CLINICAL STUDY PROTOCOL

A Phase III Open-Label, Multi-Centre, Randomised Study Comparing NUC-1031 plus Cisplatin to Gemcitabine plus Cisplatin in Patients with Previously Untreated Locally Advanced or Metastatic Biliary Tract Cancer

IMP:	NUC-1031
Protocol Number:	NuTide:121
Protocol Version, Date:	Version 4.0, 18 December 2020
Development Phase:	III
IND Number:	139058
EudraCT Number:	2019-001025-28
NCT Number:	NCT04163900
Sponsor:	**NuCana plc** 3 Lochside Way Edinburgh, EH12 9DT, UK Telephone: +44 (0)131 357 1111 Email: NuTide121@nucana.com
Approval:	Elisabeth Oelmann 18. December 2020 Dr Elisabeth Oelmann Date SVP, Clinical & Medical Development NuCana plc
Medical Monitor:	Dr Ettore Mari, MD IQVIA RDS Italy Via Fabio Filzi, 29, 20124 Milan, Italy Telephone: +39 02 2317 0756 Email: ettore.mari@iqvia.com

PRINCIPAL INVESTIGATOR AGREEMENT AND SIGNATURE

A Phase III Open-Label, Multi-Centre, Randomised Study Comparing NUC-1031 plus Cisplatin to Gemcitabine plus Cisplatin in Patients with Previously Untreated Locally Advanced or Metastatic Biliary Tract 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.

- I agree to implement and conduct this clinical study diligently and in strict compliance with the protocol, good clinical practices, and all applicable national, federal and local laws and/or regulations.
- I agree that this clinical protocol will not be modified by me or any member of my staff.
- I certify that neither I nor any member of my staff has been disqualified or debarred by the US Food and Drug Administration (FDA), European Medicines Agency (EMA) or other regulatory bodies for clinical investigations or any other purpose.
- I understand that this protocol and the accompanying clinical Investigator's Brochure contains trade secrets and/or commercial information that are privileged and/or confidential and may not be disclosed unless disclosure is required by national, federal or local laws and/or regulations.

_____ _____

Principal Investigator's signature Date (dd-mmm-yyyy)

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Principal Investigator's name (printed)

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

PROTOCOL SYNOPSIS

Study Title	A Phase III open-label, multi-centre, randomised study comparing NUC-1031 plus cisplatin to gemcitabine plus cisplatin in patients with previously untreated locally advanced or metastatic biliary tract cancer
Protocol Number	NuTide:121
IND Number	139058
EudraCT Number	2019-001025-28
Phase	III
Objectives	**Primary Objectives** • Overall survival (OS) • Objective response rate (ORR) based on blinded independent central review (BICR) in patients with measurable disease at baseline **Secondary Objectives** • Progression-free survival (PFS) based on BICR • Duration of response (DoR) based on BICR • 18- and 12-month survival • Disease control rate (DCR) • Safety • Pharmacokinetics (PK) of NUC-1031 • Patient-reported quality of life (QoL) **Tertiary Objectives** • Health economics • Assessment of tumour cell characteristics that may further an understanding of the mechanism(s) through which the clinical activity of NUC-1031 is achieved
Study Design	This is an open-label, randomised study of NUC-1031 in combination with cisplatin (Arm A) compared to gemcitabine in combination with cisplatin (Arm B), administered on Days 1 and 8 of 21-day cycles, in previously untreated patients with locally advanced or metastatic biliary tract cancer (BTC). Objective disease assessment will be performed by radiologic evaluation and assessed according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria. All known or suspected disease sites must be assessed at baseline by either computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography CT (PET-CT) scan. For each patient, the same radiological method used at baseline must be used for disease assessment throughout the duration of the patient's participation in the study. Tumour measurements and disease response assessments are to be performed every 9 weeks (±7 days) (approximating three cycles) from C1D1 until disease progression. If the patient stops study treatment for

	reasons other than radiologically confirmed progressive disease (PD), tumour measurements and disease response assessments should continue at least every 12 weeks (±14 days) thereafter until PD is radiologically confirmed (regardless of whether any subsequent anti-cancer medication has been prescribed), consent withdrawal, lost to follow up, or death, whichever occurs first. Treatment and study continuation decisions based on radiologic assessments will be made by the treating Investigator. However, primary analyses of data will use BICR assessment of radiologic evaluation, with Investigator assessment serving as a secondary analysis.
Study Centres	This study will be conducted at approximately 130 sites across North America, Europe, and Asia-Pacific.
Endpoints	**Primary Endpoints** • OS, defined as the time from randomisation to the time of death from any cause • ORR, defined as the percentage of patients achieving a confirmed complete or partial response to treatment as assessed by BICR according to RECIST v1.1 criteria. This will be assessed only in patients with measurable disease at baseline. **Key Secondary Endpoint** • PFS, based on BICR according to RECIST v1.1 criteria, defined as the time from randomisation to the first observation of objective tumour progression or death from any cause. For patients with non-measurable disease at baseline, refer to the protocol criteria for disease progression. **Other Secondary Endpoints** **Efficacy** • DoR, as assessed by BICR, defined as the time from initial clinical response (partial response [PR] or complete response [CR] that is subsequently confirmed) to the first observation of tumour progression or death from any cause • 18-month survival • 12-month survival • DCR, based on BICR according to RECIST v1.1 criteria, defined as the percentage of patients demonstrating a Best Overall Response (BOR) of CR, PR, or stable disease (SD) **Safety** Safety and tolerability will be assessed by evaluation of the following: • Treatment-emergent AEs (TEAEs), including TEAEs by severity grade using Common Terminology Criteria for Adverse Events (CTCAE) v5.0 • Serious TEAEs (SAEs) • Deaths due to TEAEs

	• Treatment discontinuations due to TEAEs • Clinically significant changes in laboratory parameters • Changes in Eastern Cooperative Oncology Group (ECOG) status, physical exam, electrocardiogram (ECG) and vital signs A sub-study will be carried out to assess the effect of the NUC-1031 + cisplatin combination on cardiac repolarisation in a subset of patients. **Pharmacokinetics of NUC-1031** Sparse PK sampling will be taken on Cycle 1 Day 1 at the end of infusion, 2 hours after the end of infusion, and 6 hours after the end of infusion, to capture C_{trough} and C_{max} plasma levels. **Patient-Reported Quality of Life** Patient-reported quality of life will be assessed using the European Organisation for Research and Treatment (EORTC) Quality of Life Questionnaire (QLQ-C30) with the QLQ-BIL21 module and the 5-level EuroQol five-dimension scale (EQ-5D-5L). **Tertiary Endpoints** **Health Economics** Health economics will be assessed through collection of core health resource use information, using case report forms (CRFs) to capture procedure codes, days in hospital, and outpatient visits. Health outcomes will be quantified using quality-adjusted life years (QALYs) and a cost-utility analysis will be conducted by creating incremental cost-utility ratios for each of the treatment groups. **Tumour Cell Characteristics** Phenotypic, genotypic, and/or pharmacodynamic characteristics of archival tumour samples that may further delineate the mechanism(s) through which NUC-1031 acts.
Study Population	Patients with histologically- or cytologically-proven biliary adenocarcinoma, including cholangiocarcinoma (intra- and extra-hepatic biliary ducts), gallbladder or ampullary cancer, that is not amenable to surgical resection and who have had no prior systemic chemotherapy for treatment of locally advanced or metastatic disease are eligible. Patients with measurable or non-measurable disease are eligible for study participation in accordance with predefined randomisation strata. In accordance with local standards of care as appropriate, patients may have received prior low-dose chemotherapy in the adjuvant setting and/or radiotherapy with or without radio-sensitising low-dose chemotherapy for localised disease if completed at least 6 months prior to randomisation. Patients must have adequate biliary drainage without evidence of biliary obstruction. Patients whose disease is characterised as combined or mixed hepatocellular/cholangiocarcinoma are not eligible for this study.

Study Treatment	Patients will be randomised to receive either: • NUC-1031 plus cisplatin (Arm A), *or* • Gemcitabine plus cisplatin (Arm B) In Arm A, cisplatin will be administered by intravenous (IV) infusion at 25 mg/m^2 in accordance with local institutional practice for BTC followed by IV infusion of NUC-1031 at 725 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle. In Arm B, cisplatin will be administered by IV infusion at 25 mg/m^2 in accordance with local institutional practice for BTC followed by IV infusion of gemcitabine at 1000 mg/m^2 in accordance with its package insert on Days 1 and 8 of each 21-day cycle.
Inclusion Criteria	1. Written informed consent and authorisation to use and disclose health information. 2. Ability to comprehend and willingness to comply with the requirements of this protocol, including the QoL questionnaires. 3. Female or male patients aged ≥18 years. 4. Histologically- or cytologically-confirmed adenocarcinoma of the biliary tract (including gallbladder, intra and extra-hepatic biliary ducts and ampullary cancers) that is locally advanced, unresectable or metastatic (AJCC edition 8, 2018). Patients with measurable (as per RECIST v1.1 criteria) or non-measurable disease are permitted. 5. Life expectancy ≥16 weeks. 6. ECOG performance status 0 or 1. 7. Adequate biliary drainage with no evidence of ongoing infection. If applicable, treatable and clinically-relevant biliary duct obstruction has been relieved by internal endoscopic drainage/stenting at least 2 weeks previously or by palliative bypass surgery or percutaneous drainage prior to study treatment, and the patient has no active or suspected uncontrolled infection. Patients fitted with a biliary stent should be clinically stable and free of signs of infection for ≥2 weeks prior to study treatment. Patients with improving biliary function who meet all other inclusion criteria may be re-tested during the screening window. 8. Adequate bone marrow, hepatic, and renal function, as evidenced by: • Absolute neutrophil count (ANC) ≥1,500/μL without colony-stimulating factor support • Platelet count ≥100,000/μL • Haemoglobin ≥9 g/dL without need for haematopoietic growth factor or transfusion support in prior 2 weeks • Total bilirubin <2 × upper limit of normal (ULN); does not apply to patients with Gilbert's syndrome. Consistent with inclusion criterion 7, patients whose whole bilirubin and biliary function is recovering may be re-tested during the screening period.

	• Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) <5 × ULN • Creatinine clearance ≥45 mL/min actual or calculated by the Cockcroft-Gault method • International normalised ratio (INR) <1.5 and activated partial thromboplastin time (aPTT) <1.5 × ULN; does not apply to patients on an anti-coagulant with stable dose 28 days prior to first dose. 9. QTc interval <450 msec (males) or <470 msec (females), in the absence of bundle branch block. In the presence of bundle branch block with consequent QTc prolongation, patients may be enrolled based on a careful risk-benefit assessment. 10. Human Immunodeficiency Virus-infected patients who are healthy and have a low risk of Acquired Immunodeficiency Syndrome-related outcomes may be included in this study. 11. Female patients of child-bearing potential (*i.e.*, all women except those who are post-menopausal for ≥1 year or who have a history of hysterectomy or surgical sterilisation) must have a negative pregnancy test within 3 days prior to the first study drug administration. All patients of child-bearing potential must agree to practice true abstinence or to use two highly effective forms of contraception, one of which must be a barrier method of contraception, from the time of screening until 6 months after the last dose of study medication. 12. Male patients with a female partner must either have had a successful vasectomy or they and their female partner meet the criteria above (not of childbearing potential or practicing highly effective contraceptive methods).
Exclusion Criteria	1. Combined or mixed hepatocellular/cholangiocarcinoma. 2. Prior systemic therapy for advanced or metastatic biliary tract cancer. However, prior chemotherapy in the adjuvant setting or low-dose chemotherapy given in conjunction with radiotherapy in the adjuvant setting and completed at least 6 months prior to enrolment is permitted. The following prior interventions are allowed provided the patient has fully recovered: • *Surgery:* non-curative resection with macroscopic residual disease or palliative bypass surgery. Patients who have previously undergone curative surgery must now have evidence of non-resectable disease requiring systemic chemotherapy. • *Radiotherapy:* prior radiotherapy (with or without radio-sensitising low-dose chemotherapy) for localised disease and there is now clear evidence of disease progression requiring systemic chemotherapy. • *Photodynamic therapy:* prior photodynamic therapy for localised disease with no evidence of metastatic disease or for localised disease to relieve biliary obstruction in the presence of metastatic disease provided there is now clear evidence of disease progression requiring systemic chemotherapy.

	• *Palliative radiotherapy:* palliative radiotherapy provided that all adverse events have resolved and the patient has measurable disease outside the field of radiation. 3. Prior treatment with or known hypersensitivity to NUC-1031, gemcitabine, cisplatin or other platinum-based agents or history of allergic reactions attributed to any parenteral excipients (*e.g.,* dimethylacetamide [DMA], Cremophor EL, Polysorbate 80, Solutol HS 15). 4. Symptomatic central nervous system or leptomeningeal metastases. 5. History of other malignancies, except adequately treated non-melanoma skin cancer, curatively treated *in situ* cancer of the cervix, surgically excised or potentially curatively treated ductal carcinoma *in situ* of the breast, or low grade prostate cancer or patients after prostatectomy not requiring treatment. Patients with previous invasive cancers are eligible if treatment was completed more than 3 years prior to initiating the current study treatment, and the patient has had no evidence or recurrence since then. 6. Concurrent serious (as deemed by the Investigator) medical conditions, including, but not limited to, New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome, uncontrolled infection, active hepatitis B or C, or other co-morbid conditions that in the opinion of the Investigator would impair study participation or cooperation. 7. Congenital or acquired immunodeficiency (*e.g.,* serious active infection with HIV). As per inclusion criterion 10, patients with HIV who are healthy and have a low risk of AIDS related outcomes are eligible. 8. Other acute or chronic medical, neurological, or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study. 9. Prior exposure to another investigational agent within 28 days prior to randomisation. 10. Major surgery within 28 days prior to randomisation; patient must have completely recovered from any prior surgical or other procedures. 11. Pregnant or breastfeeding. 12. Residual toxicities from prior treatments or procedures which have not regressed to Grade ≤1 severity (CTCAE v5.0), except for alopecia or Grade ≤2 peripheral neuropathy. 13. Concomitant use of drugs at doses known to cause clinically relevant prolongation of QT/QTc interval. 14. Administration of a live vaccination within 28 days prior to randomisation.

	15. Ongoing or recent (≤6 months) hepatorenal syndrome.
Study Duration Per Patient	Patients will continue to receive study treatment until radiographic documentation of progressive disease, evidence of unacceptable treatment-related AEs despite optimal medical management and/or dose modification, or withdrawal of consent. A patient who is receiving clinical benefit but experiencing toxicity related to the cisplatin component may continue on study receiving single agent NUC-1031 (Arm A) or gemcitabine (Arm B).
Patient Randomisation	Patients will be randomised 1:1 with the following 4 stratification factors: • Measurable disease at baseline (yes, no) as determined by BICR • Metastatic disease at baseline (yes, no) • Tumour location (gallbladder, intra-hepatic, extra-hepatic/ ampullary) • Region (Asia, non-Asia) The number of patients with non-measurable disease at baseline as determined by BICR will be capped at 82 (due to statistical requirements of ORR analysis).
Sample Size and Statistical Considerations	**Analysis Populations** The intention-to-treat (ITT) population will consist of all patients who are randomised, regardless of whether any study medication was received, and patients will be summarised on the basis of the treatment group to which they were randomised. The ITT population with measurable disease at baseline (ITTMD) will consist of the ITT population patients randomised to the stratum corresponding to having measurable disease at baseline (as assessed by BICR). The ITT population will be the primary analysis population for OS and PFS; the ITTMD will be the primary analysis population for evaluating ORR; and DoR will be analysed in the subset of ITTMD patients who have confirmed response. All safety endpoints will be analysed using the Safety population which will consist of all patients who are randomised and receive any study medication, within which patients will be summarised on the basis of the actual study medication received. **Primary Analysis for the Primary Endpoints** OS and ORR are the dual primary endpoints. The study would be viewed as positive (in terms of the primary efficacy endpoints) if statistical significance is obtained on either of the two primary endpoints. Duration of OS is defined as the time from randomisation to the time of death due to any cause. For patients who are alive at the time of a data cut-off or are permanently lost to follow-up, duration of OS will be censored at the date at which they were last known to be alive. The primary analysis of OS will be a stratified log-rank test. A stratified Cox proportional hazards model (including only a term for treatment)

	with Efron's method of handling ties will also be used to estimate the hazard ratio for OS and its associated confidence interval (CI). The Kaplan-Meier method will be used to estimate the survival curves, and the median survival time will be estimated for each treatment group, together with its CI using the Brookmeyer and Crowley method. Estimates of the 25th and 75th percentiles will also be derived together with their corresponding CIs. Subgroup analyses for OS will be carried out for each of the randomisation stratification factors as well as for other important factors. ORR will be determined using RECIST 1.1, as assessed by BICR. Timepoint response categorisation (into CR, PR, SD, PD, or Not Evaluable [NE]) will be carried out in accordance with Table 1 from Appendix 4 of the protocol. Confirmation after at least 28 days is required for CR or PR, and BOR will be determined from BICR timepoint assessments, using the rules given in Table 3 of Appendix 4 of the protocol. In patients who discontinue treatment without progression, timepoint responses will still be considered in the calculation of BOR up until the time that the patient receives a subsequent anti-cancer therapy. ORR based on BICR assessment will then be calculated as the proportion of patients with BOR of CR or PR. The primary analysis of ORR will be based on the stratified Cochran-Mantel-Haenszel (CMH) test. The corresponding odds ratio and its confidence interval will be derived. Counts for patients with a BOR of CR, PR, SD, PD, or NE, based on BICR assessment, will each also be presented. Clopper-Pearson exact 95% two-sided CIs for ORR will be provided separately by treatment group. Subgroup analyses of ORR based on BICR assessment will be provided by primary tumour site (gallbladder, intra-hepatic, extrahepatic, ampullary) and by stage of disease (locally advanced, metastatic). Additional secondary analyses of ORR will be carried out based on Investigator assessment of response. **Interim Analyses and Type 1 Error Control** Three interim efficacy analyses are planned in addition to the final analysis. • The first interim analysis will evaluate the ORR primary endpoint. It will be performed 28 weeks after 418 patients in the measurable disease stratum have been randomised. At this interim a futility analysis will also be conducted based on OS. • The second interim analysis will evaluate the ORR and OS primary endpoints. It will be the final analysis for ORR and the first interim analysis (for demonstration of efficacy) on OS. It will be performed 28 weeks after 644 patients in the measurable disease stratum have been randomised. It is estimated that approximately 425 deaths (67%) will be observed by this time.

	• The third interim analysis will evaluate the OS primary endpoint for which it will be the second interim analysis (for demonstration of efficacy). It will take place after 541 deaths (85%) have been observed. • The final analysis will evaluate the OS primary endpoint. It will take place after 637 deaths (100%) have been observed, and is expected to occur approximately 48.0 months after the first patient is randomised. PFS will be tested only at the second interim analysis, at which time it is estimated that approximately 534 patients will have had a progression or death. The Maurer & Bretz method will be used to provide strong control of Type 1 error across the two primary endpoints and the key secondary endpoint, as well as across the interim analyses. Within this graphical procedure, initially α=0.005 one-sided will be allocated to ORR, α=0.020 one-sided will be allocated to OS, and α=0 will be allocated to PFS. If ORR obtains statistical significance at Interim Analysis 1 or Interim Analysis 2 then OS will be able to be tested using an overall α=0.025 one-sided. In addition, under this graphical procedure, if OS obtains statistical significance then ORR will be able to be tested using an overall α=0.017 one-sided, and PFS will be able to be tested using an overall α=0.008 one-sided. If both ORR and OS or both PFS and OS have then obtained statistical significance, the remaining endpoint (PFS or ORR) will be tested using an overall α=0.025 one-sided. For each primary endpoint a Lan-DeMets O'Brien-Fleming-like α-spending function will be used to control the Type 1 error across the multiple looks. **Sample Size and Power** For OS a hazard ratio of 0.76 has been assumed. With 3 looks (at 67%, 85%, and 100% of the required number of events), an overall α=0.020 one-sided, and 1:1 randomisation, then a total of 637 OS events gives over 90% power. A thirty-month duration of enrolment is assumed with gradual ramp-up over the first 12 months. OS events are assumed to follow an exponential distribution, and a 11.7-month median has been assumed for the control arm as seen in the gemcitabine in combination with cisplatin arm in the ABC-02 trial. The hazard ratio of 0.76 then gives a median of approximately 15.4 months in the NUC-1031 in combination with cisplatin arm. A total of 811 patients would result in the last of the 637 events occurring at approximately 48 months. To allow for 2% of patients being lost to follow-up for OS, a total of 828 patients will be randomised. For ORR a 19% rate is assumed for the control arm. The derivation of this rate from the gemcitabine in combination with cisplatin arms within ABC-02, BT-22, and ABC-03 (allowing now for the requirement of confirmation, based on PS 0 or 1 patients only, including all randomised

	patients in the denominator, excluding patients with non-measurable disease at baseline, and adjusting for use of BICR rather than Investigator assessment) is provided in an appendix to the SAP. For the NUC-1031 in combination with cisplatin arm a 31% ORR is assumed, which gives an assumed true odds ratio of 1.92. With 2 looks for ORR (at 65% and 100%), and with an overall α=0.005 one-sided then a total of 644 patients with measurable disease at baseline (together with 418 at the interim analysis) gives 80% power. The two looks will take place 28 weeks (corresponding to three scheduled post-baseline radiographic scans plus a one week visit window) after the last of these required numbers of patients have been randomised. The number of randomised patients in the stratum for non-measurable disease at baseline is capped at 82 patients (~10%), which therefore gives at least 746 randomised patients in the measurable disease at baseline stratum.

