dFdU over the 24 hours post-dose on Cycle 1, Day 1 and

Cycle 1, Day 15, respectively. Overall, less than 1% of the dose was excreted as dFdC or NUC-1031.

In summary, the PRO-001 PK analyses revealed the following:

- After NUC-1031 administration over the dose range of 375 to 1,000 mg/m^2, NUC-1031 plasma concentrations and key exposure parameters (AUC_{0-t} and C_{max}) increased with increasing dose in an approximately dose proportional manner.
- Plasma concentrations and key exposure parameters for the primary NUC-1031 metabolites, dFdC, and dFdU, did not appear to increase in a dose proportional manner with increasing NUC-1031 dose. The lack of dose proportionality is not unexpected given that:
    - The PRO-001 study was not designed to show dose proportionality, and
    - There was a relatively small number of patients in each dose group.
- The predominant intracellular metabolite generated was dFdCTP, both in terms of concentration and key intracellular exposure parameters. Compared to published gemcitabine literature (Grunewald *et al*, 1990; Abbruzzese *et al*, 1991; Grunewald *et al*, 1992; Cattel *et al*, 2006; Peters *et al*, 2007), on an equimolar basis:
    - The median intracellular dFdCTP C_{max} following NUC-1031 administration was 217-times higher than that observed with gemcitabine.
    - The median intracellular dFdCTP AUC_{0-24} following NUC-1031 administration was 139-times higher than that observed with gemcitabine.
    - NUC-1031 administration results in intracellular dFdCTP concentrations throughout the following 24-hour period that are higher than that which is observed at the C_{max} 2-hour time point after gemcitabine administration.
- The predominant analyte found in excreted urine was dFdU; urinary excretion of NUC-1031 and dFdC was minimal.

The findings of the PRO-001 PK analyses are consistent with the clinical data, where NUC-1031 doses of 500 mg/m^2 and above demonstrated marked anti-tumor activity.

1.5 Study Rationale

Data from 18 patients in the PRO-001 study with gynecological cancer (11 ovarian, 3 endometrial, 2 cervical and 2 fallopian tube) were encouraging. Of these patients with gynecological cancer, 10 had platinum-resistant disease, 5 were platinum refractory and 14 were deemed evaluable for efficacy. The radiological evaluation shows that 2 of the 14 patients (14.3%) achieved a PR. These patients received NUC-1031 at 625 mg/m^2 and 750 mg/m^2. A further 11/14 (78.6%) patients achieved SD, resulting in a 92.9% DCR.

Data from the ongoing PRO-002 study of NUC-1031 in combination with carboplatin in advanced ovarian cancer are equally encouraging. Of the 22 patients enrolled, 20 are evaluable for efficacy and there has been 1 CR, 5 PRs, and 13 SDs, resulting in a DCR of 95% (19/20).

The data from these patients provides a strong rationale for further development of NUC-1031 in Phase II studies in ovarian cancer.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

The primary objective is to assess the anti-tumor activity of NUC-1031, as measured by Objective Response Rate (ORR) per RECIST criteria (Appendix 2) at the selected dose level (500 mg/m^2 or 750 mg/m^2). Primary assessment will be done by a blinded independent central reviewer (BICR).

2.2 Secondary Objectives

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 (per RECIST).
  - Progression-Free Survival (per RECIST).
  - Time to Disease Progression (per RECIST).
  - Disease Control Rate (CR+PR+SD, per RECIST).
  - Best GCIG Overall Response, combining the change in CA125 from baseline with RECIST assessment (per GCIG criteria).
  - Overall Survival.
- To further assess the safety profile of NUC-1031 administered over multiple cycles.
- To explore relationships between NUC-1031 PK, pharmacodynamics and clinical activity.
- To describe the effects of NUC-1031 on ovarian cancer symptoms.

2.3 Exploratory Objectives

- To establish the expression of genomic, transcriptomic and proteomic biomarkers in 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 EuroQoL five dimensions, five level (EQ-5D-5L).

2.4 Primary Endpoint

- ORR at the selected dose level (500 mg/m^2 or 750 mg/m^2) per RECIST criteria and assessed by a BICR.

2.5 Secondary Endpoints

The secondary endpoints are:

- Efficacy
  - Change from baseline in tumor size.
  - Duration of Overall Response (per RECIST).
  - Progression-Free Survival (per RECIST).
  - Time to Disease Progression (per RECIST).
  - Disease Control Rate (CR+PR+SD, per RECIST).
  - Best GCIG Overall Response, combining the change in CA125 from baseline with RECIST assessment (per GCIG criteria).
  - Overall Survival.
  - Assessment of ovarian cancer symptoms using the FOSI-18 questionnaire (Appendix 3).
- Safety
  - Treatment-emergent adverse events (per NCI CTCAE v4.03).
  - Clinically-significant laboratory parameters (per NCI CTCAE v4.03).
  - Changes in vital signs and serial ECGs.

2.6 Pharmacokinetics

Pharmacokinetic sampling (blood and urine) will be performed at a sub-set of sites specified by NuCana. The PK of single and multiple-dose NUC-1031 will be assessed, including:

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

PK of the following analytes will be measured:

- In plasma/urine: NUC-1031, dFdC and dFdU.
- In peripheral blood mononuclear cells (PBMCs): NUC-1031, dFdC, dFdCMP, dFdCDP, dFdCTP and dFdU.

2.7 Exploratory Endpoints

- Assessment of candidate genomic, transcriptomic and proteomic biomarkers of resistance/sensitivity to NUC-1031 in tumor specimens and/or plasma will be assessed. Examples of candidate markers include cytidine deaminase (CDA), deoxycytidine kinase (dCK), human equilibrative nucleoside transporter 1 (hENT1), ribonucleotide reductase M1 (RRM1) and RRM2.
- Assessment of the impact of treatment and disease state on health state utility by EuroQoL five dimensions, five level questionnaire (EQ-5D-5L; Appendix 4).

3 INVESTIGATIONAL PLAN

3.1 Overall 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/m^2 or 750 mg/m^2 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 BRCA mutation status and number of prior lines of chemotherapy (3 or >3), are balanced between the 2 dose levels. The stratification procedure will be defined in the statistical analysis plan.

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 enrollment shall continue until a total of 44 response evaluable patients are recruited at the selected dose (Figure 1).

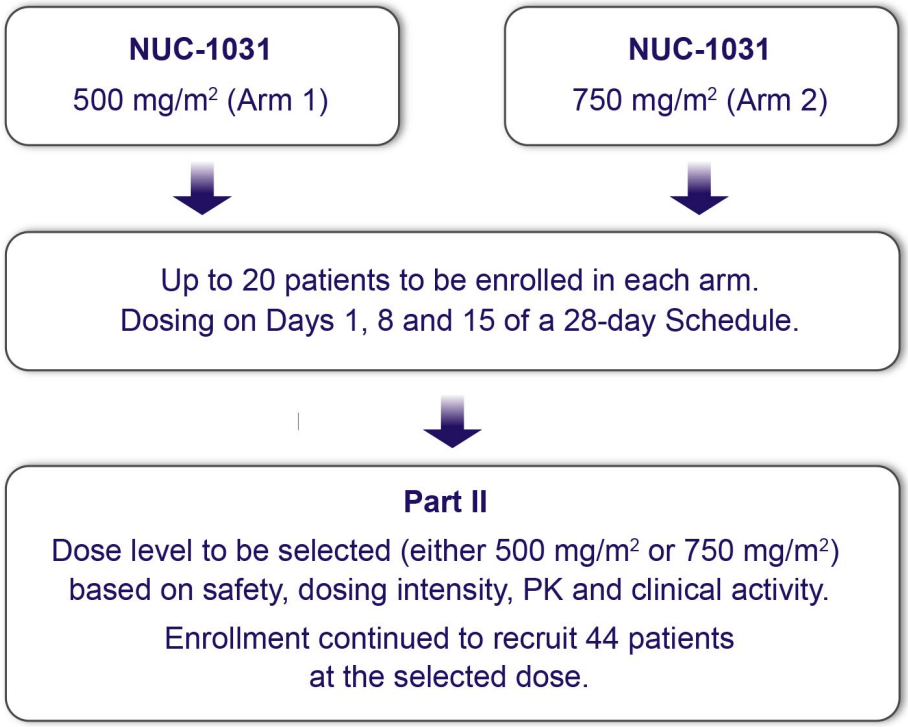

Figure 1 PRO-105 Study Schema

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 these data from Part II by the DSMC, the study may be further expanded at the selected dose level, which will be described in a protocol amendment. An efficacy update analysis may also be performed to provide more mature efficacy data.

3.2 Rationale for the NUC-1031 Dose Selected

Data from the PRO-001 study confirms the nonclinical rationale for the phosphoramidate transformation of gemcitabine. When compared to historical pharmacology data with gemcitabine, NUC-1031 generated substantially greater overall exposure to the active tri-phosphate metabolite in PBMCs isolated from patients. This appears to be the case across essentially all of the dose range studied in the Phase I study. Indeed, some level of pharmacologic activity, either safety related or efficacy related, was observed at nearly every dose level.