SUMMARY SCHEDULE OF EVENTS

Study assessments	Screening	Cycle 1		Additional cycles		End of treatment	Long-term follow-up
	Day -21 to 0	Day 1	Day 8 (±1 day)	Day 1 (±3 days)	Day 8 (±1 day)	30 days after last dose (±3 days)	Every 12 weeks (±14 days)
Informed consent	X						
Inclusion/exclusion	X						
Randomisation		X[1]					
Demographics	X						
Medical history	X						
Physical examination[2]	X	X[10]		X		X	
ECOG status	X	X[10]		X		X	
Vital signs, height, weight[3]	X	X	X	X	X	X	
12-lead ECG[4]	X	X[4]	X[4]	X[4]	X[4]	X[4]	
Holter ECG[5] (QT sub-study)		X	X	X	X		
Pregnancy test[6]	X	X[10]		X		X	
Haematology and serum chemistry[7]	X	X[10]	X	X	X	X	
Coagulation profile[7]	X	X	X	X	X	X	
Radiologic tumour assessment[8]	X[8]	Every 9 weeks (±7 days) from C1D1 until disease progression					X[11]
PK sampling (Arm A)[9]		X					
Cisplatin administration		X	X	X	X		
NUC-1031 *or* gemcitabine administration		X	X	X	X		
Concomitant medications		X (ongoing)					
Adverse events (NCI CTCAE v5.0)	X	X (ongoing)					
Patient-reported QoL assessment[12]	X	X[10]		X		X	
Health economics[13]	X	X[10]		X		X	
Survival and treatment status							X[14]
Collection of archival tumour specimen	X (may be collected at any time)						

1. Randomisation takes place up to 1 working day prior to administration of study treatment on C1D1.

2. After the screening period, the physical examination may be completed by a qualified designee.

3. Vital signs include respiration rate, pulse, temperature and blood pressure, and must be taken after the patient has been seated or in supine position for 5 minutes. Weight should be recorded at baseline, Day 1 of every cycle and at the end-of-study visit. Documentation of height at baseline only is sufficient.

4. Standard 12-lead ECG measurements must be obtained at screening and prior to dosing on Day 1 in all cycles. ECG measurements should also be taken prior to dosing and within 30 minutes (±5 minutes) post-infusion on C1D1, C1D8, C2D1 and C2D8.

   The ECGs should be performed in triplicate (keeping the leads in place and patient supine for 5 minutes prior to and during readings) and reviewed by the Investigator or a qualified designee. The QTc interval should be calculated for each ECG using the Fridericia formula and averaged.

5. At a subset of sites, a subset of 74 patients (approximately 37 in each treatment group) will participate in a 'robust QT sub-study'. Patients must be supine for at least 5 minutes prior to, and during, the ECG read timepoints detailed below:

ECG timepoint	C1D1	C1D8	C2D1	C2D8
60 minutes pre-infusion		X	X	X
45 minutes pre-infusion	X			
30 minutes pre-infusion	X			
15 minutes pre-infusion	X			
End of infusion	X	X	X	X
10 minutes post-infusion	X	X	X	X
30 minutes post-infusion	X	X	X	X
60 minutes post-infusion	X	X	X	X
2 hours post-infusion	X	X	X	X
24 hours (±30 minutes) post-infusion	X			

6. Serum or urine pregnancy testing is acceptable (women of childbearing potential only).

7. Haematology, serum chemistry and coagulation assessments may be performed up to 3 days prior to scheduled timepoint and must be completed prior to initiation of a new treatment cycle. Haematology parameters include WBC count, differential WBC count, RBC count, haemoglobin, haematocrit, and platelets. Chemistry parameters include 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.

8. Radiologic disease assessment (by CT, MRI, or PET-CT) will be performed at Screening and every 9 weeks (±7 days) from C1D1 until disease progression. Confirmatory scans should be performed at least 28 days and not more than 42 days after initial assessment of response. If a patient is found to have a response at the confirmatory scan which has improved from PR to CR, then the improved response must also be confirmed within a further 28-42 day window. Imaging completed prior to informed consent for routine clinical practice purposes can be used as the Screening radiologic disease assessment provided it was performed as per RECIST v1.1 criteria and within 28 days of randomisation. For each patient, the same imaging modality for disease assessment used at baseline should be used for the duration of the patient's participation. Additional anatomical areas, other than chest, abdomen, and pelvis, should be assessed by CT scan, MRI, or PET-CT in case of suspicion of presence of metastases based on signs, symptoms, biochemical results and/or as standard of care imaging of patients (*i.e.,* non-study related). A recently-biopsied lesion should not be designated as target lesions for the purposes of RECIST v1.1 criteria.

9. Collection of blood for PK analysis will be performed in patients in Arm A only.

A total of 3 blood samples will be collected on C1D1 only:

(i) end of infusion (within 10 minutes)

(ii) 2 hours after end of infusion (±30 minutes)

(iii) 6 hours after end of infusion (±30 minutes)

10. Does not need to be repeated if screening assessment was performed within 3 days of C1D1.

11. Patients withdrawing from study treatment with no radiological evidence of disease progression will undergo radiologic disease assessment at least every 12 weeks (±14 days) until disease progression (regardless of whether any subsequent anti-cancer medication has been prescribed), consent withdrawal, lost to follow up, or death, whichever occurs first. Patients who stop treatment following an unconfirmed response should also still have a confirmatory scan within the pre-specified 28- to 42-day window, if the scan can take place prior to the patient starting any subsequent anti-cancer therapies.

12. QoL will be assessed using the European Organisation for Research and Treatment (EORTC) Quality of Life Questionnaire (QLQ-C30) with the QLQ-BIL21 module and the 5-level EuroQol five-dimension scale (EQ-5D-5L).

Patient-reported QoL data should also be collected at the time of withdrawal from the study.

13. Health economics will be assessed through collection of core health resource use information, using case report forms (CRFs) to capture procedure codes, days in hospital, and outpatient visits.

14. Survival and initiation of new treatments will be assessed every 12 weeks (±14 days) until death. Survival status will also be requested prior to IDMC reviews, prior to each interim analysis, and prior to the final analysis.

ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCO	American Society for Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{0-t}	AUC from time zero to the last measurable concentration
AUC_{0-24}	AUC from time zero to 24 hours
BICR	Blinded independent central review
BOR	Best overall response
BSA	Body surface area
BTC	Biliary tract cancer
BUN	Blood urea nitrogen
CA19-9	Carbohydrate antigen 19-9
CFR	Code of Federal Regulations
CHW	Cui, Hung, and Wang
CI	Confidence interval
C_{max}	Maximum concentration
CMH	Cochran-Mantel-Haenszel
CNAR	Censoring not at random
CR	Complete Response
CRF	Case report form
CRO	Clinical Research Organisation
CSR	Clinical study report
CT	Computed tomography
DCR	Disease control rate
dFdCTP	Di-fluoro-deoxycytidine triphosphate
dFdU	Di-fluoro-deoxyuridine
DMA	Dimethylacetamide
DoR	Duration of response
DSUR	Development safety update report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EORTC	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-5L	5-level EuroQol five-dimension scale
EudraCT	European Clinical Trials Database
FDA	(US) Food and Drug Administration
FIH	First-in-human
G-CSF	Granulocyte colony stimulating factor
GFR	Glomerular filtration rate
IB	Investigator's Brochure

ICF	Informed consent form
ICH-GCP	International Conference on Harmonisation - Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IHC	Intrahepatic cholangiocarcinoma
IMP	Investigational medicinal product
INR	International normalised ratio
IRB/EC	Institutional review board/ ethics committee
ITT	Intention-to-treat
ITTMD	Intention-to-treat with measurable disease at baseline
IV	Intravenous
IxRS	Interactive voice- or web-based response system
LDH	Lactate dehydrogenase
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified intention-to-treat
MRI	Magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not Evaluable
N_{M28}	Number of patients randomised in the measurable disease stratum with the opportunity for ≥28 weeks of follow-up
ORR	Objective Response Rate
OS	Overall Survival
OS12	Proportion of patients alive at 12 months
OS18	Proportion of patients alive at 18 months
PBMC	Peripheral blood mononuclear cell
PD	Progressive Disease
PES	Polyethersulfone
PET	Positron emission tomography
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response
PRES	Posterior reversible encephalopathy syndrome
PV	Pharmacovigilance
PVC	Polyvinylchloride
PVDF	Polyvinylidene fluoride
QALY	Quality-adjusted life year
QLQ-BIL21	EORTC questionnaire module for patients with cholangiocarcinoma and gallbladder cancer
QLQ-C30	EORTC questionnaire to assess the quality of life of cancer patients
QoL	Quality of life
RBC	Red blood cells
RECIST	Response Evaluation Criteria in Solid Tumours (version 1.1)
RMST	Restricted man survival time
RPSFT	Rank-preserving structural failure time
RP2D	Recommended Phase II Dose
RSI	Reference Safety Information
SAE	Serious adverse event

SAP	Statistical analysis plan
SD	Stable Disease
SOC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TMG	Trial management group
ULN	Upper limit of normal
WBC	White blood cell

1 INTRODUCTION AND STUDY RATIONALE

1.1 Biliary Tract Cancer

Biliary tract cancer (BTC) encompasses a group of rare, highly fatal malignancies of the biliary system originating from the epithelium of the intra- and extra-hepatic biliary ducts, the gallbladder, and the cystic duct. Malignancies arising in the biliary tract include cholangiocarcinomas, gallbladder cancers, and carcinomas of the ampulla of Vater. These are most commonly identified histologically as adenocarcinomas (Sohal *et al*, 2016) and have the same underlying pathophysiology (Hennedige *et al*, 2014). Similar to pancreatic cancer, BTC is associated with the development of a dense stroma that contributes to a complex tumour microenvironment. This stroma not only promotes cancer development and progression but also confers resistance to chemotherapy treatment (Gentilini *et al,* 2018).

BTC is most prevalent in patients between 50 and 70 years of age, with a higher incidence in males for cholangiocarcinoma and ampullary carcinomas, and in females for gallbladder cancers. Although >90% of BTCs are adenocarcinomas, additional histological subtypes such as squamous, neuroendocrine tumours, lymphomas or sarcomas (Gourgiotis *et al*, 2008; Gatto & Alvaro, 2010) are also observed. BTC is usually advanced at the time of diagnosis (Hennedige *et al*, 2014) and progresses quickly, leading to cachexia and inanition with a consequent rapid decline in performance status (Harrington *et al,* 2018). Without treatment, patients with advanced BTC have a short survival time of just 3-4 months (Patel, 2011). The prognosis of patients diagnosed with locally advanced or metastatic BTC is poor and is dictated primarily by factors such as tumour size, lymph node invasion and vascular invasion. The 5-year survival rates for stage III and IV are 10% and 0%, respectively (AJCC, 2010). Thus, new therapies are urgently required within this area of unmet medical need.

1.2 Treatment Options for Locally Advanced or Metastatic BTC

Despite a relatively low incidence, BTC is aggressive and associated with a high mortality rate. These cancers are generally diagnosed in advanced stages when surgical resection is not feasible and palliative chemotherapy is the only treatment available. Surgical resection is possible in only a limited number of patients, most of whom experience recurrence (Ghidini *et al*, 2019). The most effective chemotherapy drugs for the treatment of BTC are gemcitabine, platinum agents and fluoropyrimidines (NCCN, 2019; Eckel & Schmid, 2007; Tsavaris *et al*, 2004). Furthermore, double-agent chemotherapy in the first-line setting has shown improvement in Objective Response Rate (ORR), Overall Survival (OS) and quality of life (QoL) compared with single-agent therapy (Eckel & Schmid, 2007; Ciombor & Goff, 2013).

1.3 Gemcitabine with cisplatin in BTC

There is no approved therapy for the treatment of BTC, but the combination of gemcitabine with cisplatin has been established as the standard of care (SOC; gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 administered by IV infusion on Days 1 and 8 every 21 days) on the basis of clinical studies. European Society for Medical Oncology (ESMO) clinical practice guidelines identify the combination of gemcitabine with cisplatin as the SOC for first-line therapy of patients with locally advanced or metastatic disease (Valle *et al*, 2016). Furthermore, the combination of gemcitabine and cisplatin is recognised by the NCCN as a Category 1 recommendation for the first-line treatment of patients with BTC (NCCN, 2019).

There have been only three published randomised studies evaluating the clinical activity of gemcitabine in combination with cisplatin at the SOC regimen in the first-line setting of BTC (Okusaka *et al*, 2010; Valle *et al*, 2010; Valle *et al*, 2015). The reported ORR (based on unconfirmed responses) from these studies ranged from 18.5–26.1%. These studies each used a different definition of the population of patients from which ORR (based on unconfirmed responses) was calculated, and when adjustments are made to allow for this, the ORR results from these three studies were still similar. The median OS across the three studies was consistent, ranging from 11.2–11.9 months.

1.3.1 Gemcitabine Resistance

Gemcitabine is associated with key cancer resistance mechanisms, which may result in limited efficacy in patients with BTC. These resistance mechanisms include:

- Inefficient uptake into cells requiring active membrane transporters, which limits the ability of gemcitabine to reach its 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 in the plasma and intracellularly prior to being phosphorylated, thus rendering the drug inactive (Kroep *et al*, 1998)

1.4 NUC-1031

NUC-1031 is a new chemical entity resulting from the phosphoramidate transformation of gemcitabine. NUC-1031 is synthesised as a pre-activated molecule bearing one protected phosphate group, termed the phosphoramidate motif, imparting several potential advantages over gemcitabine (Slusarczyk *et al*, 2014):

- NUC-1031 is more efficiently taken up by cells as it does not rely on nucleoside transporters to cross the cellular membrane, due to its lipophilicity
- 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 potentially toxic metabolites.

1.4.1 Non Clinical Data

NUC-1031 has shown *in vitro* efficacy against a range of cancer cell lines, including biliary tract, pancreatic, bladder, prostate, breast, non-small cell lung and colon. The *in vitro* studies showed a consistent increase in cytotoxicity of NUC-1031 compared to gemcitabine controls (half-maximal effective concentration 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 tumour 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, four-week toxicity, and thirteen-week toxicity studies have shown that NUC-1031 has an acceptable safety profile when administered once-weekly up to 12 mg/kg/day. The main findings included evidence of gastrointestinal mucosal irritation, suppression of the haematopoietic system, lymphoid atrophy and thymic atrophy, as well as minimal effects in the testes of male dogs. Data from genotoxicity studies suggest that NUC-1031 is only weakly genotoxic and significantly less so than gemcitabine. Further non clinical data can be found in the NUC-1031 Investigator's Brochure (IB).

1.4.2 Clinical Data

Four clinical studies with NUC-1031 have been completed, including the first-in-human (FIH) study in 68 patients with advanced solid tumours receiving NUC-1031 as a single agent (PRO-001; NCT01621854), a study in 25 patients with recurrent ovarian cancer receiving NUC-1031 in combination with carboplatin (PRO-002; NCT02303912), a study in 21 patients with locally advanced or metastatic BTC receiving NUC-1031 in combination with cisplatin (ABC-08; NCT02351765), and a study in 51 patients with platinum-resistant ovarian cancer (PRO-105; NCT03146663; pending final study report). Data from these completed studies are summarised below in Sections 1.4.2.1, 1.4.2.2, and 1.4.2.3.

There is one ongoing NUC-1031 study in metastatic pancreatic carcinoma (ACELARATE; ISRCTN 16765355). Available clinical data from ACELARATE can be found in the NUC-1031 IB.

1.4.2.1 PRO-001: First-in-Human Study in Advanced Solid Tumours

The FIH Phase I study recruited 68 patients with advanced solid tumours (Blagden *et al*, 2018). Single-agent NUC-1031 at doses ranging from 375 mg/m^2 to 1,000 mg/m^2 was shown to be well-tolerated with 8 dose-limiting toxicities (4 events of Grade 3 alanine aminotransferase [ALT] elevations, 2 events of Grade 4 thrombocytopaenia, and 1 event each of Grade 4 neutropaenia and posterior reversible encephalopathy syndrome) observed in 4 patients at doses of 725 mg/m^2 and above. Patients received a median of 3 cycles of NUC-1031 (range <1-19 cycles). Best Overall Response (BOR), assessed by RECIST v1.1, demonstrated that 5 patients achieved a PR and 33 patients achieved Stable Disease (SD), resulting in a Disease Control Rate (DCR) of 78% (38/49 evaluable patients). The Progression-Free Survival (PFS) ranged from 1 to 25 months; however, the study design did not incorporate follow-up visits after the end of treatment and so the actual PFS may have been longer.

A total of 18 patients with gynaecological cancer (11 ovarian cancer, 3 endometrial cancer, and 2 each of cervical cancer and fallopian tube cancer) were treated on the PRO-001 study, of whom 14 were evaluable for response, defined as having received ≥2 cycles and a post-treatment objective disease assessment. In this subset, two patients achieved a PR and a further 11 patients achieved SD, resulting in a DCR of 93%. The PFS ranged from 1.6 to 11.3 months, although is likely to be an underestimate.

1.4.2.2 PRO-002: NUC-1031 Combination with Carboplatin in Recurrent Ovarian Cancer

Data from the gynaecological cancer subset of patients in the PRO-001 study formed the basis for a completed Phase Ib dose escalation study of NUC-1031 in combination with carboplatin in patients with recurrent ovarian cancer (PRO-002; Blagden *et al*, 2017).

Escalating doses of NUC-1031 from 500 mg/m^2 to 750 mg/m^2 on Days 1 and 8 were combined with carboplatin at an area under the curve (AUC) of 4 or 5 on Day 1 of 21-day cycles. Patients

could receive a maximum of 6 cycles of treatment. A total of 25 patients were enrolled and most completed all 6 cycles of chemotherapy. The tolerability of the combination was good and there were no unexpected adverse events (AEs). Of the 25 patients recruited, 23 were evaluable for response, defined as having received ≥1 cycle of treatment and having undergone a post-treatment objective disease assessment. In this population, 1 patient experienced confirmed CR, 8 patients experienced PR (4 confirmed), and 13 patients had SD. The DCR was 96% and the ORR was 39% in the evaluable patient population.

1.4.2.3 ABC-08: NUC-1031 Combination with Cisplatin in BTC

Study Design

ABC-08 is a recently completed open-label, Phase Ib study of NUC-1031 in combination with cisplatin in patients with previously untreated locally advanced or metastatic BTC (McNamara *et al*, 2020). The study explored NUC-1031 administered at 625 mg/m^2 (Cohort 1 and Expansion Cohort) or 725 mg/m^2 (Cohort 2) in combination with cisplatin at 25 mg/m^2, on Days 1 and 8 of 21-day cycles. The starting dose was 625 mg/m^2, with dose escalation evaluated in a traditional 3+3 design.

The purpose of this study was to provide proof-of-concept for the efficacy and safety of NUC-1031 in combination with cisplatin and to determine the dose to carry forward into further clinical development in the treatment of patients with advanced/metastatic BTC.

The primary objectives were to assess the safety and determine the recommended Phase II dose (RP2D) of NUC-1031 in combination with cisplatin in patients with advanced BTC. The secondary objectives were to assess the anti-tumour activity and to explore the pharmacokinetic (PK) profile of the combination.