When dosing data are examined, it appears that the dose levels of 825 mg/m^2 and above required more substantial dose delays, omissions and dose reductions in order to deliver repeated cycles of therapy. Conversely, patients dosed at 750 mg/m^2 and below were largely able to maintain treatment intensity. It is also noteworthy that 4 of 5 PRs occurred in the 625 mg/m^2 to 750 mg/m^2 dose range. Accordingly, a dose of 750 mg/m^2 on days 1, 8 and 15 of a 28-day cycle has been selected for this PRO-105 study.

Furthermore, a dose of 500 mg/m^2 has been added to the PRO-105 study in accordance with pre-IND recommendations from the US Food and Drug Administration (FDA) in which they suggested that a dose lower than 750 mg/m^2 also be explored. Both patients enrolled at 500 mg/m^2 in PRO-001 achieved SD. In addition, the PK parameters were relatively constant across the dose range studied and NUC-1031 generated substantially greater intracellular levels of the active anti-cancer metabolite, dFdCTP, compared to historical data with gemcitabine.

3.3 Study Treatment

In Part I, eligible consenting patients will be randomized to receive IV NUC-1031 at a dose of either 500 mg/m^2 or 750 mg/m^2 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 enrollment 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 comes first).

Criteria for inter-cycle and intra-cycle dose delay and dose modification are specified in Section 9 of this protocol. The reasons for dose delay or dose reduction should be captured as AEs in the patient medical record and noted on the case report form (CRF).

3.4 Duration of Patient Participation

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 defined in Section 6.1. Reasons for treatment discontinuation must be captured in the patient medical record and on the Treatment Discontinuation page of the CRF.

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.

3.5 Patient Selection and Study Centers

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

4 PATIENT SELECTION

4.1 Inclusion Criteria

To be enrolled in this study, patients must meet the following criteria during the Screening period:

1. Provision of signed written informed consent. Patients with easily accessible tumor must also consent to the 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.
2. Original diagnosis and/or histological confirmation of high-grade serous, high-grade endometrioid epithelial ovarian, fallopian tube or primary peritoneal cancer.
3. Platinum-free interval since last line of platinum of less than 6 months (182 days).
4. Received at least 3 prior chemotherapy-containing regimens. Prior treatment with only non-cytotoxic agents (*e.g.* hormones, antibodies or PARP inhibitors) is permitted, but should not be considered as one of the '3 prior chemotherapy-containing regimens'. Adjuvant chemotherapy should be counted as a prior line of therapy.
5. Age ≥18 years.
6. ECOG performance status of 0 or 1.
7. Measurable disease as defined by RECIST.
8. Adequate bone marrow function as defined by: absolute neutrophil count (ANC) $\geq 1.5\times10^9$/l, platelet count $\geq 100\times10^9$/l and hemoglobin level ≥10.0 g/dl.
9. Adequate liver function, as defined by: serum total bilirubin ≤1.5×upper limit of normal (ULN), AST and ALT ≤2.5×ULN (or ≤5×ULN if liver metastases are present).
10. Adequate renal function assessed as Cr <1.5×ULN or GFR ≥50 ml/min.
11. Ability to comply with protocol requirements.
12. Patients are assumed to be infertile as a consequence of treatment for their disease, however, in the event they are not, patients must be postmenopausal (12 months of amenorrhea), agree to be abstinent, or they must agree to use two forms of contraception, one of which must be a barrier method and the other must be a highly effective method. These forms of contraception must be used from the time of signing consent, throughout the treatment period, and for 30 days following the last NUC-1031 dose administration. Oral or injectable contraceptive agents cannot be the sole method of contraception. See protocol Section 10.3.1 for more information. Patients of childbearing potential must have a negative serum pregnancy test within 72 hours prior to the first study drug administration. This criterion does not apply to patients who have had a previous hysterectomy or bilateral oophorectomy.

4.2 Exclusion Criteria

Patients who meet any of the following criteria at Screening will be excluded from the study:

1. Disease classified as primary platinum refractory (*i.e.* progression while receiving initial line of platinum-based therapy or within 4 weeks of the initial regimen).
2. Received fewer than 3 prior chemotherapy-containing regimens.
3. Prior therapy with single-agent gemcitabine (prior gemcitabine plus carboplatin combination treatment is permitted).
4. Prior history of hypersensitivity to gemcitabine.
5. History of allergic reactions attributed to the components of the diluents used with NUC-1031.
6. Mucinous, low-grade serous, low-grade endometrioid, carcinosarcoma, clear cell, or undifferentiated/unclassifiable histology.
7. Symptomatic CNS or leptomeningeal metastases.
8. Prior chemotherapy, radiotherapy (other than short cycle of palliative radiotherapy for bone pain), treatment with a VEGF inhibitor, PARP inhibitor or immunotherapy within 21 days of first receipt of study drug (within 6 weeks for nitrosoureas and mitomycin C); hormone therapy within 14 days of first receipt of study drug; or blood transfusion, or use of any hematopoietic growth factors within 28 days of first receipt of study drug.
9. Residual toxicities from chemotherapy or radiotherapy, which have not regressed to Grade ≤1 severity (NCI CTCAE v4.03), except for neuropathy (Grade 2 allowed) or alopecia.
10. Patients who have a history of another malignancy diagnosed within the past 5 years, with the exception of adequately treated non-melanoma skin cancer or curatively treated carcinoma *in situ* of the cervix or ductal carcinoma *in situ* (DCIS) of the breast. Patients with previous invasive cancers are eligible if treatment was completed more than 5 years prior to initiating the current study treatment, and the patient has had no evidence of recurrence since then.
11. Presence of an uncontrolled concomitant illness or active infection requiring IV antibiotics.
12. Presence of any serious illnesses, medical conditions, or other medical history, including laboratory results, which, in the Investigator's opinion, would be likely to interfere with the patient's participation in the study, or with the interpretation of the results.
13. Known HIV positive or known active hepatitis B or C.
14. Any condition (*e.g.* known or suspected poor compliance, psychological instability, geographical location, *etc.*) that, in the judgment of the Investigator, may affect the patient's ability to sign the informed consent and undergo study procedures.
15. Currently pregnant, lactating or breastfeeding.
16. QTc interval >450 milliseconds.
17. Concomitant use of drugs known to prolong QT/QTc interval (Appendix 1).
18. History of radiologically confirmed bowel obstruction (including sub-occlusive disease) relating to ovarian cancer within 6 months prior to the first receipt of study drug.

19. Patients who have received a live vaccination within 4 weeks of first planned NUC-1031 dose administration.

4.3 Waivers to Entry Criteria

The Investigator at each study center is responsible for ensuring the accuracy and completeness of all research records, the accountability of study drug, and the conduct of clinical and laboratory evaluations as outlined in the protocol. Waivers will **not** be granted for a patient who does not satisfy the eligibility criteria. Investigators who are unsure whether the patient satisfies all the entry criteria and wish to clarify matters of clinical discretion must contact the Medical Monitor who will consult the Sponsor before responding to the enquiry.

4.4 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 comes 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.

5 STUDY ASSESSMENTS AND PROCEDURES

Data from all procedures and assessments must be recorded in the patient's medical record for extraction into the CRF. Please refer to the Summary Schedule of Events for further details.

5.1 Informed Consent

Potential patients will be given the current approved version of the study information sheet and informed consent form (ICF). They will also receive clear verbal information about the study detailing no less than: the nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be explained that they will be free to withdraw from the study at any time, for any reason, without prejudice to future care, and with no obligation to give a reason for withdrawal. They will have at least 24 hours to consider the information provided and the opportunity to question the Investigator, their GP or other independent parties before deciding whether to participate.

The Investigator designee who obtains consent must be suitably qualified and experienced. All designees must be authorized by the Investigator to obtain consent. The Investigator is responsible for ensuring that the study consent procedures comply with ICH-GCP and any other additional local regulatory requirements. Informed consent discussions and outcomes must be well documented in the medical record. The Investigator must be satisfied that the patient has made an informed decision before taking consent. The patient and the Investigator must personally sign and date the current approved version of the ICF in each other's presence.

A copy of the study information and signed ICF will be given to the patient. The original signed form will be retained at the study site, with copies held in both the medical record and Investigator Site File. Written informed consent for participation in the study must be obtained *prior to* performing any study-specific screening tests or evaluations.

5.1.1 Informed Consent for Tumor Tissue Collection

A fresh tumor biopsy and archival tumor tissue, if available are required assessments for this 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.

An optional tumor sample may also be collected within 24 hours of NUC-1031 administration on C1D1. Participation in this element of the research requires patients to sign an addendum to the ICF. For sampling procedures, storage conditions, and shipment instructions, please refer to the accompanying Tumor Tissue Laboratory Manual.

5.2 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 of efficacy endpoints according to BRCA mutation status. 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 Medical Monitor, in consultation with the Sponsor, will confirm eligibility according to the defined inclusion and exclusion criteria. 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 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.

5.3 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 is 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 score.
- 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: WBC count, differential WBC count, RBC count, hemoglobin, hematocrit and platelets.
    - Coagulation parameters*:* PT/INR and aPTT.
    - Chemistry: 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.
    - Pregnancy testing: For women of childbearing potential serum pregnancy must be performed within 72 hours prior to C1D1.
    - CA125 (for GCIG response determination).
- Urinalysis: pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilirubin and occult blood. Dipstick testing is acceptable.

- Tumor imaging (CT, MRI and/or 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.

5.4 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.

5.5 Evaluations to Be Performed During the Study

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

5.5.1 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 score.
- 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/or 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 C1D1 and 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/or 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, differential WBC count, RBC count, hemoglobin, hematocrit and platelets.
  - Coagulation parameters*:* PT/INR and aPTT.
  - Chemistry: sodium, potassium, magnesium, urea or blood urea nitrogen, 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.

5.5.2 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.

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

- PK: multiple blood samples will be taken during Cycles 1 and 3 on Days 1 and 2. Optional urine samples may be taken during Cycle 1 on Days 1 and 2. Refer to Section 7.2 for more details.
- AE recording and causality assessment.
- Recording of new or changes to concomitant medication.

5.5.4 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/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.
- At C1D15 and 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/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.
- Blood samples drawn for:
    - Hematology: WBC count, differential WBC count, RBC count, hemoglobin, hematocrit and platelets.
    - Chemistry: sodium, potassium, magnesium, urea or blood urea nitrogen, 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.

5.5.5 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. Refer to Section 7.2 for more details.
- AE recording and causality assessment.
- Recording of new or changes to concomitant medications.

5.5.6 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.

5.5.7 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.
- 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, differential WBC count, RBC count, hemoglobin, hematocrit and platelets.
    - Coagulation parameters*:* PT/INR and aPTT.
    - Chemistry: sodium, potassium, magnesium, urea or blood urea nitrogen, 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.

5.5.8 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 PFS.

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.

6 PATIENT WITHDRAWAL

6.1 End of Treatment

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

- Progressive Disease (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 CRF.

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.

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 CRF pages as not applicable. Under these conditions, Investigators are still responsible to follow up any SAEs until resolution.

6.4 Patient Evaluability and Replacement

Enrollment will continue until there are 44 patients evaluable for a response assessment at the selected dose level. All patients with measurable disease (defined by BICR) will be considered evaluable for response assessment.

All eligible patients who receive at least one dose of NUC-1031 are considered evaluable for safety analysis.

7 SAMPLES FOR LABORATORY ANALYSIS

7.1 Clinical Laboratory Tests

All clinical laboratory testing will be performed at local sites. A serum or urine pregnancy test will be performed in women of child-bearing potential at the Screening visit. Laboratory tests may be performed either on the day of a treatment visit, or during the 3 days prior to a treatment visit.

7.2 Pharmacokinetics

PK sampling (blood and urine) will be performed at a sub-set of sites specified by NuCana. The PK schedule is designed to explore the relationship between NUC-1031 PK, pharmacodynamics and clinical activity. PK endpoints will include assessments of:

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

Blood samples will be collected at the following visits:

- Cycle 1: Days 1 and 2
- Cycle 1: Days 15 and 16
- Cycle 3: Days 1 and 2

The PK blood sampling schedule is summarized in Table 1 below:

Table 1 PK sampling schedule

Sample 1	**T_0** – pre-dose (before the start of the infusion)
Sample 2	**T_1** – end of infusion
Sample 3	**T_2** – T_1 plus 10 minutes
Sample 4	**T_3** – T_1 plus 30 minutes
Sample 5	**T_4** – T_1 plus 1 hour
Sample 6	**T_5** – T_1 plus 2 hours
Sample 7	**T_6** – T_1 plus 4 hours
Sample 8	**T_7** – T_1 plus 6 hours
Sample 9	**T_8** – T_1 plus 24 hours

Optional pooled urine collection for PK analysis will be taken 0-6 and 6-24 hours from the beginning of NUC-1031 infusion. Optional urine pooled urine collections will be collected at the following visits:

- Cycle 1: Days 1 and 2
- Cycle 1: Days 15 and 16

Standard PK parameters for each compound of interest will then be derived from the measured plasma, urine and PBMC concentrations. The PK samples will be processed and analyzed at a central laboratory. Please refer to the Guidelines for Pharmacokinetic Sample Management for details regarding PK sample collection, processing and shipping.

7.3 Tumor Tissue Biopsies

Fresh and archival tumor tissue will be submitted for laboratory analysis to understand the basis for response or resistance to treatment. Fresh and archival tumor (if available) samples are a requirement for participation in the study. However, 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 must not be designated as target lesions for the purposes of RECIST.

An optional tumor sample may be collected within 24 hours of the end of the infusion of NUC-1031 on C1D1. Specific instructions on the collection and shipment of tissue samples will be provided in the Tumor Tissue Laboratory Manual.

Correlation of response to NUC-1031 with genomic, transciptomic and proteomic tissue biomarkers of tumor sensitivity and resistance will be assessed both in the freshly obtained tumor specimens and in archival samples obtained at screening. Markers of interest include cytidine deaminase (CDA), deoxycytidine kinase (dCK), human equilibrative nucleoside transporter 1 (hENT1), ribonucleotide reductase M1 (RRM1) and RRM2.

7.4 Labeling and Confidentiality of Biological Samples

All biological samples (including blood, urine and tumor) sent to analytical laboratories will be labeled with the study number, patient number and date/time taken. Samples labels must not contain any personally identifiable information.

7.5 Withdrawal of Consent for Biological Sample Collection or Retention

A patient may withdraw consent to provide samples or allow their samples to be used for research at any time without giving a reason. The Investigator must ensure that their wishes are recorded in the medical record and CRF. The CRO should be informed accordingly. The Investigator should discuss with patients the valuable use of samples that have already been provided and under circumstances where these samples have already been processed and anonymized, it would not be possible to destroy such samples.

8 INVESTIGATIONAL MEDICINAL PRODUCT

8.1 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/ml formulated in dimethylacetamide (DMA) and Normal Saline (0.9%) in the ratio of 80:20.

8.2 NUC-1031 Supplies and Study Drug Packaging

NUC-1031 will be supplied to the pharmacy of the investigative clinical site and will be supplied as a 7 ml fill volume in 10 ml clear glass vials. The vials are packaged in a labeled cardboard outer carton, each containing 6 vials.

A Diluent Solution is supplied as a 10 ml volume in clear glass 20 ml vials. The Diluent Solution is comprised of 20% DMA, 40% Kolliphor ELP and 40% Tween 80. The Diluent Solution vials are packaged in labeled cardboard outer carton, each containing 3 vials.

8.3 Handling and Storage

NUC-1031 and Diluent Solution must be stored in an appropriately secure Investigational Pharmacy at all times until dispensed for administration to patients on protocol. NUC-1031 must be stored between 2-8°C (36-46°F) in a temperature-monitored refrigerated unit. The Diluent Solution must be stored at room temperature (15-25°C/59-77°F). Only adequately trained pharmacy staff are permitted to handle NUC-1031 and the Diluent Solution. The study medication should not be removed from the pharmacy except for the purposes of dispensing to the patient for this protocol.

If NUC-1031 or the Diluent Solution contacts the skin or the mucous membranes, it should be washed immediately and thoroughly. For additional information on study drug handling including dispensing directions, please refer to the NUC-1031 Pharmacy Manual.

8.4 Preparation

As with other cytotoxic substances, applicable local procedures should be used in the preparation and administration of NUC-1031. Please refer to the administration guidance in the current version of the Pharmacy Manual and Administration Guidelines for further information on the preparation of NUC-1031.

8.5 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 eCRF.

Dubois & Dubois BSA calculation:

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

Patients will receive IV NUC-1031 at an initial dose of 500 mg/m^2 or 750 mg/m^2 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 Section 9 of this protocol.

The Diluent Solution (Kolliphor ELP; Tween 80; DMA) is provided for use by the hospital pharmacy to prepare NUC-1031 for administration by infusion in sterile saline for injection. The pharmacy will prepare the product for administration by mixing NUC-1031 and Diluent Solution and then further diluting the appropriate dose of this mixture in 0.9% sterile saline for injection. This preparation is then administered IV over 30 minutes. The administration time may be increased to 1 hour and then to 2 hours, if required. Please refer to the current Pharmacy Manual and Administration Guidelines for further information on NUC-1031 preparation and administration.

8.6 Drug Destruction

Used vials should be destroyed in accordance with local procedures and documented in the drug accountability and drug destruction log. A copy of the disposal certificates should be kept in the study file.

8.7 Study Drug Accountability

The FDA and other applicable regulatory authorities require accounting of all study drug received by each study center. Records of drug disposition required include the date received by the center, date administered, quantity administered, and the patient to whom study drug was administered. The Investigator is responsible for the accountability of all used and unused study drug containers and unused study drug. Each study center is to use a study drug

accountability log to document study drug disposition. All items on this form are to be completed in full.