Patients enrolled in the study were males or females aged ≥18 years with non-resectable or recurrent/metastatic histologically- or cytologically-verified cholangiocarcinoma, gallbladder, or ampullary carcinoma who had not received prior systemic therapy and who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 and a life expectancy of >3 months.

Patient Disposition

A total of 21 patients were enrolled across Cohort 1 (625 mg/m^2, n=8), Cohort 2 (725 mg/m^2, n=6), and the Expansion Cohort (625 mg/m^2, n=7) forming the ITT population. Across all cohorts, the median age was 61 years (range 47–78 years) and all patients were Caucasian. Thirteen male and eight female patients with the following subtypes of BTC were included: 7 hilar, 5 distal bile duct, 5 intrahepatic, 2 ampullary, and 2 gallbladder. The majority of patients (n=17) had metastatic disease.

Safety Results

Patients in the 625 mg/m^2 cohorts received a median of 6 cycles (range 1-12 cycles) and patients in the 725 mg/m^2 cohort received a median of 7.5 cycles (range 1-14 cycles) of study treatment. The combination was well-tolerated, with no unexpected events and no patients discontinuing due to toxicities. The most frequently reported Grade 3/4 treatment-emergent AEs (TEAEs) included increased gamma-glutamyltransferase (48%), fatigue (19%), neutropaenia (19%), increased ALT (14%), decreased white blood cells (14%), and thrombus (14%). This is similar to the safety profile reported for gemcitabine in this patient population.

Efficacy Results

Of the 21 patients in the ITT population, 5 patients did not meet the criteria for inclusion in the efficacy evaluable population (patients with measurable disease who received at least one cycle of study treatment and had at least one follow-up radiographic scan); thus, 16 patients were efficacy evaluable. In the efficacy evaluable population, an ORR (based on unconfirmed responses) of 44% was achieved (1 CR and 6 PRs). In addition, 6 patients had SD, resulting in a DCR of 81% (13 of 16 patients). One further patient, who was initially assessed as having measurable disease at baseline, acheived a PR with a 67% reduction in the volume of target lesions based on Investigator assessment. However, the baseline target lesion was subsequently reclassified as non-measurable by the Sponsor resulting in the exclusion of the patient from the evaluable population. Furthermore, one patient with SD, whose tumour was initially considered unsuitable for surgical resection, became eligible for complete resection following treatment with NUC-1031 in combination with cisplatin and underwent surgery that resulted in complete removal of the tumour.

The relative changes in tumour measurements per best response to treatment in the efficacy evaluable patients are shown in Figure 1. Ten of the 16 evaluable patients had tumour shrinkage and all five BTC subtypes were sensitive to NUC-1031 in combination with cisplatin.

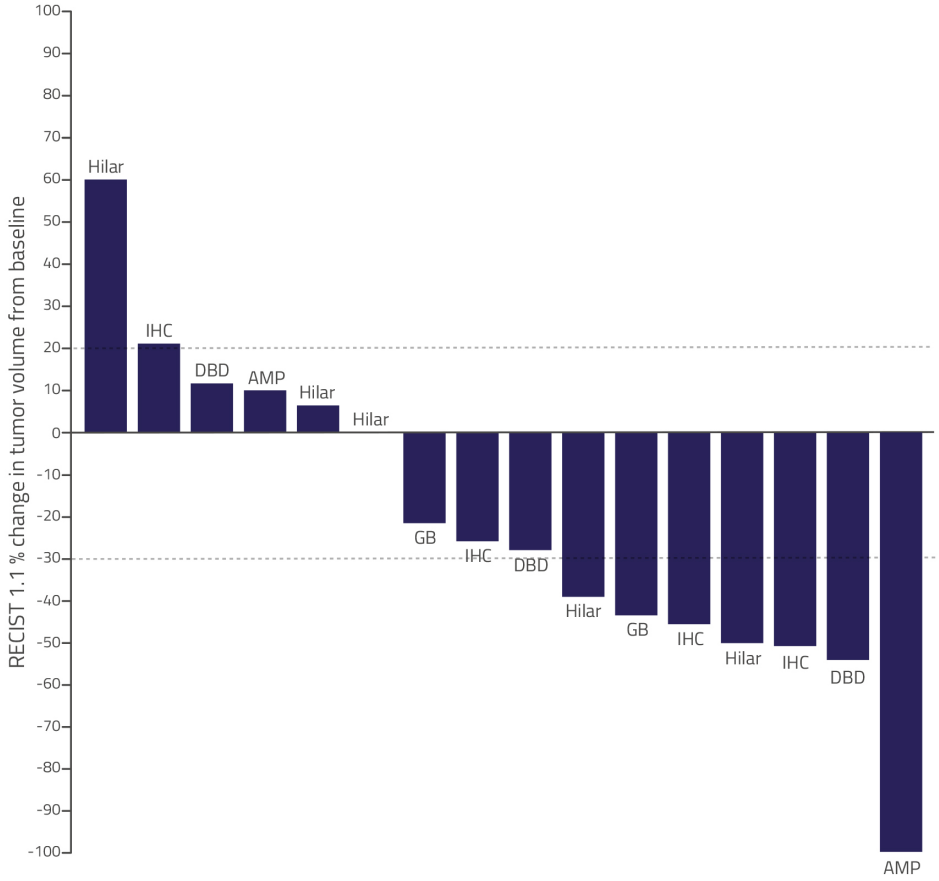

Figure 1 Best response to treatment with NUC-1031 in combination with cisplatin in efficacy evaluable patients (ABC-08 study)

Abbreviations: AMP=ampullary; DBD=distal bile duct; GB=gallbladder; IHC=intrahepatic.
The cholangiocarcinoma grouping includes DBD, hilar, and IHC. The dashed lines at 20% and -30% represent the cut-offs for progressive disease and partial response, respectively, according to RECIST v1.1.

In the ITT population (n=21), 1 patient had a CR and 6 patients had PRs, resulting in an ORR (based on unconfirmed responses) of 33%. In addition, 9 patients had SD, resulting in a DCR of 76%.

The encouraging response rate observed in this study, although in a small number of patients, compares favourably with the 18.5–26.1% response rates in efficacy evaluable populations observed in prior studies with the standard of care gemcitabine and cisplatin regimen. This improvement in ORR suggested that the combination of NUC-1031 and cisplatin may represent a more effective therapeutic regimen for patients with locally advanced or metastatic BTC, thereby addressing a critical unmet medical need.

1.4.3 Pharmacokinetics

The disposition of NUC-1031 and its metabolites in plasma, peripheral blood mononuclear cells (PBMCs), and urine following intravenous (IV) administration of NUC-1031 was investigated in the PRO-001 study (Blagden *et al*, 2018).

- 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 maximum concentration [C_{max}]) increased with increasing dose in an approximately dose proportional manner
- The predominant intracellular metabolite generated was di-fluoro-deoxycytidine triphosphate (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} in PBMCs following NUC-1031 administration was 217-times higher than that observed with gemcitabine
    - The median intracellular dFdCTP AUC_{0-24} in PBMCs following NUC-1031 administration was 139-times higher than that observed with gemcitabine
    - NUC-1031 administration resulted in intracellular dFdCTP concentrations throughout the following 24-hour period that were 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 di-fluoro-deoxyuridine (dFdU); urinary excretion of NUC-1031 and di-fluoro-deoxycytidine 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-tumour activity.

A comparison of the PK parameters from the ABC-08 study of NUC-1031 in combination with cisplatin (25 mg/m^2) in patients with BTC or the PRO-002 study of NUC-1031 in combination with carboplatin (AUC 4-5) in patients with recurrent ovarian cancer with those generated during monotherapy (PRO-001 study) indicate that the combination with either cisplatin or carboplatin does not alter the PK profile of NUC-1031.

1.5 NuTide:121 Study Rationale

Gemcitabine in combination with cisplatin prolongs the survival of patients with advanced BTC over gemcitabine alone, as demonstrated in the ABC-02 study (Valle *et al*, 2010). Efficacy was similar across the main subgroups in this study, including intra- and extra-hepatic cholangiocarcinoma and gallbladder cancer, as well as in Western and Asian patient populations, as demonstrated in a second study with identical design conducted in Japan (Okusaka *et al,* 2010; Valle *et al*, 2014).

Gemcitabine in combination with cisplatin has been established as the SOC for the first-line treatment of patients with BTC and is recognised by the National Comprehensive Cancer Network (NCCN) as a Category 1 recommendation for this patient group (NCCN, 2019). However, median survival time is very modest at less than 1 year. NUC-1031 is a new chemical entity resulting from the phosphoramidate transformation of gemcitabine, specifically designed to bypass the inherent or acquired cancer cell resistance pathways that severely limit the efficacy of gemcitabine and add to its toxicity. The combination of NUC-1031 and a platinum agent appears from our clinical studies to be very effective. The clinical activity of NUC-1031 in combination with cisplatin in patients with locally advanced or metastatic BTC was evaluated as first-line therapy in the ABC-08 study (McNamara *et al*, 2020). The observed improvement in ORR indicates that NUC-1031 in combination with cisplatin may represent a more effective first-line treatment for patients with locally advanced or metastatic BTC than gemcitabine in combination with cisplatin, thus addressing a significant unmet medical need.

On the basis of regulatory feedback and review of the ABC-08 data, NuCana designed the NuTide:121 study. Given that BTC is a rare disease for which there is currently no approved therapy, progression to a Phase III pivotal study on the foundation of promising Phase Ib data is justified in this indication in which new therapies are urgently required. NUC-1031 in combination with cisplatin has the potential to prolong survival over the SOC regimen as it is designed to overcome the key cancer resistance mechanisms associated with gemcitabine.

NuTide:121 is a 1:1 randomised study designed to compare NUC-1031/cisplatin (Arm A) to the gemcitabine/cisplatin SOC (Arm B) and is designed to detect a clinically meaningful improvement in ORR and OS.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives

- OS
- ORR based on blinded independent central review (BICR) in patients with measurable disease at baseline

2.2 Secondary Objectives

- PFS based on BICR
- Duration of response (DoR) based on BICR
- 18- and 12-month survival
- DCR based on BICR
- Safety
- PK of NUC-1031

- Patient-reported QoL

2.3 Tertiary Objectives

- Health economics
- Assessment of archival tumour sample characteristics that may further an understanding of the mechanism(s) through which the clinical activity of NUC-1031 is achieved

2.4 Primary Endpoints

- OS, defined as the time from randomisation to the time of death from any cause
- ORR, defined as the percentage of patients achieving a confirmed complete or partial response to treatment as assessed by BICR according to RECIST v1.1 criteria. This will be assessed only in patients with measurable disease at baseline.

2.5 Secondary Endpoints

2.5.1 Key Secondary Endpoint

- PFS, based on BICR according to RECIST v1.1 criteria, defined as the time from randomisation to the first observation of objective tumour progression or death from any cause. For patients with non-measurable disease at baseline, refer to the protocol criteria for disease progression (Section 11).

2.5.2 Other Secondary Endpoints

Efficacy

- DoR, as assessed by BICR, defined as the time from initial clinical response (PR or CR that is subsequently confirmed) to the first observation of tumour progression or death from any cause
- 18-month survival
- 12-month survival
- DCR, based on BICR according to RECIST v1.1 criteria, defined as the percentage of patients demonstrating a BOR of CR, PR, or SD

Objective disease assessment will be performed radiologically and assessed according to RECIST v1.1 criteria. Treatment and study continuation decisions based on radiologic assessments will be made by the treating Investigator.

Safety

Safety and tolerability will be assessed by evaluation of the following:

- TEAEs, including TEAEs by severity grade using Common Terminology Criteria for Adverse Events (CTCAE) v5.0
- Serious TEAEs (SAEs)
- Deaths due to TEAEs
- Treatment discontinuations due to TEAEs
- Clinically significant changes in laboratory parameters
- Changes in ECOG status, physical exam, electrocardiogram (ECG) and vital signs

A sub-study will be carried out to assess the effect of the NUC-1031 + cisplatin combination on cardiac repolarisation in a subset of patients.

Pharmacokinetics of NUC-1031

Sparse PK sampling will be taken on Cycle 1 Day 1 at the end of infusion, 2 hours after the end of infusion, and 6 hours after the end of infusion, to capture C_{trough} and C_{max} plasma levels. See Section 7.2 for PK sampling details.

Patient-Reported QoL

Patient-reported QoL will be assessed using the European Organisation for Research and Treatment (EORTC) QoL Questionnaire (QLQ-C30) with the QLQ-BIL21 module (Appendix 1) and the 5-level EuroQol five-dimension scale (EQ-5D-5L; Appendix 2).

2.6 Tertiary Endpoints

Health economics

Health economics will be assessed through collection of core health resource use information, using case report forms (CRFs) to capture procedure codes, days in hospital, and outpatient visits. Health outcomes will be quantified using quality-adjusted life years (QALYs) and a cost-utility analysis will be conducted by creating incremental cost-utility ratios for each of the treatment groups.

Biomarkers

Phenotypic, genotypic, and/or pharmacodynamic characteristics of the tumour cell that may further delineate the mechanism(s) through which NUC-1031 acts.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

NuTide:121 is an open-label, randomised Phase III study of NUC-1031 in combination with cisplatin (Arm A) compared to gemcitabine in combination with cisplatin (Arm B), administered on Days 1 and 8 of 21-day cycles, in previously untreated patients with locally advanced or metastatic BTC (Figure 2). A total of 828 patients will be randomised in a 1:1 ratio to Arm A or Arm B, and may continue to receive study treatment until radiographic documentation of disease progression, evidence of unacceptable treatment-related AEs despite optimal medical management and/or dose modification, or withdrawal of consent.

The study will continue until 637 deaths have occurred, unless the results for OS meet the pre-specified criterion at an interim analysis to stop for early demonstration of efficacy, or unless terminated early on the recommendation of the Independent Data Monitoring Committee (IDMC).

The aim of this study is to compare the clinical activity and tolerability of NUC-1031 administered with cisplatin against the current SOC (gemcitabine in combination with cisplatin) in patients with locally advanced or metastatic BTC.

3.2 Rationale for the Doses Selected

3.2.1 Arm A (NUC-1031 + cisplatin)

Patients will receive NUC-1031 at a dose of 725 mg/m^2 and cisplatin at a dose of 25 mg/m^2 on Days 1 and 8 of 21-day cycles. The proposed dose of, and dosing schedule for, NUC-1031 are derived predominantly from clinical data in study ABC-08, supported by Phase I and non clinical data.

In study ABC-08, NUC-1031 at doses of 625 mg/m^2 or 725 mg/m^2 and cisplatin at a dose of 25 mg/m^2 were administered on Days 1 and 8 of 21-day cycles (McNamara *et al,* 2020). The dose of NUC-1031 in Cohort 1 of study ABC-08 was 625 mg/m^2. After expansion of the cohort to 6 patients, the Trial Management Group (TMG) recommended that the dose should increase to 725 mg/m^2. Following review of clinical and PK data, the TMG determined the dose of NUC-1031 for further study as 725 mg/m^2 as patients were able to maintain a higher treatment intensity for longer at this dose. Thus, patients in the 725 mg/m^2 dose group received cumulatively more NUC-1031 and cisplatin when compared to patients in the 625 mg/m^2 dose group, suggesting that the combination is not only tolerable at this dose but also potentially therapeutically advantageous compared to the lower dose. In addition, there was no discernible difference between the two dose groups in safety or PK. The dose selection is further supported by Phase I data from completed studies and Phase III data from an ongoing study in pancreatic cancer.

Single agent NUC-1031 was evaluated in the first-in-human dose escalation study, PRO-001, in solid tumours up to doses of 1000 mg/m^2. In this study, one patient in the 725 mg/m^2 group experienced 2 occurrences of Grade 3 reversible alanine aminotransferase (ALT) elevations, one patient in the 750 mg/m^2 group experienced a reversible Grade 4 thrombocytopaenia, one patient in the 1000 mg/m^2 group experienced 2 occurrences of Grade 3 reversible ALT elevations, and another patient in the 1000 mg/m^2 group experienced reversible Grade 4 thrombocytopaenia, neutropaenia and posterior reversible encephalopathy syndrome (PRES). However, no patients in either the 825 or 900 mg/m^2 cohorts experienced dose-limiting toxicity (DLT). Expansion cohorts at doses of 825 and 900 mg/m^2 enrolled 12 and 9 patients, respectively.

NUC-1031 in combination with carboplatin was evaluated in a Phase Ib study, PRO-002, in patients with recurrent ovarian cancer. In this study, NUC-1031 was administered at doses up to 750 mg/m^2 on Days 1 and 8 of 21-day cycles in combination with carboplatin at AUC4 or 5. The combination was well tolerated, and most treatment-emergent adverse events (TEAEs) resolved allowing patients to continue treatment.

NUC-1031 is also currently being evaluated in a Phase III study, ACELARATE, in patients with advanced pancreatic cancer who are not considered suitable for combination chemotherapy. In this study, NUC-1031 is being administered at a dose of 825 mg/m^2 on Days 1, 8, and 15 of 28-day cycles. The NUC-1031 dose selected for the NuTide:121 study is 725 mg/m^2 on Days 1 and 8 of 21-day cycles, *i.e.,* 3 doses per month at 725 mg/m^2 (2175 mg/m^2/month), which is lower than the dosing regimen already shown to have an acceptable tolerability profile in the pancreatic cancer study (2475 mg/m^2 per month).

Taking all available data into consideration, and after discussion with Investigators in the ABC-08 study and the Chief Investigator for this study, a NUC-1031 dose of 725 mg/m^2 was identified as offering patients the best opportunity for clinical benefit.

3.2.2 Arm B (gemcitabine + cisplatin)

The established SOC regimen will be administered in Arm B, with 1000 mg/m^2 gemcitabine administered in combination with 25 mg/m^2 cisplatin on Days 1 and 8 of 21-day cycles. Treatment will continue until radiographic documentation of objective disease progression, unacceptable treatment-related AEs, or other requirement to discontinue treatment.

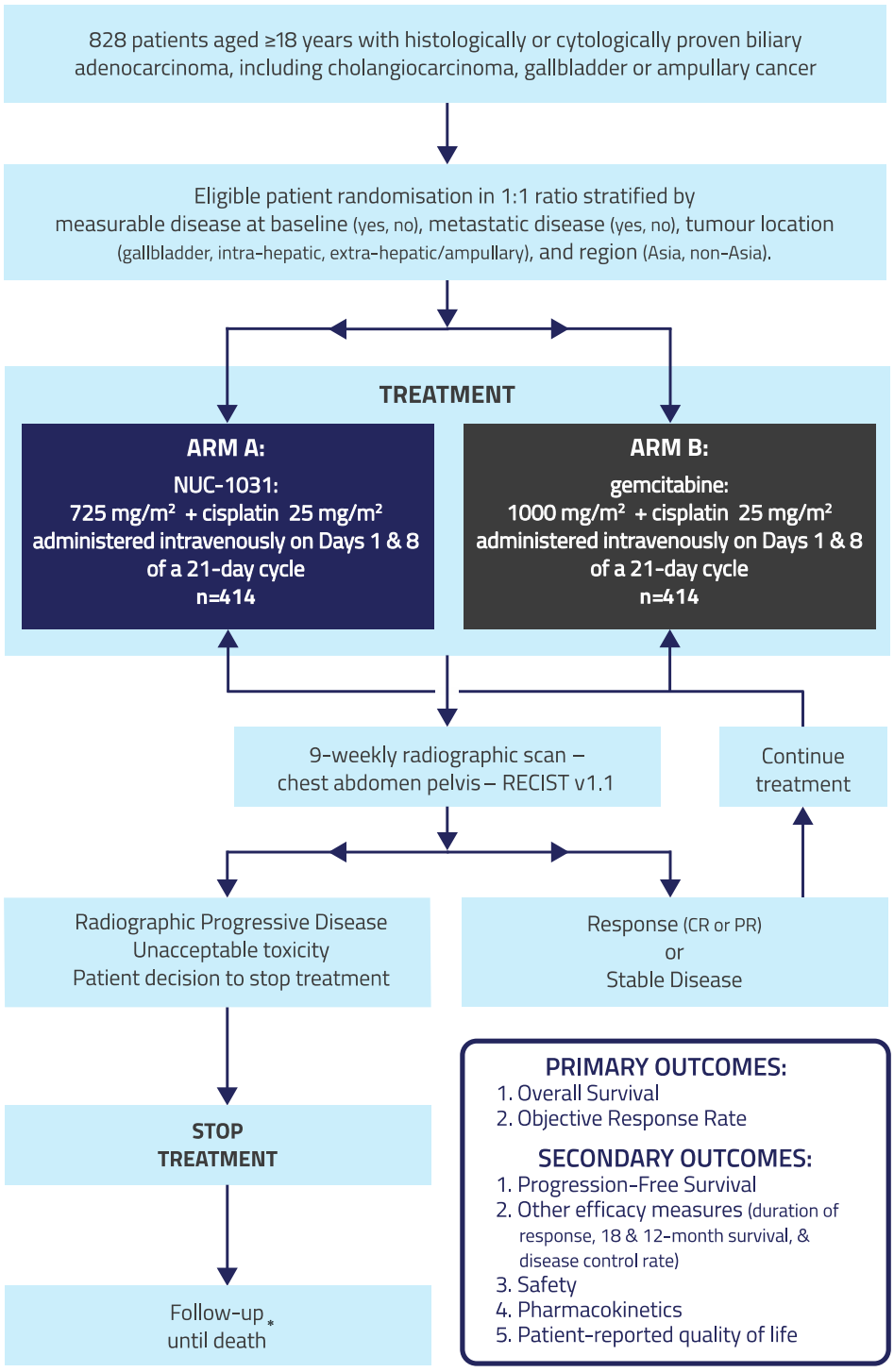

Figure 2 NuTide:121 study schema

*Patients who stop treatment with no evidence of disease progression as defined by RECIST v1.1 criteria will continue to receive scans at least every 12 weeks (±14 days) until radiographic disease progression in order to determine duration of overall response and PFS.