The Investigator identification number and patient initials (as allowed by local regulations) and identification number are to be recorded on each study drug accountability log. Each time study personnel dispense study drug for a patient, he or she is to record the date dispensed, amount of study drug dispensed, Lot number, and the dispenser's initials. Study personnel are to monitor the inventory of clinical supplies and maintain a count of all used and unused study drug. The Sponsor's designated site monitor will review study drug accountability records and remaining drug supplies during routine monitoring visits.

8.8 Management of NUC-1031 Overdose

The dose of NUC-1031 intended for use on this protocol is 500 mg/m^2 or 750 mg/m^2. In the Phase I, FIH study, the highest dose studied was 1,000 mg/m^2. Should a substantial overdose occur, there is no known antidote. Any patient, who inadvertently receives a higher dose than intended should be monitored closely, managed with appropriate supportive care, including transfusion and hematopoietic growth factors as needed, until recovery. Such overdoses should be recorded as follows:

1. If an overdose occurs in the course of the study, site personnel must inform the Investigator and monitor immediately upon discovery of the event. An overdose will be recorded on the treatment CRF page and any associated AEs/SAEs will be recorded as the AE diagnosis/symptoms on the relevant AE/SAE page in the CRF. An overdose with no associated symptoms is only reported on the treatment CRF.
2. All overdoses should be tracked as a violation.

9 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/m^2.

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.

9.1 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 2.

Table 2 Dose adjustments within a cycle (Days 8 and 15) based on ANC and platelet counts

ANC		Platelets	Starting dose (750 mg/m^2)	Starting dose (500 mg/m^2)	Starting dose (375 mg/m^2)
≥1.5×10^9/l	**AND**	≥75×10^9/l	750 mg/m^2	500 mg/m^2	375 mg/m^2
1.5-1.0×10^9/l and afebrile	**AND/OR**	50-75×10^9/l without evidence of bleeding	500 mg/m^2	375 mg/m^2	275 mg/m^2
<1.0×10^9/l, or <1.5×10^9/l with fever	**AND/OR**	<50×10^9/l, or <100×10^9/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 to the next dose level.

If a patient starts a treatment cycle at 500 mg/m^2 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 2.

If a patient has her dose permanently reduced to 375 mg/m^2, and hematologic toxicity persists on any day that a dose is scheduled, dose modification should follow the far right column of Table 2.

For all other hematologic toxicity, dose adjustments should be performed according to ***Table 3***.

Table 3 Dose adjustments for hematological 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.

9.2 Non-Hematological Toxicity – Dose Adjustment

Dose adjustment should be performed according to Table 4. 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.

Table 4 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/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.

9.3 Guidance for Dose Omissions

Table 5 outlines the guidance for omission of doses on Day 1, 8 or 15.

Table 5 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.

10 OTHER TREATMENTS (NON-IMP)

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 CRF. All prior anti-cancer therapies from initial diagnosis up until enrollment must be recorded in the CRF.

10.1 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 CRF.

10.2 Hematopoietic Growth Factor Support

The prophylactic use of hematopoietic growth factors (*e.g.* 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 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 CRF. Any blood or platelet transfusions should also be recorded in the CRF.

10.3 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 CRF.

10.3.1 Contraception Methods

Patients are assumed to be infertile as a consequence of treatment for their disease, or postmenopausal (12 months of amenorrhea).

If patients are not infertile or post-menopausal, they must agree to:

- Abstinence during her entire participation in the study and for 30 days post-last dose of study medication *or*
- Use **two** forms of contraception, one of which must be a barrier method and one must be a highly effective form (less than 1% failure rate if used consistently and correctly).

Acceptable barrier methods (which may not be considered highly effective):

- Male or female condom, with or without spermicide
- Cap, diaphragm or sponge with spermicide

Highly effective forms of contraception include:

- Oral, intravaginal or transdermal combined (estrogeen and progestogen containing) hormonal contraception associated with inhibition of ovulation
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Surgical sterilization (bilateral occlusion, vasectomized partner)
- Intrauterine device or intrauterine hormone-releasing system

These forms of contraception must be used from the time of signing consent, throughout the treatment period, and for 30 days following the last NUC-1031 dose administration. Oral or injectable contraceptive agents cannot be the sole method of contraception. Patients of childbearing potential must have a negative serum pregnancy test within 72 hours prior to the first study drug administration.

10.4 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 (Appendix 1).
- Live vaccines (must also be avoided for six weeks after last NUC-1031 dose administration).

11 TUMOR RESPONSE ASSESSMENTS

11.1 Tumor Measurements and Assessment of Disease Response

Patients must have at least one lesion that can be accurately assessed at baseline by CT, MRI or PET-CT (US only), which is suitable for repeated assessment in order to be eligible for this study. All known or suspected disease sites must be assessed at baseline by either CT, MRI or PET-CT (US only) scan. The same radiological methods at baseline must be used to follow lesions throughout the study. Disease must be measured according to RECIST criteria, with target and non-target lesions identified, measured and followed throughout the study (Appendix 2). Biopsied lesions should not be designated as target lesions for the purposes of RECIST.

Whenever possible, the same qualified physician will interpret results to reduce variability. Radiographic images will be maintained at the study center, and Investigator's findings will be filed in the patient's source documents.

In addition, digital copies of all radiographic images will be collected and stored in a central radiologic facility in order to allow for independent confirmation of the radiographic imaging results. Instructions for the collection, and submission of images are provided in a separate Imaging Manual.

Tumor measurements and disease response assessments are to be performed every 8 weeks (±7 days) from C1D1. If the patient stops study treatment for reasons other than radiologically confirmed PD, tumor measurements and disease response assessments should continue every 8 weeks (±7 days) from C1D1 thereafter until PD is radiologically confirmed.

Tumor measurements and disease response assessments also are to be performed any time disease progression is suspected.

Patients should not discontinue NUC-1031 because of raised CA125 or other clinical signs of PD until PD has been confirmed by RECIST.

CRs and PRs must be confirmed by repeated images at least 4 weeks after initial documentation.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of not less than 6 weeks.

A third-party central imaging vendor will review all study-related imaging. The imaging vendor will not be responsible for assessing images in real-time to inform on patient treatment decisions. This responsibility will remain with the Principal Investigator at the site. Please refer to the Imaging Manual for details on submission and review of images.

12 SAFETY REPORTING

12.1 Definitions

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.

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 AE (**TEAE)** is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

A Serious AE (**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 an AE or SAE.

An **Adverse Drug Reaction (ADR)** is an AE, which is considered to be causally related to any dose of NUC-1031. This means that a causal relationship between NUC-1031 and the AE is at least a reasonable possibility, *i.e.* the relationship cannot be ruled out.

An **Unexpected Drug Reaction** is an adverse drug reaction, the nature or severity of which, is not consistent with applicable product information (referring to information in IB, see RSI).

A **Suspected Unexpected Serious Adverse Reaction (SUSAR)** is a serious adverse drug reaction, the nature or severity of which is not consistent with the applicable product information (*e.g.* Investigator's Brochure for an unapproved IMP).

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. Please consult Section 12.5 for the specific mechanism by which SAEs are to be reported.

12.2 Adverse Event 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 CRF 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 CRF. 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 CRF. 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.

Pre-existing 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 pre-existing 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 v4.03]).

12.3 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).

12.4 Assessment of Severity

The severity of each AE is to be assessed by the Investigator according to NCI CTCAE, v4.03. 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 activities.
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 as described in Sections 12.6 and 12.7.

12.5 SAE Reporting

Any AE considered serious by the Investigator or sub investigator or that meets the seriousness criteria that occurs from first administration of study drug through 30 days after last study drug dose must be reported to Chiltern Pharmacovigilance (PV) within 24 hours from the time study site personnel first learn about the event. The SAE report will be completed and emailed or faxed to Chiltern PV using the contact details in Table 6.

Table 6 Chiltern pharmacovigilance contact details

Email	GlobalSAEInbox@chiltern.com
UK fax number	(+44) 00 800-529-34043
US fax number	(+1) 888-726-8416 or (+1) 888-228-2837

If the patient is hospitalized because of or during the course of an SAE, then a copy of the hospital discharge summary (if available) should be faxed to Chiltern PV, using the fax numbers listed above, as soon as it becomes available. Withdrawal from the study and all therapeutic measures will be performed at the discretion of the Investigator or sub investigator.

NuCana, or Chiltern PV, will notify appropriate regulatory authorities of any unexpected, fatal, or life-threatening experience that is determined to be related to the use of the study drug. Refer to Section 12.7 for more details.

The Investigator or sub investigator is responsible for informing the IRB/EC. Copies of SAE correspondence with all Investigators or sub-investigators, governing authorities, ethics committees, and NuCana must be submitted to Chiltern PV for filing.

A patient experiencing one or more SAE will receive treatment and follow-up evaluations by the Investigator or sub-investigator or will be referred to another appropriate physician for treatment and follow-up. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Study endpoints in ovarian cancer patients include disease-related mortality and morbidity, which will not be reported as expedited IND safety reports, unless there is a serious and unexpected event with evidence of a causal relationship between study drug and the event. As appropriate and based on the frequency of occurrence, SAEs in the study will be reported to the FDA at an appropriate interval, such as inclusion in the periodic update IND annual report.