3.3 Study Treatment

Patients who have signed the informed consent and are eligible will be randomised on C1D1 in a 1:1 ratio to receive treatment in Arm A (cisplatin at 25 mg/m^2 followed by NUC-1031 at 725 mg/m^2) or Arm B (cisplatin at 25 mg/m^2 followed by gemcitabine at 1000 mg/m^2) on Days 1 and 8 of a 21-day cycle.

The randomisation process is detailed in Section 8.5 of this protocol. 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 modification must be captured as AEs in the patient medical record and noted on the case report form (CRF).

3.4 Patient Selection and Study Centres

Patients will be randomised in this study from approximately 130 sites in North America, Europe, and Asia Pacific. Patients are eligible for the study if all of the inclusion criteria are met and none of the exclusion criteria apply.

Eligible patients will have histologically- or cytologically-proven biliary adenocarcinoma, including cholangiocarcinoma (intra- and extra-hepatic biliary ducts), gallbladder or ampullary cancer, that is not amenable to surgical resection (please refer to AJCC edition 8, 2018) and will have had no prior systemic chemotherapy for treatment of locally advanced or metastatic disease. Patients with measurable or non-measurable disease are eligible for study participation in accordance with predefined randomisation strata; however, non-measurable disease is limited to 82 patients (due to statistical requirements of ORR analysis). Determination of measurable or non-measurable disease status will be based on BICR assessment.

In accordance with local standards of care as appropriate, patients may have received prior chemotherapy in the adjuvant setting and/or radiotherapy with or without radio-sensitising low-dose chemotherapy for localised disease if completed at least 6 months prior to randomisation. Patients must have adequate biliary drainage without evidence of biliary obstruction. Patients with disease characterised as combined or mixed hepatocellular/ cholangiocarcinoma are *not* eligible for this study.

3.5 Robust QT Sub-study

A sub-study will be carried out to assess any potential effects of the NUC-1031 + cisplatin combination on cardiac repolarisation.

Holter ECG monitoring will be implemented in a subset of patients at a subset of sites to collect QT/QTc data to allow a primary analysis of the QT effect of NUC-1031 in combination with cisplatin relative to the effect of gemcitabine in combination with cisplatin, based on a by-time point analysis. A total of 74 patients (approximately 37 patients in each treatment group) will be enrolled and will have Holter ECGs conducted through the first 2 cycles of treatment. See Section 5.5 for details of ECG read timepoints.

ECGs will be centrally evaluated and measured in a blinded manner. A by-time central tendency analysis will be used as the primary analysis for assessing QTc in the sub-study. Further to this, all ECG parameters will be statistically analysed and described, including categorical outlier analysis for QT/QTc outliers as well as HR, PR and QRS which will be outlined in a separate QT Statistical Analysis Plan. Refer to Sections 5.5 and 12.11 for further details.

3.6 Duration of Patient Participation and Post-Study Care

Patients will continue to receive study treatment until radiographic documentation of objective progressive disease, evidence of unacceptable treatment-related AEs despite optimal medical management and/or dose modification, or withdrawal of consent. Reasons for treatment discontinuation must be captured in the patient medical record and on the Treatment Discontinuation page of the CRF.

A patient who is receiving clinical benefit but experiencing toxicity related to the cisplatin component may continue on study receiving single agent NUC-1031 (Arm A) or gemcitabine (Arm B).

If a patient discontinues treatment without radiological evidence of disease progression, they should continue to undergo tumour assessment at least every 12 weeks (±14 days) until such time as progression can be documented. Patients who stop treatment following an unconfirmed response should also still have a confirmatory scan within the 28- to 42-day window, if the scan can take place prior to the patient starting any subsequent anti-cancer therapies.

Following discontinuation of study treatment, patients will receive treatment in accordance with local standard of care.

3.7 End of Study

The end of study date is defined as the time when 637 deaths have occurred, unless the results for OS meet the pre-specified criterion at an interim analysis to stop for early demonstration of efficacy, or unless the study is terminated early on safety grounds on the recommendation of the IDMC.

Patients who are still receiving benefit from study treatment at the end of study date, or in the event of early termination of the study, may continue study treatment at the discretion of the Investigator and in accordance with local regulations until disease progression or until the drug becomes commercially available and accessible locally. A patient will be eligible to receive study drug after study completion if the following conditions are met:

- There is evidence of continued clinical benefit for the patient and the patient consents to continue with treatment
- There are no appropriate alternative treatment options available to the patient or a change in treatment would pose a risk to the patient
- The patient and his/her doctor comply with and satisfy any legal or regulatory requirements for continuation of study treatment

A patient will not be eligible to receive study drug after study completion if any of the following conditions are met:

- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for locally advanced or metastatic BTC
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for locally advanced or metastatic BTC
- Provision of study drug is not permitted under the laws and regulations of the patient's country

4 PATIENT SELECTION

4.1 Inclusion Criteria

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

1. Written informed consent and authorisation to use and disclose health information.
2. Ability to comprehend and willingness to comply with the requirements of this protocol, including the QoL questionnaires.
3. Female or male patients aged ≥18 years.
4. Histologically- or cytologically-confirmed adenocarcinoma of the biliary tract (including gallbladder, intra and extra-hepatic biliary ducts and ampullary cancers) that is locally advanced, unresectable or metastatic (AJCC edition 8, 2018). Patients with measurable (as per RECIST v1.1 criteria) or non-measurable disease are permitted.
5. Life expectancy ≥16 weeks.
6. ECOG performance status 0 or 1.
7. Adequate biliary drainage with no evidence of ongoing infection. If applicable, treatable and clinically-relevant biliary duct obstruction has been relieved by internal endoscopic drainage/stenting at least 2 weeks previously or by palliative bypass surgery or percutaneous drainage prior to study treatment, and the patient has no active or suspected uncontrolled infection. Patients fitted with a biliary stent should be clinically stable and free of signs of infection for ≥2 weeks prior to study treatment. Patients with improving biliary function who meet all other inclusion criteria may be re-tested during the screening window.
8. Adequate bone marrow, hepatic, and renal function, as evidenced by:

- Absolute neutrophil count (ANC) ≥1,500/μL without colony-stimulating factor support.
- Platelet count ≥100,000/μL.
- Haemoglobin ≥9 g/dL without need for haematopoietic growth factor or transfusion support in prior 2 weeks.
- Total bilirubin <2 × upper limit of normal (ULN); does not apply to patients with Gilbert's syndrome. Consistent with inclusion criterion 7, patients whose whole bilirubin and biliary function is recovering may be re-tested during the screening period.
- ALT and/or AST <5 × ULN
- Creatinine clearance ≥45 mL/min actual or calculated by the Cockcroft-Gault method.
- International normalised ratio (INR) <1.5 and activated partial thromboplastin time (aPTT) <1.5 × ULN; does not apply to patients on an anti-coagulant with stable dose 28 days prior to first dose.

9. QTc interval <450 msec (males) or <470 msec (females), in the absence of bundle branch block. In the presence of bundle branch block with consequent QTc prolongation, patients may be enrolled based on a careful risk-benefit assessment.
10. Human Immunodeficiency Virus (HIV)-infected patients who are healthy and have a low risk of Acquired Immune Deficiency Syndrome-(AIDS) related outcomes may be included in this study.

11. Female patients of child-bearing potential (*i.e.,* all women except those who are post-menopausal for ≥1 year or who have a history of hysterectomy or surgical sterilisation) must have a negative pregnancy test within 3 days prior to the first study drug administration. All patients of child-bearing potential must agree to practice true abstinence or to use two highly effective forms of contraception, one of which must be a barrier method of contraception, from the time of screening until 6 months after the last dose of study medication.
12. Male patients with a female partner must either have had a successful vasectomy or they and their female partner meet the criteria above (not of childbearing potential or practicing highly effective contraceptive methods).

4.2 Exclusion Criteria

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

1. Combined or mixed hepatocellular/cholangiocarcinoma.
2. Prior systemic therapy for advanced or metastatic biliary tract cancer. However, prior chemotherapy in the adjuvant setting or low-dose chemotherapy given in conjunction with radiotherapy in the adjuvant setting and completed at least 6 months prior to enrolment is permitted. The following prior interventions are allowed provided the patient has fully recovered:

- *Surgery:* non-curative resection with macroscopic residual disease or palliative bypass surgery. Patients who have previously undergone curative surgery must now have evidence of non-resectable disease requiring systemic chemotherapy.
- *Radiotherapy:* prior radiotherapy (with or without radio-sensitising low-dose chemotherapy) for localised disease and there is now clear evidence of disease progression requiring systemic chemotherapy.
- *Photodynamic therapy:* prior photodynamic therapy for localised disease with no evidence of metastatic disease or for localised disease to relieve biliary obstruction in the presence of metastatic disease provided there is now clear evidence of disease progression requiring systemic chemotherapy.
- *Palliative radiotherapy:* palliative radiotherapy provided that all AEs have resolved and the patient has measurable disease outside the field of radiation.

3. Prior treatment with or known hypersensitivity to NUC-1031, gemcitabine, cisplatin or other platinum-based agents or history of allergic reactions attributed to any parenteral excipients (*e.g.,* dimethylacetamide [DMA], Cremophor EL, Polysorbate 80, Solutol HS 15).
4. Symptomatic central nervous system or leptomeningeal metastases.
5. History of other malignancies, except adequately treated non-melanoma skin cancer, curatively treated *in situ* cancer of the cervix, surgically excised or potentially curatively treated ductal carcinoma *in situ* of the breast, or low grade prostate cancer or patients after prostatectomy not requiring treatment. Patients with previous invasive cancers are eligible if treatment was completed more than 3 years prior to initiating the current study treatment, and the patient has had no evidence of recurrence since then.

6. Concurrent serious (as deemed by the Investigator) medical conditions, including, but not limited to, New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome, uncontrolled infection, active hepatitis B or C, or other co-morbid conditions that in the opinion of the Investigator would impair study participation or cooperation.
7. Congenital or acquired immunodeficiency (*e.g.,* serious active infection with HIV). As per inclusion criterion 10, patients with HIV who are healthy and have a low risk of AIDS-related outcomes are eligible.
8. Other acute or chronic medical, neurological, or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study.
9. Prior exposure to another investigational agent within 28 days prior to randomisation.
10. Major surgery within 28 days prior to randomisation; patient must have completely recovered from any prior surgical or other procedures.
11. Pregnant or breastfeeding.
12. Residual toxicities from prior treatments or procedures which have not regressed to Grade ≤1 severity (CTCAE v5.0), except for alopecia or ≤Grade 2 peripheral neuropathy.
13. Concomitant use of drugs at doses known to cause clinically relevant prolongation of QT/QTc interval (see Appendix 3).
14. Administration of a live vaccination within 28 days prior to randomisation.
15. Ongoing or recent (≤6 months) hepatorenal syndrome.

4.3 Waivers to Entry Criteria

The Investigator at each study site 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 NuCana before responding to the enquiry.

4.4 Study Completion

The study will continue until 637 deaths have occurred, unless the results for OS meet the pre-specified criterion at an interim analysis to stop for early demonstration of efficacy, or unless the study is terminated early on the recommendation of the IDMC after the interim analysis.

Patients who are still receiving benefit from study treatment at the end of study date, or in the event of early termination of the study, may continue study treatment at the discretion of the Investigator in accordance with local regulations until disease progression or until the drug becomes commercially available and accessible locally.

An AE present at the time of study withdrawal should continue to be assessed for up to 30 days following the last dose of study drug or until resolution to baseline value, whichever occurs first.

These measures should ensure that sufficient information is available to enable assessment of the primary endpoints and other critical secondary endpoints including safety. When the criterion for the interim analysis or final analysis to take place is reached, there will be a data cut-off. In the weeks subsequent to this, a date for database lock will be assigned, and any outstanding queries concerning data elements will be resolved prior to this.

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 STUDY ASSESSMENTS AND PROCEDURES

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 authorised by the Investigator to obtain consent. The Investigator is responsible for ensuring that the study consent procedures comply with International Council for Harmonisation Good Clinical Practice (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.

If new safety information results in significant changes in the risk/benefit assessment, the patient information sheet and associated consent form would be reviewed and updated if necessary. If the patient information sheet and consent form is updated with new safety information, all patients (including those already being treated) would be informed of the new information, given a copy of the revised documents, and asked to re-consent to continue in the study.

5.2 Informed Consent for Collection of Archival Tumour Tissue Specimen, Robust QT Sub-study, and Follow-up of Pregnancy in Partners

During the process described in Section 5.1, patients will also be asked to consent separately to the submission of an archival tumour tissue specimen and participation in the robust QT sub-study (at participating sites only; see Section 3.5 for details of the sub-study). In addition, should the female partner of a male patient become pregnant during his participation in the study, she will be asked to sign a pregnant partners ICF. If the partner agrees, she will be followed up until she gives birth and the health of the baby will be followed up until 6 months of age.

The submission of an archival tumour tissue specimen, generally from diagnosis or resection, is requested to allow for future analyses directed at further understanding and/or confirming the mechanism(s) of action of NUC-1031. The lack of an available archival tissue specimen, or the refusal to consent to submission of a specimen, will not preclude an eligible patient from the study.

In the event that the archival tumour tissue specimen was only recently obtained, the biopsied lesion should not be designated a target lesion for the purposes of RECIST v1.1 criteria unless sufficient time has elapsed that the lesion has fully recovered.

If a primary cancer specimen is unavailable, a specimen from a metastatic site is acceptable. Where local regulations prohibit submission of blocks of tumour tissue, a predetermined number of slides of representative tumour tissue may be substituted in response to this request.

For slide preparation, storage conditions and shipment instructions, please refer to the accompanying Tumour Tissue Laboratory Manual.

Shipment of archival samples can occur at anytime during the study treatment or follow-up periods, as long as the patient does not withdraw consent.

5.3 Screening Assessments

All screening activities must be performed within 21 days prior to C1D1. A Screening Log must be kept of all patients considered for the study (*i.e.,* all patients screened, including 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 Clinical Research Organisation (CRO) upon request, but without patient identifiers.

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. Imaging completed prior to informed consent for routine clinical practice purposes is acceptable provided it was performed as per RECIST v1.1 criteria and within 28 days of randomisation. All protocol-required assessments that are not deemed standard of care should not be performed prior to written informed consent.

Screening assessments of consented patients will be comprised of the following:

- Provision of written informed consent
- Eligibility confirmation, including histological or cytological diagnosis of adenocarcinoma of the biliary tract (please refer to AJCC edition 8, 2018)
- Interactive voice- or web-based response system (IxRS) registration
- Recording of demographic data
- Assessment of medical and surgical history and prior medications
- Routine physical examination
- ECOG performance status
- Assessment of vital signs, including measurement of pulse rate, respiratory rate, blood pressure and temperature, after the patient has been seated or in the supine position for 5 minutes
- Measurement of height and weight

- 12-lead ECG should be performed in triplicate (keeping the leads in place and patient supine for 5 minutes prior to and 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:
    - Haematology: white blood cell (WBC) count, differential WBC count, red blood cell (RBC) count, haemoglobin, haematocrit and platelets
    - Coagulation parameters*:* PT/INR and aPTT
    - Chemistry: sodium, potassium, magnesium, urea or blood urea nitrogen (BUN), creatinine, glucose, phosphate, total protein, albumin, adjusted calcium, total bilirubin, bicarbonate, chloride, uric acid, alkaline phosphatase, AST, ALT and lactate dehydrogenase (LDH)
    - Pregnancy testing: For women of childbearing potential, serum or urine pregnancy must be performed within 3 days prior to C1D1
- Tumour imaging (computed tomography [CT], magnetic resonance imaging [MRI] and/or positron emission tomography CT (PET-CT) of thorax, abdomen and pelvis). Additional anatomical areas, other than chest, abdomen, and pelvis, should be assessed by CT scan, MRI, or PET-CT in case of suspicion of presence of metastases based on signs, symptoms, biochemical results and/or as standard of care imaging of patients (*i.e.,* non-study related). A recently-biopsied lesion should not be designated as target lesions for the purposes of RECIST v1.1 criteria
- Assessment of patient-reported QoL using EORTC QLQ-C30 with the QLQ-BIL21 module (Appendix 1) and the EQ-5D-5L (Appendix 2)
- Assessment of health economics through collection of core health resource use information, using case report forms (CRFs) on days in hospital and outpatient visits
- Collection of archival tissue specimen (may occur at any time during study participation)

Carbohydrate antigen 19-9 (CA19-9) will not be measured as part of the study but may be measured as part of standard of care for the patient.

5.4 Re-Screening Patients Who Fail Inclusion/Exclusion Criteria

If a patient does not meet the inclusion criteria upon first assessment because of residual toxicity from prior therapy or because of laboratory abnormalities, the patient can be reassessed as needed during the 21 day screening period. Patients who fail at re-screening are ineligible and may not be re-screened.

5.5 Robust QT Sub-study

Holter ECG monitoring will be implemented at a subset of sites to collect QT/QTc data for a total of 74 patients (approximately 37 patients in each treatment group) during the first 2 cycles of treatment to allow robust analysis of ECG parameters, including QT/QTc analysis.

A centralised ECG vendor will provide standardised and calibrated Holter ECG equipment to these sites along with training on correct lead positioning, machine use, and transmission of the digital Holter ECG data in real time to the centralised vendor on an ongoing basis. The Holter recording will be reviewed to ensure quality and, if required, issues flagged for purposes of retraining as needed.

ECGs will be taken using a continuous Holter device on Day 1 and Day 8 of Cycle 1 and 2, with readouts at the following timepoints:

ECG timepoint	C1D1	C1D8	C2D1	C2D8
60 minutes pre-infusion		X	X	X
45 minutes pre-infusion	X			
30 minutes pre-infusion	X			
15 minutes pre-infusion	X			
End of infusion	X	X	X	X
10 minutes post-infusion	X	X	X	X
30 minutes post-infusion	X	X	X	X
60 minutes post-infusion	X	X	X	X
2 hours post-infusion	X	X	X	X
24 hours (±30 minutes) post-infusion	X			

Holter devices must be fitted at least 15 minutes prior to the first reading and patients must remain supine for 5 minutes before, and during, each timepoint.

ECGs will be centrally evaluated and measured in a blinded manner. A by-time central tendency analysis will be used as the primary analysis for assessing QTc in the sub-study. Further to this, all ECG parameters will be statistically analysed and described, including categorical outlier analysis for QT/QTc outliers as well as HR, PR and QRS which will be outlined in a separate QT Statistical Analysis Plan.

5.6 Evaluations to Be Performed During the Study

During the treatment period, the assessments detailed in the sections below and summarised in the Summary Schedule of Events will be performed.

5.6.1 Each Cycle, Day 1

All procedures are to be completed prior to dosing, except for post-infusion PK sampling in participating patients. Holter ECG (where applicable), safety ECG, and PK (Arm A only) must be completed in that order. Safety laboratory assessments, physical examination, and patient-reported QoL assessments may be performed up to 3 days prior to Day 1 of each cycle.

- Routine physical examination (may be completed by a qualified designee)
- ECOG performance status
- Assessment of vital signs, including measurement of pulse rate, respiratory rate, blood pressure and temperature, after the patient has been seated or in the supine position for 5 minutes
- Measurement of weight
- For sites participating in the robust QT sub-study, a continuous ECG assessment will be carried out using Holter monitors provided by an ECG vendor. Holter monitors must be fitted at least 15 minutes prior to the first reading.
    - On Cycle 1 Day 1, the Holter monitor will be started 45 minutes before the start of infusion and should run until at least 2 hours after end of infusion and may continue to run until 24 hours after the end of infusion to capture the 24-hour timepoint or may be stopped after the 2-hour timepoint and the patient may be discharged but must return for the 24-hour timepoint where the Holter monitor would be reattached and run for at least 30 minutes to capture the 24-hour timepoint. Patients should remain supine for 5 minutes before, and during, the following timepoints to ensure appropriate reads are available: 45, 30 and 15 minutes before the start of infusion, at the end of infusion, and at 10, 30, 60, 120 minutes, and 24 hours following the end of infusion on Cycle 1 Day 1.
    - On Cycle 2 Day 1, the Holter monitor will be started at a timepoint within 60 minutes before the start of infusion and should run until at least 2 hours after end of infusion. Patients should remain supine for 5 minutes before, and during, the following timepoints to ensure appropriate reads are available: within 60 minutes before the start of infusion, at the end of infusion, and at 10, 30, 60, and 120 minutes following the end of infusion on Cycle 2 Day 1. The Holter monitoring should be stopped and data transmitted as per the central ECG manual. Holter ECGs will be recorded on Day 1 and Day 8 of Cycles 1 and 2 only.
- 12-lead ECGs should be performed prior to beginning treatment, within 30 minutes (±5 minutes) post-infusion on C1D1 and C2D1 only, and prior to initiation of treatment on Day 1 in subsequent cycles. The ECGs should be performed in triplicate (keeping the leads in place and patient supine for 5 minutes prior to and 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:
  - Haematology: WBC count, differential WBC count, RBC count, haemoglobin, haematocrit and platelets
  - Chemistry: sodium, potassium, magnesium, urea or BUN, creatinine, glucose, bicarbonate, chloride, uric acid, phosphate, total protein, albumin, adjusted calcium, total bilirubin, alkaline phosphatase, AST, ALT and LDH
  - Coagulation parameters*:* PT/INR and aPTT
  - Pregnancy testing (serum or urine; for women of childbearing potential)
- Cycle 1 Day 1 only - Blood samples collected for PK assessment (Arm A only). A total of 3 blood samples are collected: (i) end of infusion, (ii) 2 hours after the end of infusion, and (iii) 6 hours after the end of infusion
- Assessment of patient-reported QoL using EORTC QLQ-C30 with the QLQ-BIL21 module (Appendix 1) and the EQ-5D-5L (Appendix 2)
- Assessment of health economics through collection of core health resource use information, using case report forms (CRFs) on days in hospital and outpatient visits
- IV administration of cisplatin followed by NUC-1031 (Arm A) or gemcitabine (Arm B)
- Recording of concomitant medications
- AE recording and causality assessments

5.6.2 Each Cycle, Day 8

All procedures to be completed prior to dosing, except for post-infusion PK sampling. Holter ECG (where applicable) should be completed before safety ECG.

- Assessment of vital signs, including measurement of pulse rate, respiratory rate, blood pressure and temperature, after the patient has been seated or in the supine position for 5 minutes
- For sites participating in the robust QT sub-study, a continuous ECG assessment will be carried out using Holter monitors provided by an ECG vendor. Holter monitors must be fitted at least 15 minutes prior to the first reading. The Holter monitor will be started at a timepoint within 60 minutes prior to infusion and should run until 2 hours after the end of infusion. Patients should remain supine for 5 minutes before, and during, the following timepoints to ensure appropriate reads are available: within 60 minutes before the start of infusion, end of infusion, and at 10, 30, 60, and 120 minutes following the end of infusion. The Holter monitoring should be stopped and data transmitted as per the central ECG manual. Holter ECGs will be recorded on Day 1 and Day 8 of Cycles 1 and 2 only.
- 12-lead ECGs should be performed prior to beginning treatment, within 30 minutes (±5 minutes) post-infusion on C1D8 and C2D8, and prior to initiation of treatment on Day 1 in subsequent cycles. The ECGs should be performed in triplicate (keeping the leads in place and patient supine for 5 minutes prior to and 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:
  - Haematology: WBC count, differential WBC count, RBC count, haemoglobin, haematocrit and platelets
  - Chemistry: sodium, potassium, magnesium, urea or BUN, creatinine, glucose, bicarbonate, chloride, uric acid, phosphate, total protein, albumin, adjusted calcium, total bilirubin, alkaline phosphatase, AST, ALT and LDH
  - Coagulation parameters*:* PT/INR and aPTT
- IV administration of cisplatin followed by NUC-1031 (Arm A) or gemcitabine (Arm B).
- Recording of concomitant medications
- AE recording and causality assessment

5.6.3 End of Treatment Visit

The End of Treatment visit should occur within 30 days (±3 days) of the last administration of study treatment. The assessments should be performed upon discontinuation due to radiographic disease progression or early treatment discontinuation for other reasons (*e.g.,* withdrawal of consent).

- Routine physical examination (may be completed by a qualified designee)
- ECOG performance status
- Assessment of vital signs, including 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 at the end of treatment visit. The ECGs should be performed in triplicate (keeping the leads in place and patient supine for 5 minutes prior to and 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:
  - Haematology: WBC count, differential WBC count, RBC count, haemoglobin, haematocrit and platelets
  - Coagulation parameters*:* PT/INR and aPTT
  - Chemistry: sodium, potassium, magnesium, creatinine, glucose, chloride, phosphate, albumin, adjusted calcium, total bilirubin, alkaline phosphatase, AST, ALT and LDH
  - Pregnancy testing (serum or urine; for women of childbearing potential)
- Assessment of patient-reported QoL using EORTC QLQ-C30 with the QLQ-BIL21 module (Appendix 1) and the EQ-5D-5L (Appendix 2). Patient-reported QoL data should also be collected at the time of withdrawal from the study.
- Assessment of health economics through collection of core health resource use information, using case report forms (CRFs) on days in hospital and outpatient visits

- Recording of concomitant medications
- AE recording and causality assessment

5.6.4 Follow-Up

Patients who stop treatment with no evidence of disease progression as defined by RECIST v1.1 criteria will continue to receive scans at regular intervals (at least every 12 weeks [±14 days]) until radiographic disease progression (regardless of whether any subsequent anti-cancer medication has been prescribed), consent withdrawal, lost to follow up or death, whichever occurs first, in order to determine duration of overall response and PFS. Patients who stop treatment following an unconfirmed response should still have a confirmatory scan within the 28- to 42-day window, if the scan can take place prior to the patient starting any subsequent anti-cancer therapy. If a patient is found to have a response at the confirmatory scan which has improved from PR to CR, then the improved response must also be confirmed within a further 28- to 42-day window, if the scan can take place prior to the patient starting any subsequent anti-cancer therapy.

To ensure current and complete data on ORR for each of the first two interim analyses, in the 6 weeks prior to the scheduled data cut-off date any patients with an unconfirmed response (with no earlier confirmed response) based on Investigator assessment (with no earlier confirmed response) will be identified. For such patients, Investigators will be reminded to schedule the confirmatory radiographic scan as soon after 28 days as possible, provided that the patient has not stopped treatment and started any subsequent anti-cancer therapy.

Patient survival and initiation of new treatments (along with response to these new treatments) will be assessed approximately every 12 weeks (±14 days) until death, in order to determine duration of OS. To ensure current and complete survival data at the time of database locks, updated survival status may be requested prior to but not limited to IDMC review, interim analyses, and the final analysis.

6 PATIENT WITHDRAWAL

6.1 End of Treatment

Study treatment is to be continued until one of the following occurs:

- Progressive Disease (PD) as defined by RECIST v1.1 criteria. Patients should not discontinue treatment because of raised tumour marker levels or other clinical signs of PD until PD has been confirmed by RECIST v1.1 criteria.
- Unmanageable toxicity defined as an AE that is considered by the Investigator to warrant permanent discontinuation of study treatment including the following:
    - AE resulting in a dosing delay of more than 21 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.
- Radiologically-confirmed pneumonitis
- Radiologically-confirmed posterior reversible encephalopathy syndrome (PRES)

- Lack of further clinical benefit or unfavourable risk/benefit profile as judged by the Investigator in consultation with the medical monitor
- Inter-current illness that prevents further administration of study treatment
- 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 and in consultation with the medical monitor, make the patient unsuitable for further treatment with study drugs
- Lost to follow-up
- NuCana request

All study procedures outlined for the End of Treatment visit are to be completed within 30 days (±3 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 in either treatment group who have documented disease progression defined by RECIST v1.1 criteria while receiving study medication will discontinue treatment but will enter the follow-up period. Treatment should not be discontinued because of raised tumour marker levels or other clinical signs of PD until disease status has been assessed by objective measures and PD has been determined by RECIST v1.1 criteria.

Patients in either treatment group who stop treatment with no evidence of disease progression will enter the follow-up period and should attend clinic at least every 12 weeks (±14 days) for follow-up scans, assessments, and information regarding subsequent anti-cancer medications prescribed. This follow-up for both treatment groups should continue (regardless of whether any subsequent anti-cancer medication has been prescribed) until radiographic disease progression or death. Patients in either treatment group who no longer attend clinic every 12 weeks should continue to be followed for progression status (unless progression has already been documented), for details on any new anti-cancer treatments, and for survival status. If a patient in either treatment group becomes uncontactable, then the Investigator should follow up on their status by other means (such as GP contact, next of kin contact), in line with patient consent. Patients who stop treatment following an unconfirmed response should also still have a confirmatory scan within the 28- to 42-day window, if the scan can take place prior to the patient starting any subsequent anti-cancer therapies. If a patient is found to have a response at the confirmatory scan which has improved from PR to CR, then the improved response must also be confirmed within a further 28- to 42-day window, provided that they have not yet started subsequent anti-cancer therapy.

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.

Due to the importance of collection of survival data, if a patient wishes to discontinue from the study, and withdraw consent for further visits and participation, it should be confirmed with them whether they agree for the Investigator to follow up on their status by other means (such as GP contact, next of kin contact) or if they truly wish to withdraw so that no further data is collected on their status. Confirmation of this will be recorded in source data at site.

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 Replacement

Patients that are randomised but not treated will not be replaced. Section 13.1 provides details on patient populations to be used for analysis of all efficacy and safety endpoints.

7 SAMPLES FOR LABORATORY ANALYSIS

7.1 Clinical Laboratory Tests

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

Samples will be analysed for the following parameters:

- Haematology: WBC count, differential WBC count, RBC count, haemoglobin, haematocrit and platelets
- Coagulation parameters*:* PT/INR and aPTT
- Chemistry: sodium, potassium, magnesium, urea or BUN, creatinine, glucose, phosphate, total protein, albumin, adjusted calcium, total bilirubin, bicarbonate, chloride, uric acid, alkaline phosphatase, AST, ALT and LDH

Clinically-significant abnormal laboratory results will be recorded as AEs, see Section 12.2 for further information.

CA19-9 will not be measured as part of the study but may be measured as part of standard of care for the patient.

7.2 Pharmacokinetics

Blood samples for PK analyses will be collected. Blood sampling will be performed for patients in Arm A. The PK sampling scheme is designed to allow for application of a population PK model in order to estimate exposure (*e.g.*, AUC, C_{max}, C_{min}) to NUC-1031, dFdC and dFdU.

Blood samples will be collected on Cycle 1 Day 1 only at the timepoints described in Table 1.

Table 1 PK sampling schedule

Sample 1	**T0 – end of infusion (within 10 minutes)**
Sample 2	**T1 – 2 hours after the end of infusion (± 30 minutes)**
Sample 3	**T2 – 6 hours after the end of infusion (± 30 minutes)**

Standard PK parameters for each compound of interest will be derived from the measured plasma concentrations using a population PK model derived from Phase I data. The results of the PK analyses will be reported separately. The PK samples will be processed and analysed at a central laboratory. Please refer to the Guidelines for Pharmacokinetic Sample Management for details regarding PK sample collection, processing, storage and shipment.

7.3 Collection of Archived Tumour Specimen

Specific instructions on the collection and shipment of tissue samples will be provided in the Tumour Tissue Laboratory Manual.

Tissue samples may be stored for a maximum timeframe in accordance with local regulations following the last patient's last visit for the study at a facility selected by NuCana to enable further analysis of biomarkers.

7.4 Labeling and Confidentiality of Biological Samples

All biological samples sent to analytical laboratories will be labelled with the study number, patient number and date/time taken. Sample labels must not contain any personally identifiable information.

8 STUDY MEDICINAL PRODUCTS

8.1 NUC-1031

NUC-1031 for injection is an investigational medicinal product presented as a sterile solution in clear glass vials at a concentration of 250 mg/mL formulated in DMA and normal saline in the ratio of 80:20. NUC-1031 for injection is not administered directly to patients, but must be diluted into saline to generate a NUC-1031 saline-based formulation.

NUC-1031 saline-based formulation for infusion is prepared by mixing NUC-1031 for injection with a Diluent Solution and subsequent withdrawal of the required dose for addition to the saline infusion bag.

8.1.1 NUC-1031 Supplies and Study Drug Packaging

NUC-1031 for injection is manufactured by NuCana plc and 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 labelled cardboard outer carton, each containing 6 vials.

The Diluent Solution is manufactured by NuCana plc and supplied to the pharmacy of the investigative site and will be 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 labelled cardboard outer carton, each containing 3 vials.

8.1.2 NUC-1031 and Diluent Solution Handling and Storage

NUC-1031 for injection 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 for injection 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 for injection or the Diluent Solution contacts the skin or the mucous membranes, it should be washed immediately and thoroughly.

Due to known issues regarding DMA and its compatibility with polycarbonate, polyvinylchloride (PVC), polyvinylidene fluoride (PVDF) and polyethersulfone (PES), do not use syringes or syringe filters made of these materials in the preparation of the NUC-1031 saline-based formulation.

For additional information on study drug handling including dispensing directions, please refer to the NUC-1031 Pharmacy Manual.

8.1.3 NUC-1031 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 document for information on the preparation of NUC-1031.

8.2 Cisplatin

Cisplatin is commercially available and may be centrally provided by NuCana or sourced locally by investigative sites in accordance with local regulatory requirements. Descriptive information for cisplatin can be found in the package insert and should be stored as detailed on the product label and according to manufacturer's instructions. Further information can be found in the Pharmacy Manual.

For administration, any device containing aluminium that may come in contact with cisplatin (sets for IV infusion, needles, catheters, syringes) must be avoided.

8.3 Gemcitabine

Gemcitabine is commercially available and may be centrally provided by NuCana or sourced locally by investigative sites in accordance with local regulatory requirements. Descriptive information for gemcitabine can be found in the package insert and should be stored as detailed on the product label and according to manufacturer's instructions. Further information can be found in the Pharmacy Manual.

8.4 Treatment Administration

All study drugs will be administered to each patient based on their body surface area (BSA) at baseline. If a patient's weight increases or decreases by ≥10% during the course of the study, the doses of the drugs should be recalculated. The Dubois & Dubois BSA calculation is the preferred method, however other standard calculations can also be used. Sites should document the method used in the electronic CRF (eCRF).

Dubois & Dubois BSA calculation:

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

The drug administration schedule in Arm A and Arm B is shown in Table 2. 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.

Table 2 Drug administration schedule in Arm A and Arm B

Arm	Agent	Dose	Route	Schedule	Duration
A	NUC-1031	725 mg/m^2	IV	D1 and D8 of each 21-day cycle	Until radiographic disease progression or unmanageable toxicity
	Cisplatin	25 mg/m^2	IV		
B	Gemcitabine	1000 mg/m^2	IV		
	Cisplatin	25 mg/m^2	IV		

8.4.1 Arm A (NUC-1031 in combination with cisplatin)

Patients in Arm A will receive cisplatin by IV infusion at 25 mg/m^2 followed by IV infusion of NUC-1031 saline-based formulation at 725 mg/m^2 on Days 1 and 8 of each 21-day cycle.

Cisplatin should be administered in accordance with local institutional practice for BTC, including the use of an appropriate hydration protocol.

Cisplatin administration is then followed by NUC-1031 (725 mg/m^2) administered by IV infusion in 500 mL of 0.9% sterile saline for injection given over 30 minutes. The administration time may be increased to 60 minutes 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.

8.4.2 Arm B (gemcitabine in combination with cisplatin)

Patients in Arm B will receive cisplatin by IV infusion at 25 mg/m^2 followed by IV infusion of gemcitabine at 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle.

Cisplatin should be administered in accordance with local institutional practice for BTC, including the use of an appropriate hydration protocol.

Cisplatin administration is then followed by gemcitabine (1000 mg/m^2) administered by IV infusion in accordance with the package insert.

8.5 Randomisation

Patients may be randomised up to 1 working day prior to C1D1 using an independent IxRS system. At this time, the Investigator will enter into the IxRS system their site information, metastatic disease at baseline (yes, no), and the primary tumour location (gallbladder, intra-hepatic, extra-hepatic or ampullary). The BICR will have already entered into the IxRS system whether the patient has measurable disease at baseline (yes, no). The IxRS will then indicate to which treatment group the patient has been randomised and the study site will obtain the patient's identification number from the IxRS.

The randomisation will be in a 1:1 ratio to receive treatment in Arm A (NUC-1031 plus cisplatin) or Arm B (gemcitabine plus cisplatin). Randomisation will be stratified by the following 4 factors:

- Measurable disease at baseline (yes, no) as determined by BICR
- Metastatic disease at baseline (yes, no)
- Tumour location (gallbladder, intra-hepatic, extra-hepatic/ampullary)
- Region (Asia, non-Asia)

The number of patients with non-measurable disease at baseline as determined by BICR is capped at 82 (due to statistical requirements of ORR analysis).

8.6 Drug Destruction

Used vials should be destroyed in accordance with local procedures and documented in the drug accountability and drug destruction log. Where this is not possible due to local regulations, used vials should be stored on site and returned to NuCana/vendor for destruction. A copy of the disposal certificates should be kept in the study file.

8.7 Drug Accountability

The US Food and Drug Administration (FDA) and other regulatory authorities require accounting of all study drug received by each study site. Records of drug disposition required include the date received by the site, 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 used and unused study drug. Each study site 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. NuCana's designated site monitor will review study drug accountability records and remaining drug supplies during routine monitoring visits.

8.8 Management of Overdose and Medication Errors

Overdoses and errors for all study drugs should be recorded as follows:

1. If an overdose/error occurs in the course of the study, site personnel must inform the Investigator and monitor immediately upon discovery of the event. An overdose/error 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/error with no associated symptoms is only reported on the treatment CRF.
2. All overdoses/errors should be tracked as a deviation.

8.8.1 NUC-1031

The dose of NUC-1031 for administration on this protocol is 725 mg/m^2. In the Phase I first-in-human study, the highest dose studied was 1,000 mg/m^2. Should a substantial overdose or medication error occur, there is no known antidote. Any patient who inadvertently receives a dose of NUC-1031 higher than intended should be monitored closely, managed with appropriate supportive care, including transfusion and haematopoietic growth factors as needed, until recovery.

8.8.2 Cisplatin

In case of overdose (>200 mg/m^2) or medication error, direct effects on the respiratory centre are possible, which might result in life threatening respiratory disorders and acid base equilibrium disturbance due to passage of the blood brain barrier.

An acute overdose of cisplatin may result in renal failure, liver failure, deafness, ocular toxicity (including detachment of the retina), significant myelosuppression, untreatable nausea and vomiting and/or neuritis. An overdose may be fatal.

There is no specific antidote in the event of an overdose of cisplatin. Even if haemodialysis is initiated 4 hours after the overdose, it has little effect on the elimination of cisplatin from the body following a strong and rapid fixation of cisplatin to proteins.

Treatment in the event of an overdose or error consists of general support measures. Efficient hydration and osmotic diuresis can aid in reduction of toxicity, provided this is applied immediately after overdose.

8.8.3 Gemcitabine

There is no known antidote for overdose of gemcitabine. Doses as high at 5700 mg/m^2 have been administered by IV infusion over 30-minutes every 2 weeks with clinically acceptable toxicity. In the event of suspected overdose or medication error, the patient should be monitored with appropriate blood counts and receive supportive therapy, as necessary.