The following SAEs will not be reported individually in an expedited manner because they are anticipated to occur in the ovarian cancer study population receiving standard of care treatment at some frequency independent of study drug exposure:

- Progression of disease.
- Death as a consequence of the underlying malignancy.

12.6 Expedited Reporting of SAEs

The following SAE reporting requirements apply regardless of the Investigator's assessment of the causality or expectedness of the SAE. If an SAE occurs that requires reporting, a SAE

Report Form should be completed and faxed within 24 hours of Investigator awareness to the Chiltern PV contact details provided above.

If the SAE has not been reported within the specified timeframe, a reason for the delay must be provided when sending the SAE Report Form. SAEs that are fatal or life-threatening must be notified immediately. For all SAEs, the Investigator is obliged to pursue and provide all required information in accordance with the timelines provided above.

12.7 SUSAR Reporting

All SUSARs must be reported to the responsible Regulatory Authorities and Institutional Review Boards/ Ethics Committees (IRBs/ECs) within the required timelines:

- Fatal or life threatening SUSARs will be reported within 7 days of receipt. Any additional information will be reported within 8 days of sending the first report.
- All other SUSARs will be reported within 15 days of receipt.

In addition, other safety issues qualify for expedited reporting where they might materially alter the current risk assessment of NUC-1031 or be sufficient to change NUC-1031 administration or the overall conduct of the study.

NuCana, or Chiltern PV, will notify appropriate regulatory authorities by telephone or fax transmission of any fatal, or life-threatening experience that is determined to be related to the use of the study drug (expedited report) as soon as possible but no later than 7 calendar days after the initial receipt of the information. Initial notification will be followed by a written report within 15 calendar days.

For unexpected events associated with the use of the study drug which are not fatal or life threatening, NuCana or Chiltern PV will notify the regulatory authorities as soon as possible, but no later than 15 days of the initial receipt of information.

The Investigator or Sub-Investigator is responsible for informing the IRB/EC. Copies of SAE correspondence with all Investigators or Sub-Investigators, regulatory authorities, IRBs/ECs and NuCana must be submitted to Chiltern PV for filing.

12.8 Terms and Grading of Events

All AEs and toxicities must be graded according to NCI CTCAE v4.03.

12.9 Pregnancy

Patients who become pregnant should be withdrawn from study treatment immediately. Pregnancies (in a patient or partner) occurring during the study require expedited reporting. A Pregnancy Notification Report should be completed and submitted to Chiltern PV within the same timelines and using the same contact details as an SAE. All reported pregnancies should be followed up and the outcome reported using the Pregnancy Follow-up Report. If the outcome of the pregnancy meets any of the criteria for seriousness, it must also be reported as an SAE.

Examples of pregnancy outcomes that are SAEs include reports of:

- Congenital anomalies or developmental delay, in the fetus or the child.

- Fetal death and spontaneous abortion.
- Suspected adverse reactions in the neonate that are classified as serious.

12.10 Events Exempt from Being Reported as AE/SAEs

12.10.1 Progression of Underlying Disease

Disease progression and resultant death will be captured on the CRF. AEs including hospitalization that are clearly consistent with disease progression will not be reported as individual AE/SAEs. Clinical symptoms of disease progression will only be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Every effort should be made to document the objective progression of underlying malignancy. In some cases, the determination of clinical progression may be based on symptomatic deterioration. For example, progression may be evident from clinical symptoms, but is not supported by tumor measurements. Or, the disease progression is so evident that the Investigator may elect not to perform further disease assessments.

12.10.2 Death on Study Attributed to Malignancy

Death due to disease under study is to be recorded on the Death CRF form, provided that the death is not unexpected and no causal relationship is suspected. The Investigator must clearly state whether the death was expected or unexpected and whether a causal relationship to NUC-1031 or other protocol treatment intervention is suspected.

12.10.3 Elective Admissions and Supportive Care

Elective admissions to hospital for patient convenience or for planned procedures or investigations or treatment as specified in this protocol and standard supportive care are not SAEs, and do not require SAE reporting.

12.11 Informing Investigators of New Safety Information

NuCana will ensure that all Investigators are kept informed, in a timely manner, as new safety information becomes available. Investigators are responsible for briefing their study team as appropriate.

12.12 Reference Safety Information (RSI) for Assessment of Expectedness

The IB supplied by NuCana for NUC-1031 contains a defined table, which will act as the RSI for the study. Only the IB version with current regulatory and IRB/EC approval for use in the study will be used to assess SAE reports to identify SUSARs.

- **Significant Changes to the RSI**: If patient safety or the risk/benefit assessment has changed or new expected reactions have been added, then approval of the updated IB by applicable Regulatory Authorities and IRBs/ECs will be sought. If new expected reactions have been added to the IB or events have downgraded to 'expected', a justification for the changes will be included in the amendment request. Changes to the IB that impact on patient safety or alter the risk/benefit assessment may require changes to the study documentation such as the ICF. NuCana will identify any such required changes and ensure ICF revisions are made and approved by applicable Regulatory Authorities and IRBs/ECs, and patients re-consented as applicable. Significant updates to the IB shall be attached to the DSUR (once approved by applicable Regulatory Authorities and IRBs/ECs); however the IB in effect at the start of the DSUR reporting period serves at the RSI during the reporting period.
- **Non-Significant Changes to the RSI**: If changes to the IB are minor and do not include new/removed expected reactions, do not impact on patient safety or alter the benefit/risk assessment, then sites will not receive the updated IB until the end of the DSUR reporting period and this decision will be made by NuCana.

If the non-significant updated IB *is* to be implemented in the new DSUR reporting period, then Regulatory Authority and IRB/EC should be informed of the intention to implement the updated IB after the DSUR reporting period ends. The updated IB will be attached to the DSUR. If new expected reactions have been added to the IB or events have downgraded to 'expected', then the updated IB must receive approval before it is implemented. The IB will be sent to the study sites with a covering letter documenting the changes. This will be circulated after the DSUR has been submitted at the start of the new DSUR reporting period.

12.13 Data Safety Monitoring Committee (DSMC)

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. Members of the DSMC will include:

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

13 STATISTICAL CONSIDERATIONS

A Statistical Analysis Plan (SAP) will be finalized before database lock and conduct of the final analysis is undertaken. The main features of the planned statistical analysis are included below.

13.1 Sample Size

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. The study will be considered to have met its primary endpoint if a minimum of 4 confirmed responses (CR or PR) is 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.

Upon review of the data from Part II by the DSMC, the study may be further expanded at the selected dose level, which will be described in a protocol amendment.

13.2 Missing, Unused and Spurious Data

All available safety, PK, and efficacy data will be included in tabulations and patient-level listings. No imputation of values for missing data will be performed.

13.3 Analysis Populations

The analysis of time to progression, PFS, OS and health-related quality of life (HRQoL) data will be summarized and analyzed in all patients enrolled, regardless of treatment received (the full analysis set, FAS) on an intention-to-treat (ITT) basis.

The primary analysis of response rate will be based on a blinded independent central review (BICR) of confirmed response rate by RECIST. Only patients with measurable disease at baseline (defined by BICR) will be included in the Evaluable for Response population. This population will be analyzed for all related response measurements. Sensitivity analyses will be performed including using the investigator-recorded assessment. For the purposes of dose selection, unconfirmed responses will be taken into account but for all other analyses confirmation of response is required.

As warranted by the data, efficacy may also be assessed in sub-populations, as defined by NuCana prior to database lock. Any sub-group analyses will be exploratory and their purpose would be to assess consistency of treatment effect across potential or expected prognostic factors, or biomarkers. Analyses will not be performed if there are too few events available for a meaningful analysis of a particular sub-group.

For the assessment of safety and tolerability, summaries will be produced based on the Safety Analysis Set. This will include all patients who receive at least one dose of study treatment.

PK analyses will be performed on the PK population, defined as all patients who receive any amount of NUC-1031 and have sufficient data for PK analysis.

13.4 Patient Disposition

Data tabulations will summarize the following patient numbers:

- Enrolled
- At least one dose of NUC-1031 received
- Evaluable for safety and efficacy
- Protocol violations
- Withdrew from study due to:
    - AE
    - Investigator request
    - Withdrew consent
    - Lost to follow-up
    - Other reasons, as collected in the CRF.

13.5 Statistical Methods

13.5.1 Demographics and Baseline Data

Demographic and baseline characteristics of patients will be summarized using descriptive statistics:

- Age
- Sex
- Race
- Ethnicity
- Baseline ECOG performance score
- Primary diagnosis
- Disease stage at diagnosis and baseline
- Prior therapies, including systemic therapies, radiation, and surgeries
- Other baseline characteristics, as collected in the CRF.

13.5.2 Concomitant Medications

The number and proportion of patients in the Safety analysis set using different concomitant medications will be tabulated and summarized by WHO DD anatomical, therapeutic, chemical class and preferred term.

Use of hematopoietic growth factors and transfusions are of special interest.