8.9 Interaction with Other Drugs

NUC-1031 is not a substrate for, nor is metabolised by, Cytochrome P450 enzymes. Patients receiving NUC-1031 should be carefully managed for potential drug interactions according to local practice.

Interactions between cisplatin, gemcitabine, and any concomitant medications should be checked with the respective package inserts in accordance with local practice. Local practice and guidelines should be followed for the management of any potential cisplatin or gemcitabine/concomitant medication interactions.

9 MANAGEMENT OF TOXICITY

9.1 Criteria for Continuation of Treatment Post-Cycle 1

Patients must meet all of the following criteria prior to receiving study treatment on commencement of subsequent cycles (Day 1). Laboratory results may be assessed within 24 hours of the first scheduled dose.

- ANC ≥1000/μL: use of short-acting granulocyte colony stimulating factor (G-CSF) is permitted after Cycle 1 but must be stopped in advance of the start of a cycle to allow stabilisation of neutrophil count (at least 5 days for short-acting growth factors). Growth factors should only be used as per American Society for Clinical Oncology (ASCO) guidelines.
- Haemoglobin ≥8 g/dL (transfusions are permitted)
- Platelet count ≥100,000/μL (without platelet transfusions)
- No evidence of disease progression (based on radiographic assessment)
- Recovery from all clinically significant toxicities to ≤Grade 2 or to baseline grade

If the above criteria are not met for Day 1 of a cycle, dosing with study treatment should be delayed by 1 week and then lab parameters re-evaluated. If the delay is >21 days, the patient must be withdrawn from treatment, unless the patient is receiving a clinical benefit.

9.2 Criteria for Day 8 Dosing

On Day 8 of a cycle, patients should be dosed according to the criteria in Table 3. If the below criteria are not met for Day 8 of a cycle, or a patient is already at dose level -2, dosing with study treatment should be delayed for up to 6 days and then lab parameters re-evaluated.

Table 3 Dose adjustments within a cycle (Day 8) based on ANC and platelet counts

ANC (/µL)		Platelets (/µL)	NUC-1031 Dose Management	Gemcitabine Dose Management	Cisplatin Dose Management
≥1000	**AND**	≥100,000	No dose change	No dose change	No dose change
500 - <1000	**AND/OR**	50,000 - <100,000	Reduce 1 dose level	Reduce 1 dose level	No dose change
<500	**AND/OR**	<50,000	Hold[*§]	Hold[*§]	Hold[*§]

ANC=absolute neutrophil count.

[*]The dose of NUC-1031 or gemcitabine will be re-escalated to full dose upon recovery of haematological toxicity despite a previous Day 8 dose reduction in order to maintain the dose intensity of therapy.

[§]When held, treatment must not be reinstated within a cycle until the ANC reaches ≥500/µL and the platelet count reaches ≥50,000/µL.

If there is a 1-week delay of Day 8 of a cycle, then omit and restart with Day 1 of the next cycle (provided Day 1 re-treatment criteria are met).

Patients must also meet the following criteria prior to receiving treatment on Day 8 of all cycles:

- Recovery from all clinically significant toxicities to ≤Grade 2 or to baseline grade
- No evidence of disease progression (based on radiographic assessment)

9.3 Dose Modifications

Dose modifications for gemcitabine and cisplatin should be performed in accordance with their package inserts. For NUC-1031, the proposed Level-1 reduction takes the dose to one that was well tolerated in the Phase I study (PRO-001), and which is expected to provide appropriate mitigation of AEs.

Adverse events may be managed by dose delays and/or dose reductions according to the clinical situation. Advice on how to modify dosing for haematological and non-haematological toxicities is given in Table 4.

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 so long as the patient meets the criteria for doing so, or it may be a permanent dose reduction (based on the Investigator's judgement) which would apply to all subsequent cycles. Over the whole dosing period, each patient may have a maximum of 2 permanent NUC-1031 or gemcitabine dose reductions, after

which treatment will be discontinued. The lowest dose of NUC-1031 which may be administered is 425 mg/m^2 and the lowest dose of gemcitabine which may be administered is 500 mg/m^2. Cisplatin can be dose reduced 25% before discontinuation.

It is expected that some patients will interrupt or discontinue cisplatin but continue on NUC-1031 or gemcitabine until progression. Patients may **not** proceed on cisplatin alone.

Table 4 Dose modification guidelines

Dose Level	NUC-1031 Dose	Gemcitabine Dose	Cisplatin Dose
Starting	725 mg/m^2	1000 mg/m^2	25 mg/m^2
Dose Level -1	575 mg/m^2	750 mg/m^2	19 mg/m^2
Dose Level -2	425 mg/m^2	500 mg/m^2	Omit

Treatment between cycles can be delayed for up to 21 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 study treatment, unless the patient is receiving clinical benefit.

Should a patient experience multiple toxicities, dose adjustments will be based on the most severe toxicity.

9.3.1 Haematological Toxicity – Dose Adjustment

Study treatment administration should be given according to the ANC and platelet count on the day of dosing. On Day 1 of each 21-day cycle, if the ANC is ≥1000/µL and the platelet count is ≥100,000/µL, then study treatment should be given at full dose unless the patient has previously been permanently dose-reduced.

On Day 1 of each 21-day cycle, if the ANC is 500/µL to 1000/µL and the platelet count is 50,000/µL to <100,000/µL without evidence of bleeding, then study treatment should be given at a reduced dose unless the patient has received 2 prior dose reductions.

Within a cycle, should patients experience neutropaenia or thrombocytopaenia, dosing on Day 8 should be adjusted per Table 3.

If there is a 1-week delay of Day 8 of a cycle, then omit Day 8 of that cycle and proceed with Day 1 of the next cycle (provided Day 1 re-treatment criteria are met).

9.3.2 Non-Haematological Toxicity – Dose Adjustment

Dose adjustment should be performed according to Table 5. No dose reductions or modifications are required for Grade 1-2 fatigue, nausea/vomiting, diarrhoea, oedema, or any grade alopecia. If dose omission is required, treatment should be delayed until the toxicity has resolved to ≤Grade 2. 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 5 Dose adjustment for non-haematological toxicities

Toxicity	NUC-1031 / gemcitabine dose management	Cisplatin dose management
GFR <45 mL/min*	No dose change	Hold cisplatin**
Grade 3 or 4 fatigue***	Reduce 1 dose level. Stop treatment if it persists despite 2 dose reductions.	Reduce dose by 25%. Stop treatment if it persists despite dose reduction.
Grade 3 or 4 nausea/vomiting***	Ensure optimal use of antiemetics and bowel routine (according to local policy). Delay until recovery to ≤Grade 2 then reassess. If better optimised, proceed without dose reduction. If Investigator feels optimisation was in place during Grade 3 or 4 episode, wait until recovery to ≤Grade 2 and dose-reduce cisplatin. If no improvement after reducing cisplatin it should be omitted and Investigator may consider reducing NUC-1031 or gemcitabine dose by 1 dose level. For further episodes of Grade 3 or 4, supportive care measures should be revisited. If nausea/vomiting persists despite dose reductions and after optimal anti-emetics or dose reduction, stop treatment.	
≥Grade 3 ALT/AST documented in prior cycle but recovered to <5 × ULN for Day 1 of next cycle	No dose change	No dose change
Hy's Law (see Section 12.12) (ALT or AST >8 × ULN; ALT or AST >5 × ULN for more than 2 weeks; ALT or AST >3 × ULN with total bilirubin >2 × ULN; ALT or AST >3 × ULN and INR >1.5)	If liver dysfunction is due to drug-related toxicity consider discontinuation of treatment or, if patient is deriving benefit in the opinion of Investigator, consider holding treatment until values are <3 x ULN for AST and/or ALT and <2 x ULN for total bilirubin, then restart treatment at a reduced dose (as per Table 4). Laboratory values must be closely monitored and study treatment must be discontinued if patients meets criteria for a second time despite dose reduction. See Section 10.3.3 for instructions if liver dysfunction is due to underlying biliary issues.	
Grade 3 peripheral neuropathy	No dose change	Hold cisplatin until recovery to ≤Grade 2, then reduce dose by 25%. If Grade 3 recurs, discontinue cisplatin.
Grade 4 peripheral neuropathy	No dose change	Stop treatment
Grade 3 or 4 oedema	Dipstick urine test for protein followed by full 24-hour urinary protein estimation if result ≥1+. Delay until recovery to ≤Grade 2 (with use of appropriate diuretics), then reduce 1 dose level. If recurs after dose modification and use of appropriate diuretics, stop treatment.	No dose change, but delay to restart with NUC-1031 or gemcitabine
Tinnitus	No dose change	No dose change if full recovery between cycles. Omit if no recovery between cycles.
Grade 2 to 4 pulmonary toxicity (including ARDS and pneumonitis)	Stop treatment. Supportive therapy (high dose steroids) should be initiated immediately.	

Toxicity	NUC-1031 / gemcitabine dose management	Cisplatin dose management
Grade 3-4 pulmonary oedema	Stop treatment and initiate supportive care. Note: in the case of mild exacerbation of pre-existing pulmonary oedema by IV chemotherapy or fluids (Grade 1-2), interrupt study treatment to adjust supportive care measures and resume treatment at Investigator's discretion when returned to baseline condition.	
Radiologically confirmed posterior reversible encephalopathy syndrome	Stop treatment	Stop treatment
Febrile neutropaenia during previous cycle	Reduce 1 dose level	No dose change
Haemolytic uremic syndrome	Stop treatment	Stop treatment
Capillary leak syndrome	Stop treatment	Stop treatment
Anaphylactoid reactions	Stop treatment	Stop treatment

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GFR=glomerular filtration rate; ULN=upper limit of normal.

*Repeat the creatinine clearance assessment ensuring the patient is adequately hydrated. Proceed with cisplatin if repeat reading is ≥45 mL/min, otherwise hold until recovery of renal function.

**If the Investigator wishes to continue cisplatin after the recovery period with persistent GFR >30 mL/min (*i.e.,* at next assessment of GFR on Day 1 of subsequent cycle), the dose of cisplatin can be reduced by 25%. If GFR <30 mL/min, discontinue cisplatin.

***If the delay is >21 days (from scheduled Day 1) for non-haematological toxicity, the patient should be withdrawn from treatment unless receiving clinical benefit, support for the toxicity was not optimally managed, and/or the Investigator feels it is in the patient's best interest to continue.

9.3.3 Management of Nausea and Vomiting

- Consider anti-emetic medications. Examples of anti-emetic medications include granisetron, palonosetron, dexamethasone, metoclopramide, domperidone, cyclizine
- Maintain adequate hydration including use of IV fluids if indicated
- Supplement electrolytes, particularly potassium and magnesium, to recommended levels
- Discontinue any concomitant medications that could contribute to nausea and vomiting
- Rule out other potential aetiologies (for example, gastrointestinal tract obstruction)
- Consider prophylactic anti-emetic medications (per ASCO guidelines for chemotherapy regimens of moderate emetic risk) prior to next dose of study drug.

9.3.4 Management of Pulmonary Toxicity

Dyspnoea has been reported to occur in approximately 25% of patients treated with gemcitabine, whereas serious pulmonary toxicities are much less common, occurring in approximately 0.3% of patients. If pneumonitis is suspected or confirmed, immediately discontinue NUC-1031 or gemcitabine and refer to specialist respiratory physician for assessment. Normally, this is treated with inhaled or oral steroids. NUC-1031 or gemcitabine should not be re-initiated in a participant

who has developed radiologically-confirmed pneumonitis, even if symptoms have resolved after appropriate management.

9.3.5 Management of Diarrhoea

- All available anti-diarrhoeal medications including loperamide and opiate preparations should be considered for treatment
- Maintain adequate hydration, including use of IV fluids if indicated
- Supplement electrolytes, particularly potassium and magnesium, to recommended levels to minimise risk of related AEs
- Avoid oral supplementation of electrolytes since the diarrhoea could be exacerbated in some cases
- Rule out other potential causes including infectious aetiologies for diarrhoea
- Discontinue any concomitant medications that could exacerbate diarrhoea.

9.3.6 Management of Infusion-Related Reactions

Symptoms of infusion-related reactions include pyrexia, chills, flushing, hypotension, dyspnoea, wheezing, back pain, abdominal pain, and urticaria. Symptoms should be managed according to the following guidelines:

NCI-CTCAE Grade	Treatment Modification
Grade 1 (mild) Mild transient reaction; infusion interruption not indicated; intervention not indicated	Decrease the infusion rate by 50% and monitor closely for any worsening
Grade 2 (moderate) Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (*e.g.,* antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for 24 hours	Temporarily discontinue infusion Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening
Grade 3 or Grade 4 (severe or life-threatening) Grade 3: Prolonged (*e.g.,* not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for clinical sequelae Grade 4: Life-threatening consequences; urgent intervention indicated	Stop the infusion immediately and disconnect infusion tubing from the patient Patients have to be withdrawn immediately from treatment and must not receive any further treatment
IV=intravenous; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs=nonsteroidal anti-inflammatory drugs	

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 study treatment through the End of Treatment Visit must be recorded in the CRF.

All prior anti-cancer therapies from initial diagnosis up until enrolment must be recorded in the CRF, regardless of time taken prior to first dose.

Should a patient discontinue study treatment, information on subsequent anti-cancer therapies, along with response to these therapies, must be recorded in the CRF.

10.1 Support Medication

Patients may receive standard prophylactic and support medications so long as they are not listed as a prohibited therapy in Section 10.3.1. All such medications must be recorded in the CRF.

10.2 Haematopoietic Growth Factor Support

The Investigator may prescribe G-CSF as treatment for Grade 3 or higher neutropaenia according to local protocols and as prophylaxis after the first event of Grade 3 neutropaenia or for any febrile neutropenic episode in order to enable the patient to continue on study. All haematopoietic growth factors used from 30 days prior to date of consent until 30 days after administration of last dose of study drug 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 study drug must be recorded in the CRF.

10.3.1 Prohibited Therapies

Refer to the cisplatin and gemcitabine package inserts for information regarding drug interactions.

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy, for diseases other than indicated in this protocol
- Radiotherapy (palliative radiotherapy to a non-target lesion is allowed)
- Immunotherapy including immunosuppressive therapy
- Radioimmunotherapy
- Hormone therapy (other than contraceptives, hormone-replacement therapy, or megestrol acetate)
- Biologic agents intended for the treatment of BTC (other than haematopoietic 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 BTC, whether approved by local regulatory authorities or investigational
- Any drugs at doses known to cause clinically-relevant prolongation of QT/QTc interval (see Appendix 3)

- Anti-convulsant treatment with phenytoin
- Live vaccines (must also be avoided for six weeks after last study drug dose administration)

10.3.2 Therapies to be Used with Caution

The following medications and/or treatments are permitted with caution and should be monitored during the study:

- Drugs that are known substrates of either CYP3A, CYP1A2, P-gp, BCRP, MATE1 or OCT2:

In vitro studies are being conducted to assess the drug-drug interaction potential of NUC-1031. Although it is not anticipated that NUC-1031 will cause drug-drug interactions, there may be the possible risk of perpetrating drug-drug interactions through CYP3A inhibition, CYP3A induction (some transporters such as P-gp might also be co-induced), CYP1A2 repression, or inhibition of several transporters (P-gp, BCRP, MATE1, OCT2). The clinical impact of these *in vitro* observations is not known and patients who are taking concurrent drugs that are known substrates of either CYP3A, CYP1A2, P-gp, BCRP, MATE1 or OCT2 should be carefully monitored. A list of such drugs can be consulted in:

- Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007) (http://medicine.iupui.edu/clinpharm/ddis/)
- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

The following therapies are to be used with caution when given concomitantly with cisplatin during the study:

- Anti-hypertensive agents containing furosemide, hydralazine, diazoxide, and propranolol
- Nephrotoxic agents (*e.g.*, cephalosporins, aminoglycosides, amphotericin B, or contrast media)
- Ototoxic agents (*e.g.,* aminoglycosides or loop diuretics)
- Anti-histamines, buclizine, cyclizine, loxapine, meclozone, phenothiazines, thioxanthenes, or trimethobenzamines
- Anti-convulsive agents
- Oral anti-coagulants
- Agents whose elimination is primarily through the renal pathway (*e.g.*, bleomycin or methotrexate)
- Ifosfamide
- Paclitaxel
- Pyroxidine and altretamine
- Bleomycin and vinblastine
- Bleomycin and etoposide

10.3.3 Biliary Stenting

In the event of the development of obstructive jaundice or other adverse medical condition thought to be due to or historically associated with biliary tract obstruction, including but not limited to pain, pruritus, hepatocellular dysfunction, biliary cirrhosis, and cholangitis, appropriate measures will be undertaken to diagnose (*e.g*., by ultrasound and/or CT scan) and relieve the obstruction (*e.g.,* by endoscopic retrograde cholangiopancreatography/ percutaneous transhepatic cholangiography +/- stent insertion/drainage). Patients do not need to be taken off study treatment permanently if this occurs.

Chemotherapy may be deferred until the liver function tests have improved to pre-treatment eligibility levels (total bilirubin <2 × ULN; ALT and/or AST <5 × ULN) and/or other associated medical issues have resolved to the point that the treating physician feels, in keeping with standard of care, it is appropriate to resume treatment. Re-initiation of study treatment should be considered to be Day 1 of the next cycle.

Dose delays for biliary tract obstruction and/or stent placement or replacement are considered separately from dose adjustments for treatment-related AEs.

If complications as a result of plastic stenting are deemed to be the cause of the obstruction or other adverse medical condition, consider replacement of the plastic stent with a metal stent. Stent replacement is permitted and patients are permitted a treatment-free interval as necessary to recover from this procedure, at the Investigator's discretion.

10.4 Contraception Methods

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

- True abstinence (when this is in line with the preferred and usual lifestyle of the patient) during the entire participation in the study and for 6 months 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)

True abstinence is defined as refraining from heterosexual intercourse during the entire study period and for 6 months after the last dose of study medication; periodic abstinence (such as calendar, ovulation, symptothermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.

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 (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Surgical sterilisation (bilateral occlusion, vasectomised 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 6 months following the last study drug administration. Oral or injectable contraceptive agents cannot be the sole method of contraception. Patients of childbearing potential must have a negative pregnancy test within 3 days prior to the first study drug administration.

Patients of childbearing potential must also refrain from donating sperm or eggs from the time of first study drug administration until 6 months after the last study drug administration.

10.5 Fertility

In accordance with the cisplatin package insert, genetic consultation is recommended if the patient wishes to have children after ending treatment. Since treatment with cisplatin may cause irreversible infertility, it is recommended that patients, who wish to become parents in the future, ask for advice regarding cryo-conservation of their sperm or eggs prior to treatment. Due to the poor prognosis of patients with a diagnosis of advanced BTC, Investigator's discretion should be used before conversations concerning this subject matter are broached.

11 TUMOUR RESPONSE ASSESSMENTS

Many of the primary and secondary efficacy endpoints (including ORR, PFS, DoR, and DCR) are based on assessment of tumour response to treatment (see Section 13 for further details).

Objective disease assessment will be performed by radiologic evaluation and assessed according to RECIST v1.1 criteria (as described in detail for this study in Appendix 4). Treatment and study continuation decisions based on radiologic assessments will be made by the treating Investigator. However, primary analyses of data will use BICR assessment of radiologic evaluation using blinded double reads with adjudication (see Section 11.2), and secondary analyses will be carried out based on Investigator assessment.

11.1 Tumour Measurements and Assessment of Disease Response

Patients with measurable disease at baseline (as assessed by BICR) must have at least one lesion that can be accurately assessed at baseline by CT, MRI, or PET-CT, and which is suitable for repeated assessment in order to be considered evaluable for response. All known or suspected disease sites must be assessed at baseline by either CT, MRI or PET-CT scan. For each patient, the same radiological method used at baseline must be used for disease assessment throughout the duration of the patient's participation in the study. Additional anatomical areas, other than chest, abdomen, and pelvis, should be assessed by CT scan, MRI, or PET-CT in case of suspicion of presence of metastases based on signs, symptoms, biochemical results and/or as standard of care imaging of patients (*i.e.,* non-study related). 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).

Disease must be measured according to RECIST v1.1 criteria, with target and non-target lesions identified, measured and followed throughout the study, as well as new lesions identified (Appendix 4). Biopsied lesions must not be designated as target lesions for the purposes of RECIST v1.1 criteria, unless sufficient time has elapsed that the lesion has fully recovered.

Whenever possible, the same qualified physicians will interpret the radiologic assessments to reduce variability. Radiographic images will be maintained at the study centre, 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 a blinded independent assessment of the radiographic imaging results. Instructions for the collection, and submission of images are provided in a separate Imaging Manual.

Tumour measurements and disease response assessments are to be performed every 9 weeks (±7 days) (approximating three cycles) from C1D1 until radiographic disease progression. If the patient stops study treatment for reasons other than radiologically-confirmed PD, tumour measurements and disease response assessments should continue at least every 12 weeks (±14 days) thereafter until PD is radiologically observed.

Objective disease assessment is also to be performed any time disease progression is suspected.

Patients should not discontinue study treatment because of raised tumour marker levels or other clinical signs of PD until PD has been confirmed radiographically by RECIST v1.1 criteria.

All responses (CRs and PRs) must be confirmed by repeated imaging more than 28 days but less than 42 days after initial documentation. If a patient is found to have a response at the confirmatory scan which has improved from PR to CR, then the improved response must also be confirmed within a further 28-42 day window.

Patients who stop treatment following an unconfirmed response should also still have a confirmatory scan within the 28- to 42-day window, if the scan can take place prior to the patient starting any subsequent anti-cancer therapies. If a patient is found to have a response at the confirmatory scan which has improved from PR to CR, then the improved response must also be confirmed within a further 28-42 day window, if the scan can take place prior to the patient starting any subsequent anti-cancer therapy.

In the case of SD, measurements must have met the SD criteria at least once after C1D1 at a minimum of 8 weeks later (*i.e.,* allowing for the 8-10 week time window for the first scheduled scan at Week 9).

Assessment of progression for the purposes of measuring PFS in patients with non-measurable disease will be performed according to RECIST v1.1 recommendations (Eisenhauer *et al*, 2009). Unequivocal progression of non-measurable disease is defined as an increase in overall disease burden that is comparable in magnitude to the increase that would be required to declare PD for measurable disease, *i.e.,* an increase in tumour burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localised to widespread, or an increase sufficient to require a change in therapy. If unequivocal progression is observed, the patient should be considered to have had overall PD at that point.

11.2 Blinded Independent Central Review

The BICR of all radiological imaging data will be carried out using RECIST v1.1. All radiological scans at baseline (prior to randomisation) will be provided to the BICR for their determination of whether or not the patient has measurable disease at baseline. This will be used for determining whether the patient is randomised to the measurable disease at baseline stratum or to the non-measurable disease at baseline stratum.

All radiological scans for all patients at baseline and post-baseline (including scans from unscheduled visits, or visit outside of windows) will be provided to the BICR. The imaging scans will be reviewed by 2 independent radiologists and assessed using RECIST v1.1 criteria; in the case that both radiologists do not agree, a third independent radiologist will provide adjudication.

Results of these independent reviews will not be communicated to Investigators, and all patient treatment decisions will continue to be made by the Investigators at the site. To ensure that the BICR do not become unblinded the following information will not be provided to the BICR when radiographic data is transmitted: the treatment group (or any data that might unblind the treatment group); assessments made by the Investigator, situational specific descriptions of the scans including whether scans are confirmatory or end of treatment; the total number of exams for a patient (to exclude progression bias); the results of assessments of other reviewers participating in the review process (except during adjudication); and any clinical data that may influence the independent reviewers. Further details of the BICR are documented in a separate BICR Charter.

Please refer to the NuTide:121 Imaging Manual for details on submission and review of images.

12 SAFETY ASSESSMENT AND 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 authorised 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 severity after exposure to study drug.

A Serious AE (**SAE)** is defined as any event that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a significant medical event in the Investigator's judgment (*e.g.,* may jeopardise the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

Disease progression 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 study drug. This means that a causal relationship between study drug and the AE is at least a reasonable possibility, *i.e.,* the relationship cannot be ruled out.

An **Unexpected Drug Reaction** is an ADR, 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 ADR, the nature or severity of which is not consistent with the applicable product information (*e.g.,* IB for an unapproved IMP).

Important medical events that may not result in death, be life threatening, or require hospitalisation may be considered an SAE when, based upon appropriate medical judgment, they may jeopardise 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 hospitalisation, 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 hospitalised, 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, aetiology, 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 study drug).

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 utilises the more clinically-oriented terminology (for example, 'anaemia' is preferable to 'haemoglobin 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', 'dyspnoea') and also reports the appropriate term indicating the allergic reaction ('allergic reaction' or 'anaphylaxis' if appropriate [Immune System Disorders; CTCAE v5.0]).

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 recorded on the CRF in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be recorded.

The relationship of an AE to study drug should be classified using the following guidelines:

Definitely Related: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Probably Related: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Possibly Related: There is some evidence to suggest a causal relationship (*e.g.,* because the event occurs within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the event (*e.g.,* the patient's clinical condition, other concomitant treatments).

Unlikely Related: There is little evidence to suggest a causal relationship (e.g., the event did not occur within a reasonable time after administration of the study drug). There is another reasonable explanation for the event (*e.g.,* the patient's clinical condition, other concomitant treatments).

Not Related: There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given.

12.4 Assessment of Severity

The severity of each AE is to be assessed by the Investigator according to NCI CTCAE, v5.0. 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 daily 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 the date of consent through 30 days after last study drug dose must be reported to the CRO pharmacovigilance (PV) department within 24 hours from the time study site personnel first learn about the event.

The SAE report will be completed using the eCRF. Contact details for safety reporting issues are provided in Table 6.

Table 6 Pharmacovigilance contact details

Email	PHV_NUC1031@iqvia.com

If the patient is hospitalised because of or during the course of an SAE, then a copy of the hospital discharge summary (if available) should be sent to the CRO PV department, using the contact details 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 the CRO PV department, 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 their Institutional Review Board (IRB)/Ethics Committee (EC). Copies of SAE correspondence between all Investigators or sub-Investigators, governing authorities, IRB/ECs, and NuCana must be submitted to the CRO PV department 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 stabilisation.

Expected outcomes in patients with BTC include disease-related mortality and morbidity, which will not be reported as expedited Investigational New Drug 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, and other regulatory authorities as applicable, at an appropriate interval, such as inclusion in the periodic update IND annual report.

The following SAEs should **not** be reported in an expedited manner because they are anticipated to occur in the BTC 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

- Morbidity as a consequence of the underlying malignancy
- Any hospital admission which is due to sepsis or other medical event as a result of biliary tract obstruction or cholangitis
- Any hospital admission which is due to obstructive jaundice or other medical event as a result of biliary stent blockage

12.6 Expedited Reporting of SAEs

The 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, the SAE CRF page should be completed within 24 hours of Investigator awareness to the CRO PV contact details provided above (or paper SAE form completed and faxed or emailed if the CRF is not available).

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 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 study drug or be sufficient to change study drug administration or the overall conduct of the study.

NuCana, or CRO 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 CRO PV will notify the regulatory authorities as soon as possible, but no later than 15 days of the initial receipt of information.

The IRB/EC will be informed in line with local regulations. Copies of SAE correspondence with all Investigators or Sub-Investigators, regulatory authorities, IRBs/ECs and NuCana must be submitted to CRO PV for filing.

12.8 Terms and Grading of Events

All AEs and toxicities must be graded according to NCI CTCAE v5.0.

12.9 Pregnancy

A patient who becomes pregnant should be withdrawn from study treatment immediately. Pregnancies (in a patient or partner) occurring during study treatment, and up to 6 months after the end of study treatment, require expedited reporting. Should the female partner of a male patient become pregnant during his participation in the study, she will be asked to consent to follow-up of the pregnancy until birth and the health of the baby up until 6 months of age. A Pregnancy Notification Report should be completed and submitted to the CRO PV department 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 foetus or the child
- Foetal 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 will be captured on the CRF. AEs including hospitalisation 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 BTC.

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 tumour 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, BTC, is to be recorded on the Death CRF form, provided that the death is not unexpected and no causal relationship with study drugs or other protocol-prescribed treatment intervention is suspected. The Investigator must clearly state whether the death was expected or unexpected and whether a causal relationship to study drug 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 Electrocardiograms

12.11.1 Standard ECG Monitoring

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, who will record their overall assessment as either normal, abnormal but not clinically significant, or abnormal clinically significant. ECG assessments may be retained for review centrally, where results will be provided to the study site and retained as source data.

12.11.2 Robust QT Sub-study

Intensive ECG monitoring will be implemented at a subset of sites to collect QT/QTc data for 74 patients (approximately 37 patients in each treatment group) during the first 2 cycles of treatment to allow robust analysis of ECG parameters.

ECGs will be centrally evaluated and measured in a blinded manner. A by-time central tendency analysis will be used as the primary analysis for assessing QTc in the sub-study. Further to this, all ECG parameters will be statistically analysed and described, including categorical outlier analysis for QT/QTc outliers as well as HR, PR and QRS which will be outlined in a separate QT Statistical Analysis Plan.

12.12 Abnormal Laboratory Test Result Values

The Investigator will identify and record clinically significant laboratory test results. Not every laboratory test result abnormality qualifies as an AE; however, a laboratory test result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (*e.g.,* dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (*e.g.,* potassium supplementation for hypokalaemia) or a change in concomitant therapy
- Is clinically significant in the Investigator's judgement

It is the Investigator's responsibility to review all laboratory test result findings. Medical and scientific judgement should be exercised in deciding whether an isolated laboratory test result abnormality should be classified as an AE.

If a clinically significant laboratory test result abnormality is a sign of a disease or syndrome (*e.g.,* alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), the diagnosis (*i.e.,* cholestasis) should be recorded only on the AE eCRF.

If a clinically significant laboratory test result abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the AE eCRF, along with a descriptor indicating whether the test result is above or below the normal range (*e.g.,* "elevated potassium," as opposed to "abnormal potassium"). If the laboratory test result abnormality can be characterised by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or INR must be recorded (FDA, 2009).

These cases are defined by Hy's law if they meet one of the following criteria:

- Treatment-emergent ALT or AST >8 × ULN
- Treatment-emergent ALT or AST >5 × ULN for more than 2 weeks
- Treatment-emergent ALT or AST >3 × ULN with total bilirubin >2 × ULN
- Treatment-emergent ALT or AST >3 × ULN and INR >1.5

And none of the following criteria:

- No initial finding of cholestasis (elevated serum ALP)
- No other reason can be found to explain the increases in ALT/AST and bilirubin or INR, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; biliary duct obstruction; or another drug capable of causing the observed injury

For patients meeting Hy's law criteria due to drug-related toxicity, consider discontinuation of treatment or, if the patient is deriving benefit in the opinion of Investigator, consider holding treatment until values are <3 × ULN for AST and/or ALT and <2 × ULN for total bilirubin, then restart treatment at a reduced dose (as per Table 4). Laboratory values must be closely monitored and study treatment must be discontinued if patients meets criteria for a second time despite dose reduction.

Patients meeting Hy's law criteria with clear progression of liver metastases must discontinue study treatment; however, they will continue to be assessed for safety.

Refer to Section 10.3.3 for instructions on handling patients who meet Hy's law criteria due to underlying biliary issues.

12.13 Abnormal Vital Sign Values

The Investigator will identify and record clinically significant vital sign results.

Not every vital sign abnormality qualifies as an AE; however, a vital sign result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (*e.g.,* dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the Investigator's judgement

It is the Investigator's responsibility to review all vital sign result findings. Medical and scientific judgement should be exercised in deciding whether an isolated vital sign value abnormality should be classified as an AE.

If a clinically significant vital sign value abnormality is a sign of a disease or syndrome (*e.g.,* high blood pressure), the diagnosis (*i.e.,* hypertension) should be recorded only on the AE eCRF.

12.14 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.

12.15 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 NUC-1031 reference safety information (RSI) for the study. Only the IB version with current regulatory and IRB/EC approval for use in the study should 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 development safety update report (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.

The approved SmPCs (section 4.8) for cisplatin and gemcitabine will serve as their respective RSIs, which are also summarised in the appendix section of the NUC-1031 IB.

12.16 Independent Data Monitoring Committee (IDMC)

An IDMC will review the safety, dosing intensity, and clinical activity data from the study. The IDMC is an independent expert advisory group commissioned and charged with the responsibility of evaluating cumulative safety and efficacy data as well as other clinical study data at regular intervals. Actions of the IDMC will be governed by an IDMC charter and the data to be reviewed will be outlined within an IDMC Statistical Analysis Plan. Members of the IDMC will include:

- Independent therapeutic experts in BTC with relevant clinical study experience
- Independent biostatistician

The IDMC will meet at the following timepoints to review the clinical safety and efficacy data:

- The IDMC will review the safety data from approximately the first 50 randomised patients who have completed one cycle (approximately 25 patients in each treatment group)

- The IDMC will meet at least every 6 months thereafter to review safety data
- Additional reviews of the safety data may be requested by the IDMC or by the Sponsor at additional points during the study

In addition, the IDMC will review efficacy and safety data as follows:

- Interim Analysis 1 with a data cut-off 28 weeks after 418 patients have been randomised to the "measurable disease at baseline" stratum. This will assess ORR for demonstration of efficacy, and assess OS for futility
- Interim Analysis 2 with a data cut-off 28 weeks after 644 patients have been randomised to the "measurable disease at baseline" stratum. This will assess ORR for demonstration of efficacy (ORR Final Analysis), and will also assess OS for efficacy (OS Interim Analysis 1), based on approximately 425 OS events
- Interim Analysis 3 after 541 OS events have occurred, which will assess OS for efficacy (OS Interim Analysis 2)

BTC is a highly complex and variable disease, with malignancies occurring along any part of the biliary tract from the ampulla of Vater to the smallest intrahepatic ductules and the gallbladder. Multiple imaging modalities are used to assess different forms of BTC. However, BTC is a rare disease and so experience in radiologic assessment of BTC will be critical to assessment of many of the proposed endpoints in this study.

Following reviews of safety, futility, and/or efficacy, the IDMC will recommend whether the study should continue unchanged, be stopped, or be modified in any way. Once the IDMC has reached a recommendation, a report will be provided to NuCana. This report will include the recommendation together with any proposed amendments to the protocol. The final decision to modify or stop the study will be made by NuCana.

The NuTide:121 IDMC charter contains details on the IDMC members and their responsibilities.

13 STATISTICAL CONSIDERATIONS

Full details of the planned analyses will be provided in a separate Statistical Analysis Plan (SAP) which will be finalised prior to the start of randomisation. The statistical principles applied in the design and planned analyses of this study are consistent with ICH E9 and FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018).

13.1 Analysis Populations

The following sections define the populations that will be used for statistical analyses.

13.1.1 Intention-to-Treat (ITT) Population

The ITT population will consist of all patients who are randomised, regardless of whether any study medication was received. Patients will be summarised on the basis of the treatment group to which they were randomised.

13.1.2 Intention-to-Treat with Measurable Disease at Baseline (ITTMD) Population

The ITTMD population will consist of all patients who are randomised to the stratum corresponding to having measurable disease at baseline (as assessed by BICR), regardless of whether any study medication was received. Patients will be summarised on the basis of the treatment group to which they were randomised.

13.1.3 Modified Intention-to-Treat (MITT) Population

The MITT population will consist of all patients who are randomised and received any study medication. Patients will be summarised on the basis of the treatment group to which they were randomised.

13.1.4 Safety Population

The Safety population will consist of all patients who are randomised and receive any study medication. Patients will be summarised on the basis of the actual study medication received, *i.e.,* NUC-1031 in combination with cisplatin (Arm A), or gemcitabine in combination with cisplatin (Arm B). Any patients receiving study medication from both arms will be summarised under Arm A.

13.1.5 Primary Analysis Populations

The ITTMD will be the primary analysis population for evaluating ORR and DCR. DoR will be analysed in the subset of ITTMD patients who have confirmed response. For evaluating all other efficacy endpoints, the primary analysis population will be the ITT population. The MITT population will be used only for a secondary analysis of the OS primary endpoint. The Safety population will be the primary analysis population for evaluating all safety endpoints.

13.2 Patient Disposition

For the ITT population, counts and percentages will be provided by treatment group for each of the following: treated or untreated; treatment ongoing or treatment ended; primary reason for end of treatment; and whether the patient discontinued the study overall and by reason. For each treatment group, the number of patients in each analysis population will be summarised. Major protocol deviations (as defined in a separate Protocol Deviation Management Plan) will also be summarised by reason and overall.

13.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarised by treatment group for the ITT, ITTMD, and Safety populations. Full details on the variables summarised are provided within the SAP.

13.4 Primary Efficacy Endpoints

This study has OS and ORR as dual primary endpoints. The study will be viewed as positive (in terms of the primary efficacy endpoints) if statistical significance is obtained on either of the two primary endpoints. The control of Type 1 error by the Maurer & Bretz (2013) method across the two primary endpoints and the key secondary endpoint (PFS), as well as across the interim analyses, is described in Section 13.10.1.

13.4.1 Overall Survival

13.4.1.1 Definition of Overall Survival

Duration of OS is defined as the time from randomisation to the time of death due to any cause. For patients who are alive at the time of a data cut-off or are permanently lost to follow-up, duration of OS will be censored at the date at which they were last known to be alive.

The date at which the patient is last known to be alive is defined as the latest date of: (i) last site visit; (ii) last date at which the patient had a radiographic scan; and (iii) last date at which the patient, the study investigator, their other physicians, or a family member confirmed that the patient was alive.

13.4.1.2 Primary Analysis for Overall Survival

The primary analysis of OS will be performed using the ITT population. As described further in Section 13.10 and summarised there in Table 10 and Table 12, OS will be assessed for demonstration of efficacy on 3 occasions, *i.e.,* after approximately 425 OS events (67%), after 541 OS events (85%), and after 637 OS events (100%). At each of these 3 looks, the treatment effect for OS will be assessed by the stratified log-rank test. The one-sided p-value will be compared with the critical values as derived in Section 13.10.1 to determine if statistical significance has been obtained at that time.

The stratification factors to be included within the stratified log-rank test are defined by a rule given in the SAP. This rule starts with the design's four stratification factors and successively eliminates factors (as needed) in a pre-defined manner, so that for both treatment groups combined there is no combination of the stratification factors with less than 10 OS events. For each stratification factor, the values from the IxRS at randomisation will be used, even if it is subsequently found that these values were incorrect for one or more patient. The rule will be implemented at Interim Analysis 2 which is the first look at which OS determination of efficacy is to be made. The same resultant set of stratification factors will also be used (without change) for all analyses of OS at Interim Analysis 2, Interim Analysis 3 and at the Final Analysis. It will also be used for the analysis of PFS.

A stratified Cox proportional hazards model with Efron's method of handling ties will be used to estimate the hazard ratio for OS. The model will include a term for treatment and the same set of stratification factors as used within the stratified log-rank test. The 100(1-2α)% two-sided confidence interval (CI) for the hazard ratio will also be derived where "α" is the "Critical p-value (1-sided)" for OS derived as described in Section 13.10.1 and illustrated in Table 12.

The non-parametric Kaplan-Meier method will also be used to estimate the survival curves, within which Greenwood's formula will be used to derive the standard error. The number of patients at risk at the start of each month after randomisation will also be displayed. The median survival time will be estimated for each treatment group, together with its CI using the Brookmeyer & Crowley (1982) method. Estimates of the 25^{th} and 75^{th} percentiles will also be derived together with their corresponding CIs.

13.4.1.3 Secondary and Supportive Analyses for Overall Survival

A secondary analysis of OS based on a stratified Cox proportional hazards model will be carried out in the same manner as described in Section 13.4.1.2, but with terms for treatment and ECOG status at baseline (0 or 1), as well as including terms for any of the design stratification factors which (based on the rule given within the SAP) are not able to be included as analysis stratification factors.

Subgroup analyses of OS for each of the randomisation stratification factors as well as for other important factors will be provided as described in Section 13.12.

The analyses of OS described in Section 13.4.1.2 will also be carried out based on the MITT population (which is the subset of the ITT population including only those patients that received any study medication), and these analyses will be viewed as supportive.

The methods described in Section 13.4.1.2 assume censoring is at random. Since censoring may depend upon progression, and progression is expected to be affected by treatment group, it is possible that censoring may be informative, *i.e.*, may vary systematically between treatment groups. Therefore, methods which assume censoring not at random (CNAR) will be used to assess the robustness of the inference from the primary analysis for OS.