13.5.3 Extent of Exposure

Descriptive statistics for patients treated, including the number of infusions received, total dose given, and infusions delayed or missed, will be presented.

13.5.4 Efficacy Analysis

The primary response evaluation is based upon the determination of response using RECIST (Appendix 2) by a BICR:

- **ORR** is defined as the number of patients achieving a confirmed response (CR or PR). Number and percentage of patients achieving a response, with confidence intervals, will be provided. In addition, the number and percentage of patients achieving individual best response criteria of CR, PR, SD, PD, or NE will be described.
- **Change from baseline in tumor size** is measured as the percentage change in the total measurements of target lesions from the pre-treatment scan, measured at each scheduled scan.
- **Duration of Overall Response** is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started). Only responses that were later confirmed, will be considered when calculating the DoR. 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.
- **PFS** is defined as the time from the date of study treatment initiation (start of treatment) to the first date of objectively determined PD or death from any cause. 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. 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 prior to the date of subsequent therapy.

  The number of overall censored patients, number of patients with events and Kaplan-Meier estimates median time will be provided. In addition, the results will be presented graphically in Kaplan-Meier plots.
- **Time to Disease Progression** is measured from the start of the treatment until the criteria for progression are first met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements. For patients who were lost to follow-up, or died 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.

  The number of overall censored patients, number of patients with events and Kaplan-Meier estimates median time will be provided. The results will also be presented graphically in Kaplan-Meier plots.
- **Disease Control Rate** is defined as the number of patients achieving confirmed response (CR or PR) or SD as best overall response (as defined in RECIST).
- **Best GCIG Overall Response** (CR, PR, SD, PD, NE): number and percentage of patients with responses defined per GCIG criteria will be described.
- **OS** is defined as the time from randomization 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.

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

13.5.5 PRO Analysis

13.5.5.1 EQ-5D-5L

Descriptive statistics, graphs and listings will be reported for health state utility values and visual analogue scale by visits as well as change in these scores from baseline. Further details will be included in the SAP.

13.5.5.2 FOSI-18

Descriptive statistics, graphs and listings will be reported to explore the impact of NUC-1031 on symptoms and HRQoL. The relationship between PROs, efficacy and AEs will be explored using descriptive summaries. Further details of the exploratory analysis based on the FOSI-18 will be outlined in the SAP.

13.5.6 Safety Analysis

Safety analyses in addition to those described in the following subsections may be determined at any time without prejudice, in order to most clearly enumerate rates of toxicities and to define further the safety profile of NUC-1031.

13.5.6.1 Adverse Events

AEs will be considered treatment-emergent (TEAE) if they start on or after the time of the first dose of study treatment and up to 30 days after the last dose of study treatment. AEs will be summarized by MedDRA™, Version 18.1 (or higher), System Organ Class (SOC) and preferred term (PT). The severity of AEs will also be summarized by NCI CTCAE v4.03 (or higher), grade. Non-treatment-emergent AEs will be included in the patient listings and flagged as such but will not be included in the summary tables. Where an AE date is partial or missing, and it is unclear whether the AE is treatment-emergent, the AE will be assumed to be treatment-emergent.

The following summaries will be produced by dose cohort for all TEAEs:

- An overview table of the incidence of TEAEs, Grade 3+ TEAEs, SAEs, TEAEs leading to treatment discontinuation and TEAEs leading to death, by dose and overall.
- Summary of TEAEs by SOC and preferred term: Both the number and percentage of patients in each category (patient-level summary) and the number of episodes (episode-level summary).
- Summary of TEAEs occurring in at least 10% of patients, sorted in descending order of frequency (*i.e.* most frequent event shown first). The order of frequency will be determined by the most frequent preferred term across all cohorts.
- Summary of CTCAE Grade 3 and above TEAEs by preferred term.
- Summary of SAEs by preferred term.

In addition, the following will be listed:

- AEs with outcome of death along with the date of onset, study day, dose at onset, treatment status at onset (pre-treatment, ongoing or post-treatment) and investigator's assessment of severity and relationship to study drug.
- All SAEs along with the date of onset, study day, dose at onset, treatment status at onset (pre-treatment, ongoing or post-treatment), date of resolution (if AE is resolved), investigator's assessment of severity and relationship to study drug.
- AEs leading to discontinuation of study medication, listed along with the date of onset, study day, dose at onset, treatment status at onset (pre-treatment, ongoing or post-treatment) and investigator's assessment of severity and relationship to study drug.
- If an AE is reported more than once during the study period the greatest severity and the worst-case attribution will be presented in summary tables. Any AEs commencing >30 days after discontinuation of study treatment will not be included in the tabulations of AE data.

13.5.6.2 Laboratory Parameters

Laboratory results (hematology, serum chemistry, coagulation parameters and urinalysis) will be classified according to NCI CTCAE v4.03 (or higher). Laboratory results not corresponding to an NCI CTCAE term will not be graded.

Shift tables will be shown for intra-individual changes from Baseline in NCI CTCAE grade for each study visit. Laboratory parameters will also be listed.

13.5.6.3 Vital Signs

Vital sign parameters (including blood pressure and heart rate) and body weight will be listed.

13.5.6.4 ECOG Performance Status

ECOG performance status will be listed. The ECOG Performance Scale is provided in Appendix 5.

13.5.6.5 Physical Examination

Physical examination findings will be listed.

13.5.6.6 ECGs

ECG parameters will be described at each timepoint. The site will be required to review ECGs as a safety check. This will be done immediately by a qualified investigator or cardiologist at the study site. ECG assessments may be retained for review centrally, where results will be provided to the study site and retained as source data.

13.5.6.7 Pharmacokinetics

The PK of single and multiple-dose NUC-1031 will be assessed, including:

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

PK of the following will be measured:

- In plasma/urine: NUC-1031, dFdC and dFdU.
- In peripheral blood mononuclear cells: NUC-1031, dFdC, dFdCMP, dFdCDP, dFdCTP and dFdU.

All above PK parameters will be analyzed in the PK population.

13.5.6.8 Exploratory Endpoints

Assessment of candidate genomic, transcriptomic and proteomic biomarkers of resistance/sensitivity to NUC-1031 in tumor specimens will be analysed in the ITT population. The candidate genomic, transcriptomic and proteomic biomarkers will be defined in the SAP.

13.5.7 Primary Analysis and Interim Analyses

The primary analysis of Part II 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).

Up to three interim analyses may be performed during Part I in order to select a dose to take forwards into Part II. For the purpose of the dose selection analyses only, unconfirmed responses may be taken into account, provided that the response is unconfirmed due to insufficient follow-up data being available, rather than because the subsequent data is available and does not confirm the initial response.

An additional efficacy update analysis may be performed following the primary analysis of Part II. The purpose of this analysis would be to provide more mature efficacy data. As such, the timing of such an analysis, if required, will be determined following review of the primary analysis.

Timings of all analyses will be described in the statistical analysis plan. Upon review of the data from Part II by the DSMC, the study may be further expanded at the selected dose level, which will be described in a protocol amendment.

13.5.8 Changes to the Planned Statistical Methods

Planned statistical analyses will be documented in the final SAP before database lock. Any changes to the planned statistical methods will be documented in the clinical study report.

14 PATIENT DATA HANDLING AND CONFIDENTIALITY

14.1 Case Report Forms

As part of the responsibilities assumed by participating in the study, the Investigator or Sub-Investigator agrees to maintain adequate case histories for the patients enrolled as part of the research under this protocol. The Investigator agrees to maintain accurate CRFs and source documentation as part of the case histories. These source documents include laboratory reports and MRI or CT scans.

An electronic CRF (eCRF) will be used, please refer to the CRF Completion Guidelines for further information. The Investigator must review each completed eCRF in a timely manner. The Investigator will be required to review and electronically sign and date the CRFs once the patient's data is complete.

14.2 Monitoring of the Study

Monitoring and auditing procedures developed by NuCana or designee will be followed, in order to comply with ICH-GCP guidelines. Before a study center can enter a patient into the study, a representative of NuCana or designee will visit the study center to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of NuCana or its representatives. This will be documented in a Clinical Study Agreement between NuCana and the Investigator.

During the study, a monitor from NuCana or appointed CRO will have regular contacts with the study center, for the following:

- Provide information and support to the Investigators.
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the source documents and eCRFs, and that drug accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (*e.g.* clinic charts).
- Record and report any protocol deviations not previously sent to NuCana.
- Confirm AEs and SAEs have been properly documented in the eCRFs and confirm any SAEs have been forwarded to NuCana or designee, and those SAEs that met criteria for reporting have been forwarded to the IRB/EC.

The monitor will be available between visits if the Investigator or other staff needs information or advice.

14.3 Patient Confidentiality

Personal data recorded on all documents will be regarded as highly confidential. To preserve each patient's anonymity, only their patient study number, initials and date of birth (or other

identified as appropriate to country regulations and agreed with NuCana) will be recorded on the eCRFs.

The Investigator site must maintain the patient's anonymity in all communications and reports related to the research. The Investigator site team must keep a separate log of enrolled patients' personal identification details as necessary to enable them to be tracked. These documents must be retained securely, in strict confidence. They form part of the Investigator Site File and are not to be released externally.

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Good Clinical Practice Compliance

NuCana, Investigators, and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with ICH-GCP, US 21 Code of Federal Regulations (CFR) 11, 21 CFR 50, 21 CFR 54, 21 CFR 56, 21 CFR 312 and all other applicable regulations.

15.2 Institutional Review Board/ Ethics Committees

The applicable Institutional Review Boards/ Ethics Committees (IRBs/ECs) will review all appropriate study documentation in order to safeguard the rights, safety, and well being of the patients.

The final study protocol and ICF must be approved in writing by the applicable IRBs/ECs for each site. Written IRB/EC approval must be received by NuCana or appointed CRO before a study center can enroll any patients into the study. In addition, the IRB/EC must approve all advertising used to recruit patients for the study.

In the US, the protocol (and associated documents, including amendments) must be re-approved by the IRB/ECs annually, as local regulations require. Progress reports will be provided to the IRB/EC according to local regulations and guidelines.

15.3 Regulatory Authority Approval

Authorization to conduct the study will be obtained from the applicable Regulatory Authorities prior to initiating the study in each participating country.

15.4 Protocol Amendments

All protocol amendments (and amendments to related study documentation) will be approved by the applicable IRBs/ECs and Regulatory Authorities prior to implementation.

15.5 Protocol Violations and Deviations

The Investigator, or designee, must document and explain in the patient's source documentation any deviation from the approved protocol.

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the Sponsor and the IRB/EC and agreed to by the Investigator or Sub-Investigator. Deviations usually have an impact on individual patients or a small group of patients and do not involve inclusion/exclusion or primary endpoint criteria.

Deviations will be tracked by the CRO along with the corrective and preventative actions by responsible party.

A protocol violation occurs when there is nonadherence to the protocol that results in a significant, additional risk to the patient, when the patient of Investigator has failed to adhere to significant protocol requirements (*e.g.* inclusion/exclusion criteria and the patient was enrolled without prior Sponsor approval), or when there is nonadherence to the FDA or other applicable ICH-GCP guidelines.

The clinical monitor will document protocol violations and deviations throughout the course of monitoring visits. The monitor will notify the Investigators during a visit and in writing of all violations and deviations. The IRB/EC should be notified of all protocol violations and deviations in a timely manner.

15.6 Serious Breaches

A serious breach is defined as a breach of ICH-GCP or the study protocol which is likely to effect to a significant degree the:

- Safety or physical or mental integrity of the patients of the study; *or*
- Scientific value of the study

Investigators will notify the CRO within one working day if any serious breach of ICH-GCP or the protocol is suspected. Upon confirmation of a serious breach, the CRO will notify the applicable Regulatory Authorities. Typically, serious breach notifications should be made within seven days of the CRO becoming aware; however, this timeline may differ as specified by applicable local regulatory requirements.

15.7 Study Reporting Requirements

The Investigator agrees to submit progress reports to their IRB/EC as appropriate. The Investigator also agrees to provide the Sponsor with an adequate report shortly after completion of their participation in the study.

15.8 Financial Disclosure

The Investigators and Sub-Investigators are required to provide financial disclosure information to allow NuCana to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the Investigator and Sub-Investigators must provide NuCana with a commitment to update this information promptly if any relevant changes occur during the course of the investigation and for one year after study completion.

Neither NuCana nor the CRO, Chiltern, is financially responsible for further testing/treatment of any medical condition, which may be detected during the screening process. In addition, in the absence of specific arrangements, neither NuCana nor Chiltern is financially responsible for further treatment of the patient's disease.

15.9 Investigator Documentation

Before beginning the study, each investigative site will have all applicable essential documents available, in accordance with ICH-GCP section 8.2.

15.10 Study Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of NUC-1031 clinical development. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with NuCana. It is the responsibility of NuCana to inform the Investigator or Sub-Investigator or institution as to when these documents no longer need to be retained.

If the Investigator becomes unable for any reason to continue to retain study records for the required period, NuCana should be prospectively notified. The study records must be transferred to a designee acceptable to NuCana, such as another Investigator, another institution, or to an independent third party arranged by NuCana. The Investigator must obtain written permission from NuCana before disposing of any records, even if retention requirements have been met. Retention and storage of central laboratory records supporting PK endpoints and the disposition of samples donated via the study must also comply with applicable legislation.

15.11 Audit and Regulatory Inspection

The Investigator, Sub-Investigators, and institutions involved in the study will permit study-related monitoring, audits, IRB/EC review, and regulatory inspection(s) by providing direct access to all study records. In the event of an audit, the Investigator or Sub-Investigator agrees to allow NuCana, representatives of NuCana, the FDA, or other regulatory agency access to all study records.

The Investigator should promptly notify NuCana and the appointed CRO of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to NuCana.

16 PUBLICATION POLICY

An ICH E3-compliant clinical study report (CSR) will be generated based on the final data listings of this study. The final CSR will be submitted to Regulatory Authorities and IRBs/ECs in accordance with the stipulated timelines.

16.1 Communication of Results by NuCana

NuCana shall publicly disclose study results through posting on ClinicalTrials.gov, the European Clinical Trials Database (EudraCT) and any other applicable public registries in accordance with local laws and regulations.

Final study results will be submitted to ClinicalTrials.gov within one year of the primary completion date, which is defined as ‘the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated’. Final study results will be posted to EudraCT within one year of the end of study date, as defined in this protocol.

16.2 Publication by Investigators

Investigators may not publish or disclose results until the study is completed. In addition, Investigators shall acknowledges that, due to the limited patient population in its treatment group, the data generated from its individual participation in the study and evaluation of its

individual results, may not be sufficient from which to draw any meaningful scientific conclusion.

NuCana will provide authorship rights to Investigators in order of greatest contribution of evaluable patients to the study. Publication of study results may also be described in the agreement between NuCana and each Institution. In addition, NuCana may form a publication committee to evaluate and give approval of any submission for publication.

The proposed publication (manuscript, abstract or poster) or presentation will be provided to NuCana by the Investigator for review and comment at least 60 days prior to the planned submission. The Investigator understands and agrees that participation in the study may involve a commitment to publish the study results in a cooperative publication with other Investigators. No publication of confidential information shall be made without NuCana's prior written approval. The Investigator agrees, upon NuCana's request, to delete any confidential information that may impact intellectual property protection from the proposed publication. Investigators will comply with recognized ethical publications and authorship standards, including Section II of the 'Ethical Considerations in the Conduct and Reporting of Research' of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, established by the International Committee of Medical Journal Editors (http://www.icmje.org/index.html#authorship).

17 REFERENCES

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18 APPENDICES

Appendix 1: Concomitant medications that may prolong QTc interval

Medications with a known risk of torsade de pointes (*i.e.* significant evidence they cause QT prolongation and are associated with a risk of causing torsade de pointes) are listed below.

Appendix 1. Table 1. Drugs known to prolong QT/QTc interval

Generic Name	Brand Names (Partial List)
Amiodarone	Cordarone®, Pacerone®, Nexterone®
Anagrelide	Agrylin®, Xagrid®
Arsenic trioxide	Trisenox®
Astemizole (removed from market)	Hismanal®
Azithromycin	Zithromax®, Zmax®
Bepridil (removed from market)	Vascor®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®, Largactil®, Megaphen®
Cilostazol	Pletal®
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®
Cisapride (removed from market)	Propulsid®
Citalopram	Celexa®, Cipramil®
Clarithromycin	Biaxin®, Prevpac®
Cocaine	Cocaine
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Domperidone (only on non-US market)	Motilium®, Motillium®, Motinorm Costi®, Nomit®
Donepezil	Aricept®
Dronedarone	Multaq®
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®
Erythromycin	E.E.S.®, Robimycin®, EMycin®, Erymax®, Ery-Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythrocin Stearate Filmtab®, Erythrocot®, E-Base®, Erythroped®, Ilosone®, MY-E®, Pediamycin®, Zineryt®, Abboticin®, Abboticin-ES®, Erycin®, PCE Dispertab®, Stiemycine®, Acnasol®, Tiloryth®
Escitalopram	Cipralex®, Lexapro®, Nexito®, Anxiset-E® (India), Exodus® (Brazil), Esto® (Israel), Seroplex®, Elicea®, Lexamil®, Lexam®, Entact® (Greece), Losita® (Bangladesh), Reposil® (Chile), Animaxen® (Colombia), Esitalo® (Australia), Lexamil® (South Africa)
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®
Fluconazole	Diflucan®, Trican®
Gatifloxacin (removed from market)	Tequin®
Grepafloxacin	Raxar®
Halofantrine	Halfan®
Haloperidol	Haldol® (US & UK), Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol® (Germany), Einalon S®, Eukystol®, Halosten®, Keselan®, Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®

Generic Name	Brand Names (Partial List)
Ibutilide	Corvert®
Ibogaine (only on non-US market)	None
Levofloxacin	Levaquin®, Tavanic®
Levomepromazine (only on non-US market)	Nosinan®, Nozinan®, Levoprome®
Levomethadyl (removed from market)	Orlaam®
Levosulpiride (only on non-US market)	Lesuride®, Levazeo®, Enliva® (with rabeprazole)
Mesoridazine (removed from market)	Serentil®
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®, Physeptone®, Heptadon®
Moxifloxacin	Avelox®, Avalox®, Avelon®
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®, Setronax®
Oxaliplatin	Eloxatin®
Papaverine HCl	None
Pentamidine	Pentam®
Pimozide	Orap®
Probucol (removed from market)	Lorelco®
Procainamide	Pronestyl®, Procan®
Propofol	Diprivan®, Propoven®
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®
Roxithromycin (only on non-US market)	Rulide®, Xthrocin®, Roxl-150®, Roxo®, Surlid®, Rulide®, Biaxsig®, Roxar®, Roximycinv®, Roxomycin®, Rulid®, Tirabicin®, Coroxin®
Sevoflurane	Ulane®, Sojourn®
Sotalol	Betapace®, Sotalex®, Sotacor®
Sparfloxacin (removed from market)	Zagam®
Sulpiride (only on non-US market)	Dogmatil®, Dolmatil®, Eglonyl®, Espiride®, Modal®, Sulpor®
Sultopride (only on Non-US market)	Barnetil®, Barnotil®, Topral®
Terfenadine (removed from market)	Seldane®
Terlipressin (only on non-US market)	Teripress®, Glypressin®, Terlipin®, Remestyp®, Tresil®, Teriss® and others
Terodiline (only on non-US market)	Micturin®, Mictrol® (not bethanechol)
Thioridazine	Mellaril®, Novoridazine®, Thioril®
Vandetanib	Caprelsa®

Note: Medicines on this list are reviewed on an ongoing basis to assure that the available evidence supports their continued placement on this list. The list changes regularly and we recommend checking the website at crediblemeds.org for the most up-to-date information. There may be many additional brand names that are not listed on this table.

Disclaimer and Waiver: The information presented is intended solely for the purpose of providing general information about health-related matters. It is not intended for any other purpose, including but not limited to medical advice and/or treatment, nor is it intended to substitute for the users' relationships with their own health care providers. To that extent, by use of this website and the information it contains, the user affirms the understanding of the purpose and releases AZCERT, Inc. from any claims arising out of his/her use of the website and its lists. The absence of drugs from these lists should not be considered an indication that they are free of risk of QT prolongation or torsades de pointes. Many medicines have not been tested for this risk in patients, especially those with congenital long QT syndrome.

Woosley, RL and Romero, KA, www.Crediblemeds.org, QT drugs List, [Accessed February 2017], AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755, USA.

See more at: https://www.crediblemeds.org/#sthash.vzyRSgay.dpuf

Appendix 2: Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

The following paragraphs are a quick reference to the RECIST criteria (v1.1). The complete criteria are available at http://www.eortc.be/RECIST and are included in the published RECIST document:

Eisenhauer *et al*. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45: 228–247.

Measurability of Tumor Lesions at Baseline – Definitions

Measurable disease – the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions – *tumor lesions* that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with chest x-ray, and as ≥10 mm with CT scan or clinical examination [using callipers]. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥10 mm by CT scan). *Malignant lymph nodes* must be ≥15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters) by use of a ruler or callipers. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Non-measurable lesions – all other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Nodes that have a short axis <10 mm at baseline are considered non-pathological and should not be recorded or followed.

Target lesions – when more than one measurable tumor lesion or malignant lymph node is present at baseline all lesions up to *a maximum of 5 lesions total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological nodes must meet the criterion of a short axis of ≥15 mm by CT scan and only the *short* axis of these nodes will contribute to the baseline sum.

At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be calculated and recorded.

Non-target lesions – all non-measurable lesions (or sites of disease) including pathological nodes (those with short axis ≥10 mm but <15 mm), plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

Methods of Measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment arm dependent. While on study, all target lesions recorded at baseline should have their actual measurements recorded on the CRF at each subsequent evaluation, even when very small (*e.g.* 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

Clinical lesions – clinical lesions will only be considered measurable when they are superficial and ≥10 mm as assessed using callipers (*e.g.* skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

Chest X-ray – chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI – CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans). While PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

Ultrasound – ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT should be obtained.

Endoscopy, Laparoscopy – the utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when

biopsies are obtained or to determine relapse in studies where recurrence following complete response or surgical resection is an endpoint.

Tumor markers – tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.

Cytology, Histology – these techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (*e.g.* with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

Tumor Response Evaluation

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below. Complete or PRs may be claimed only if the criteria for each are met at a subsequent time point at least 4 weeks later. Refer to the Tables 1 and 2 below.

Complete Response (CR) – disappearance of all *target* and *non-target* lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures <10 mm (Note: continue to record the measurement even if <10 mm and considered CR). Tumor markers must have normalized. Residual lesions (other than nodes <10 mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted.

Partial Response (PR) – at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non-target lesions must be non-PD.

Stable Disease (SD) – neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD) – at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment, for example where the tumor burden appears to have increased by at least 73% in volume (which is the increase in volume when all dimensions of a single lesion increase by 20%). Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but on further documentation, the earlier date must be used.

Appendix 2. Table 1. 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 at least once ≥4 weeks from baseline
CR	Non-CR/Non-PD	No	PR	Documented at least once ≥4 weeks from baseline
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.				

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point at least 4 weeks later. The best overall response can be interpreted from Appendix 2 Table 2 on the next page.

Appendix 2. Table 2. Response Assessment after Subsequent Scan

Response: First Time Point	Subsequent Time Point	BEST Overall Response	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 is PD.			

Frequency of Tumor Re-Evaluation

Tumors should be assessed at the end of every 2nd cycle.

Date of Progression

This is defined as the first day when the RECIST (v1.1) criteria for PD are met.

Reporting of Tumor Response

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: complete response, partial response, stable disease, progressive disease, early death from malignant disease, early death from toxicity, early death from other cause or unknown (not assessable, insufficient data).

'Early death' is defined as any death occurring before the first per protocol time point of tumor re-evaluation. The responsible investigator will decide if the cause of death is malignant disease, toxicity or other cause. Patients for whom response is not confirmed will be classified as "unknown", unless they meet the criteria for stable disease (or the criteria for partial response in case of an unconfirmed complete response). Patients' response will also be classified as "unknown" if insufficient data were collected to allow evaluation per these criteria.

Appendix 3: FOSI-18 Questionnaire

Below is a list of statements that other people with your illness have said are important.
Please circle or mark one number per line to indicate your response as it applies to <u>the past 7 days.</u>

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy	0	1	2	3	4
DRS-P	GP4	I have pain	0	1	2	3	4
DRS-P	GP6	I feel ill	0	1	2	3	4
	O3	I have cramps in my stomach area	0	1	2	3	4
	HI7	I feel fatigued	0	1	2	3	4
	Cx6	I am bothered by constipation	0	1	2	3	4
	O1	I have swelling in my stomach area	0	1	2	3	4
	C3	I have control of my bowels	0	1	2	3	4
DRS-E	GF5	I am sleeping well	0	1	2	3	4
DRS-E	GE6	I worry that my condition will get worse	0	1	2	3	4
	GP2	I have nausea	0	1	2	3	4
TSE	B5	I am bothered by hair loss	0	1	2	3	4
	GP5	I am bothered by side effects of treatment	0	1	2	3	4
	O2	I have been vomiting	0	1	2	3	4
	BMT15	I am bothered by skin problems	0	1	2	3	4

F W B	BMT5	I am able to get around by myself	0	1	2	3	4
	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

Appendix 4: EQ-5D-5L Questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITES (*e.g.* work, study, housework, family or leisure activities)

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

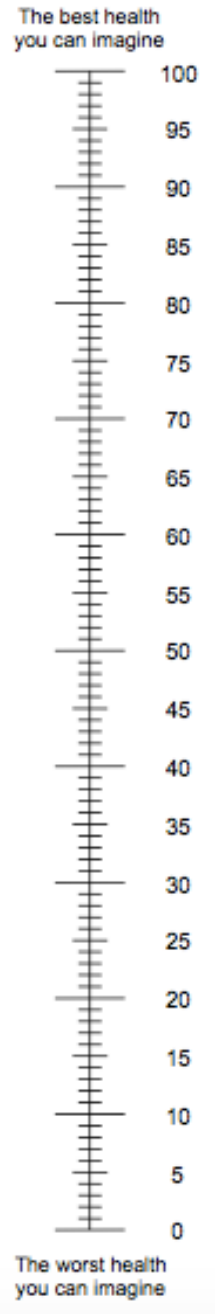
PAIN/DISCOMFORT

I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY/DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
  - 100 means the best health you can imagine.
  - 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.



Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐

Appendix 5: ECOG Performance Scale

Activity Performance Description	Score
Fully active, able to carry out all on all pre-disease performance without restriction.	**0**
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, *e.g.* light housework, office work.	**1**
Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	**2**
Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.	**3**
Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.	**4**
Dead	**5**