To allow straightforward comparison with the planned Cox proportional hazards regression analysis, multiple imputation of time to event using the Cox model will be used to implement the CNAR analyses (Lipkovich *et al,* 2016). Full details of the methodology and its assumptions are presented in the paper cited. The analysis will use the SAS macro publicly available at missingdata.org.uk. Refer to the SAP for further information.

A tipping point approach will be used. For all patients censored in the primary analysis of OS for whom a progression has occurred, irrespective of treatment group, this analysis will as a first step assume censoring at random but will then impose a multiple of the estimated hazard of death – say *delta* – before imputing censored times to event. In a tipping point analysis, the quantity *delta* is successively increased in a sequence of analyses, *i.e.,* the assumption about post-censoring hazard is made more severe. Note that the patients thus censored not at random in the tipping point approach would be only those patients who are censored in the primary analysis (excluding patients administratively censored due to reaching the data cut-off date) and who progressed at any time whether the progression occurred while on study treatment, or if it occurred after discontinuing study treatment, and even if it occurred after starting another cancer treatment. Depending upon the patterns of censoring there may be a *delta* large enough such that inference made by the primary analysis no longer holds – this would be the “tipping point”. If the “tipping point” *delta* exists and is judged unrealistically high, then this provides evidence to help assess the robustness of inference from the primary analysis to the assumption of censoring at random.

The Restricted Mean Survival Time (RMST) method at 12 months and 18 months may also be conducted for OS to account for any possible non-proportional hazards and to estimate the absolute benefit of experimental treatment.

13.4.1.4 Additional Sensitivity Analyses for Overall Survival as a Result of the COVID-19 Pandemic

All analyses for Overall Survival in Sections 13.4.1.2 and 13.4.1.3 are based on all-cause mortality, *i.e.,* include OS events with cause of death not reported as COVID-19 as well as OS events with COVID-19 cause of death. All analyses in those two sections also include all OS events regardless of whether or not the patient discontinued treatment due to a COVID-19 infection.

A first set of COVID-19-related sensitivity analyses for OS will be carried out using each method described in Section 13.4.1.2, but where in each case patients with COVID-19 recorded as the cause of death will be censored at their date of death. Frequencies and percentages based on the ITT population will also be derived for each treatment group separately for: (i) OS with cause of death related to reasons other than COVID-19; and (ii) OS with cause of death reported as COVID-19.

A second set of COVID-19-related sensitivity analyses for OS will be carried out using each method described in Section 13.4.1.2, but where patients discontinuing treatment due to a COVID-19 infection will be censored at the date of such treatment discontinuation. Any patients that did not discontinue treatment due to a COVID-19 infection but who died with COVID-19 as cause of death will be censored at their date of death. Frequencies and percentages based on the ITT population will also be derived for each treatment group separately for: (i) OS with cause of death related to reasons other than COVID-19 in patients who did not discontinue treatment due to a COVID-19 infection; and (ii) all other deaths.

In addition to the sensitivity analyses for OS described above, further sensitivity analyses for OS may ultimately be needed once the nature and extent of the direct and indirect impact of COVID-19 becomes clearer, and such additional analyses will then be described within the SAP.

13.4.2 ORR

13.4.2.1 Derivation of Best Overall Response

Radiographic disease assessment will be made by BICR using RECIST v1.1 for all randomised patients. For all scheduled and unscheduled visits at which radiographic scans take place, these scans will be reviewed by two independent radiologists, each of whom will record all details as described within Appendix 4. The two radiologists will independently derive each timepoint response categorisation (into CR, PR, SD, PD, or NE) in accordance with Table 1 from Appendix 4, *i.e.,* the response obtained overall at each visit by assessing target lesions, non-target lesions, and new lesions. The BICR Charter describes the process by which the reviewer who made what is regarded as the "definitive assessment" is identified in the case that adjudication is required. All statistical analyses based on BICR assessment will, for a given patient, be based only on the independent reviewer who provided this "definitive assessment".

Then, based on the timepoint response categorisations made by this independent reviewer, the Best Overall Response (BOR) from BICR will be derived programmatically using the rules given in Table 3 from Appendix 4, taking into account:

(i) Confirmation after at least 28 days is required for CR or PR;

(ii) For classification as SD, the radiographic assessment on which this is based must have met the SD criteria at least once after C1D1 at a minimum of 8 weeks later (*i.e.,* allowing for the earlier possible time from the 8-10 week window for the first scheduled scan);

(iii) In patients who discontinue treatment without progression, timepoint responses will be considered in the calculation of BOR only up until the time that the patient receives a subsequent anti-cancer therapy; and

(iv) The rules given in Appendix 3 of the SAP for when patients have one or more intermediate visits with timepoint responses of NE.

From the Investigator's review of the imaging scans, their recorded tumour response data will be used to programmatically determine each patient's timepoint response categorisation (into CR, PR, SD, PD, or NE) in accordance with Table 1 from Appendix 4 for patients in the ITTMD population, or categorisation (into CR, non-CR/non-PD, PD, or NE) in accordance with Table 2 from Appendix 4 for patients randomised to the non-measurable disease at baseline stratum. The BOR will then be derived programmatically using the rules given in Table 3 from Appendix 4, taking into account (i)-(iv) above.

Note: The Independent reviewer's timepoint response categorisation is used prior to programmatically deriving BOR based on BICR assessment. However, for BOR based on Investigator assessment, the timepoint response is also derived programmatically.

13.4.2.2 Primary Analysis for ORR

All analyses of ORR will be based only on patients randomised to the stratum corresponding to having measurable disease at baseline. As described further in Section 13.10 and summarised there in Table 10 and Table 11, ORR will be assessed for demonstration of efficacy on 2 occasions, which are scheduled to take place 28 weeks after 418 patients in this stratum and 28 weeks after 644 patients in this stratum have been randomised. This minimum period of follow-up allows for three scheduled post-baseline radiographic scans plus a one week visit window. Let N_{M28} denote the actual number of patients in the ITTMD population that were randomised ≥28 weeks before the data cut-off for a given interim analysis.

The primary analysis of ORR at a given look will be performed based on the N_{M28} patients in the ITTMD population (randomized ≥28 weeks before the data cut-off), where ORR is then defined as the proportion of the N_{M28} patients within the treatment group that have BOR of CR or PR based on BICR assessment.

Note: At the time of the data cut-off for each of the two interim analyses at which ORR is assessed, there will be some of the N_{M28} patients who have an unconfirmed response based on Investigator assessment at their most recent radiographic scan (with no earlier confirmed response based on Investigator assessment) but who have not yet had their confirmatory radiographic scan. The date of the latest unconfirmed response over all such patients will be determined. Radiographic assessments (by BICR and by the Investigator) from those confirmatory scans which are scheduled to take place within at most 6 weeks after this date will be included at the interim analyses only in the calculation of counts with confirmed CR, counts with confirmed PR, and in ORR.

At each of these two looks, the odds ratio for ORR will be assessed by the stratified Cochran-Mantel-Haenszel (CMH) test. The one-sided p-value will then be compared with the critical values as derived in Section 13.10.1 to determine if statistical significance has been obtained at that time for ORR. The stratification factors to be included within the stratified CMH test are defined for ORR by a rule given in the SAP. This rule starts with the design's following three stratification factors: metastatic disease (yes, no), primary tumour location (gallbladder, intra-hepatic, extra-hepatic/ampullary), and region (Asia, non-Asia). It successively eliminates factors (as needed) in a pre-defined manner, so that for both treatment groups combined there is no combination of the stratification factors with less than 10 patients. Measurable disease (yes/no) will not be used because all ITTMD patients were randomised to the measurable disease at baseline stratum. Here, for these three factors the values from the IxRS at randomisation will be used, even if it is subsequently found that these values were incorrect for one or more patient. The rule will be implemented on the N_{M28} patients at Interim Analysis 1, which is the first look at which ORR determination of efficacy is to be made. The same resultant set of stratification factors will also be used (without change) for analysis of ORR at Interim Analysis 2.

The 100(1-2α)% two-sided CI for the odds ratio will also be derived where "α" is the "Critical p-value (1-sided)" for ORR derived as in Section 13.10.1 and summarised in Table 11.

Counts for patients with a BOR of CR, PR, SD, PD, or NE, based on BICR assessment, will also be presented by treatment group for the N_{M28} patients.

Clopper-Pearson exact 95% two-sided CIs for ORR based on BICR assessment will be provided separately by treatment group (Clopper & Pearson, 1934).

13.4.2.3 Secondary and Supportive Analyses for ORR

Let N_M denote the total number of patients in the ITTMD population that were randomised before the data cut-off for a given interim analysis (regardless of how long beforehand they were randomised). As a supportive analysis, the CMH test as described in Section 13.4.2.2 will also be carried out for ORR using BICR assessment, based on the N_M patients. Counts for patients with a BOR of CR, PR, SD, PD, or NE, based on BICR assessment, will also be presented by treatment group for the N_M patients.

Counts will also be provided by treatment group for the number out of the N_M patients in the ITTMD population that have tumour resection. Counts will also be provided separately by the number of such patients that: (i) previously had a confirmed PR; or (ii) did not previously have a confirmed PR.

A secondary analysis of ORR will also be provided in terms of the difference in proportions based on BICR assessment. This estimate of the difference in ORRs and corresponding 100(1-2α)% two-sided CI will be calculated for the N_{M28} patients in the ITTMD population using CMH methodology and adjusted for the same three stratification factors.

Subgroup analyses of ORR based on BICR assessment will be provided as described in Section 13.12.

The analyses of ORR based on BICR assessment as described in Section 13.4.2.2 will also be carried out based on the subset of the N_{M28} patients in the ITTMD population that received any treatment, and these analyses will be viewed as supportive.

Additional secondary analyses of ORR will be based on Investigator assessment of response. All analyses described for BICR assessment (except for the subgroup analyses) will also be conducted based on Investigator assessment. In addition, a concordance analysis will be performed in which, separately for each treatment group, the categories (PR/CR or SD/PD/NE) of BOR for BICR assessment will be presented cross-classified with the corresponding categories based on Investigator assessment.

13.4.2.4 Additional Sensitivity Analyses for ORR as a Result of the COVID-19 Pandemic

For ORR, additional sensitivity analyses that account for the impact of COVID-19 will be described in a future protocol amendment, with further details provided in the SAP, once the nature and extent of the impact becomes clearer. Potential impacts of COVID-19 on ORR include death due to COVID-19 prior to response, treatment discontinuation or interruption due to COVID-19, delayed or missing regular scheduled radiographic scans, and delayed or missing confirmatory radiographic scans (following a PR or CR). For radiographic scans, these delays could be directly related to COVID-19 such as resulting from the patient's COVID-19 infection, or the delays could be indirectly related to COVID-19 such as caused by regional lockdowns (or by other logistical reasons). These sensitivity analyses will clearly specify whether only the direct impact of COVID-19 is to be taken into account, or whether the indirect impact of COVID-19 will also be taken into account.

13.5 Secondary Efficacy Endpoints

13.5.1 Progression-Free Survival

PFS will be calculated as the time from randomisation until objective disease progression or death from any cause, whichever occurs earlier. PFS based on BICR assessment is the single key secondary efficacy parameter.

Progression will be based on radiographic assessments only, and whether or not a patient has a progression will be determined for each scheduled visit and for any unscheduled visits. For patients with target lesions at baseline (and so having measurable disease at baseline), whether or not a patient has PD at a timepoint will be determined on the basis of the guidelines provided in Table 1 of Appendix 4. For patients with no target lesions at baseline (and so having non-measurable disease at baseline), whether or not a patient has PD at a timepoint will be determined on the basis of the guidelines provided in Table 2 of Appendix 4, where "unequivocal PD" will be determined as described in Section 11. For the primary analysis of PFS, the censoring scheme described in Table 7 will be used.

The SAP provides details on what constitutes an ‘adequate tumour assessment’ and provides further details on the handling of cases where data are partially missing from adequate tumour assessment visits.

The rules within Table 7 are consistent with European Medicines Agency (EMA) Appendix 1 to the guideline on the evaluation of anti-cancer medicinal products in man (2012). The rules in Table 7 are also fully consistent with the rules given in Table C2 from FDA Guidance for Industry: Clinical Trial Endpoints for the approval of non-small cell lung cancer drugs and biologics (2015).

The primary analysis of PFS will be performed using the ITT population. As described further in Section 13.10.1, PFS will be assessed for demonstration of efficacy only at Interim Analysis 2, at which time approximately 534 PFS events are projected to have occurred. PFS will be assessed by

the stratified log-rank test, with the same set of stratification factors as identified for use with OS. If statistical significance is obtained for both ORR and OS (see Section 13.10.1) then PFS will be tested at the 2.5% one-sided significance level. A stratified Cox proportional hazards model with Efron's method of handling ties will be used to estimate the hazard ratio for PFS, in which the model only includes the term for treatment. The 95% two-sided CI for the hazard ratio will also be derived for PFS from this model. If instead statistical significance is obtained for OS but not for ORR (see Section 13.10.1), then the above testing will be carried out at the 0.8% one sided significance level and the CI for the hazard ratio will be 98.4% two-sided.

Table 7 Censoring scheme used in the primary analysis of PFS

Case	Situation	Date of Progression or Censoring	Outcome
1	Incomplete or no baseline tumour assessments	Randomisation	Censored
2	Progression documented between scheduled visits	Earliest time at which progression can be declared: • Date of first progression assessment showing new lesion (if progression is based on new lesion); or • Date of first radiological assessment of target lesions showing a predefined increase in the sum of the target lesion measurements	Progressed
3	No progression	Date of last progression assessment with no documented progression	Censored
4	Treatment discontinuation for undocumented progression	Date of last progression assessment with no documented progression	Censored
5	Death or progression after treatment discontinuation for toxicity or other non-progression related reason	Date of progression or death, whichever occurs first	Progressed
6	Death or progression after new anti-cancer treatment started	Date of progression or death, whichever occurs first	Progressed
7	Death before first scheduled PD assessment	Date of death	Progressed
8	Death after adequate progression assessment visit or death after one missed visit (where in either situation there is no previous documentation of progression)	Date of death	Progressed
9	Death or progression after more than one missed visit	Date of progression or death, whichever occurs first	Progressed

Note: Missed visit includes visits that were completely missed or visits that did not have an adequate tumour assessment (ATA), and "progression assessment" in the above censoring rules only refers to visits with ATA.

The Kaplan-Meier method will also be used to estimate the survival curves for PFS in each treatment group, within which Greenwood's formula will be used to derive the standard error. The number of patients at risk at the start of each month will also be displayed. The median will be estimated for each treatment group, together with its CI using the Brookmeyer & Crowley (1982) method. Estimates of the 25th and 75th percentiles will also be derived together with their corresponding CIs.

The first sensitivity analysis of PFS will follow the primary analysis except for the following change to Case 6:

- Patients with new anti-cancer treatment started (with no prior documented progression) will be censored at the date of their last progression assessment (prior to starting new anti-cancer treatment).

The second sensitivity analysis of PFS, which is fully consistent with Table C1 from FDA Guidance for Industry: Clinical Trial Endpoints for the approval of non-small cell lung cancer drugs and biologics (2015), will follow the rules from the first sensitivity analysis but will also make the following changes to Cases 5 and 9:

- Patients with treatment discontinuation (for toxicity or for another non-progression-related reason) and no documented prior progression will be censored at the date of the last progression assessment (prior to treatment discontinuation).
- Patients that die or progress after more than one missed visit will be censored. The date of censoring will be the date of last progression assessment with documented non-progression, or date of randomisation if all post-baseline progression assessments were missed.

Note: In the second sensitivity analysis, any patient who meets the conditions for both Case 5 and Case 6 will be censored at the earliest of the two possible censoring dates.

Supportive analyses of PFS based on Investigator assessment will also be carried out using each of the three sets of censoring rules defined above.

In case the proportional hazards assumption is not valid, supportive analyses using the RMST method may be conducted for PFS to account for a possible non-proportional hazards effect.

For PFS, additional sensitivity analyses that account for the impact of COVID-19 will be described in a future protocol amendment, with further details provided in the SAP, once the nature and extent of the impact becomes clearer.

13.5.2 Duration of Response

DoR as determined by BICR, using RECIST v1.1 criteria, is defined as the time from the first occurrence of a confirmed objective response to the time of disease progression, or death due to any cause, whichever occurs first. The time of progression or death, and censoring, will each be based on the rules used for the primary analysis of PFS as described in Section 13.5.1.

DoR will be summarised for the subgroup of patients in the ITTMD population with confirmed response using the Kaplan-Meier method and will also be displayed graphically. The median event

time will be estimated for each treatment group, together with its CI using the Brookmeyer & Crowley (1982) method. Estimates of the 25th and 75th percentiles will also be derived together with their corresponding CIs.

In addition, DoR based on Investigator assessment will be summarised in the same way, and this will be considered a supportive analysis.

13.5.3 18-Month and 12-Month Survival

The proportion of patients alive at 18 months (OS18) will be defined as the Kaplan-Meier estimate of OS at 18 months. For each treatment group the 95% CI will also be derived using Greenwood's method. A comparison between treatment groups for OS18 will also be carried out using the method described in Klein *et al* (2007).

The proportion of patients alive at 12 months (OS12) will be analysed in the same way as OS18.

13.5.4 Disease Control Rate

DCR is the proportion of the N_{M28} (defined in Section 13.4.2.2) patients within the treatment group that have a BOR of CR, PR, or SD. The primary analysis of DCR is based on BICR assessment and a supportive analysis will also be conducted based on Investigator assessment.

13.6 Patient-Reported Outcomes

QoL will be assessed using the EORTC-QLQ-C30 with the QLQ-BIL21 module (Appendix 1) and the EQ-5D-5L (Appendix 2).

The ECOG performance status scale will be used to assess patients' ability to perform daily living tasks and their range of basic physical ability. A copy of the ECOG scale is provided in Appendix 5.

Patient Reported Outcomes will be collected using electronic tablets provided to the patients during the study visits to facilitate accurate and timely capture of the QoL data. Missing data points will be queried and centralised compliance monitoring will identify any trends in errors or missing data to allow retraining intervention, should this be required.

13.6.1 EORTC-QLQ-C30 with the QLQ-BIL21 Module

The EORTC QLQ-C30 is a self-administered cancer-specific questionnaire with multi-dimensional scales. It consists of both multi-item scales and single-item measures, including five functional domains, a global QoL domain, three symptom domains, and six single symptom measures. Scoring of the EORTC QLQ-C30 data will be completed following the procedures recommended by the EORTC Study Group on Quality of Life. For each domain or single-item measure, a linear transformation will be applied to standardise the raw score to range between 0 and 100. QoL data will be analysed to test for clinically meaningful differences between the two treatment groups. Questionnaire compliance rates will be ascertained for each treatment group at each measurement timepoint. Mean baseline scores for each subscale and summary scores will be calculated.

The principal QoL analysis will be based on Kaplan-Meier estimates and log-rank tests on time to definitive QoL deterioration, as measured by the EORTC QLQ-C30 physical function and global QoL scores, in each treatment group. The event of interest is the time to a definitive QoL deterioration, which is defined as the minimum time where two consecutive post-baseline visits

have a 5-point or greater deterioration from baseline scores by subtracting baseline scores for each individual from his/her own scores. The 5-point change has been reported to represent "a little' change in QLQ-C30 (Osoba *et al*, 1998; Cocks *et al,* 2012). It has been shown that this is a degree of change that is perceptible to patients (Osoba *et al*, 1998). A minimal change approach is being taken by using a 5-point decrement in physical functioning so that any perceptible change could be captured, but a more definite change may be a 10-point decrement. Indeed, Raman *et al* (2018) have reported asymmetries between improved and worsened states of physical functioning, with worsening requiring roughly a three-fold difference in numeric score compared with the improved state (see Table 8).

Secondary QoL analyses will include analyses of the domains of the QLQ-C30 in which patients are categorised as either improved, stable, or worsened (Raman *et al,* 2018), as described in Table 8.

Table 8 QLQ-C30 domain minimal clinically important differences (MCIDs)

Domain	Improved	Worsened
Physical functioning	≥5	<-15
Role functioning	≥12	<24
Emotional functioning	≥8	<18
Cognitive functioning	≥5	<14
Social functioning	≥8	<20
Fatigue	<-13	≥19
Pain	<9	≥21
Nausea & vomiting	≥-4	≥9
Appetite	<9	≥19

The domain specific minimal clinically important difference (MCID) changes will be used to classify patients as improved, stable, or worsened. As an example, using Table 8, patients with ≥5-point change in Physical Functioning will be classified as improved. If their score is between +5 and -15, then they will be classified as stable. If their score has <-15 change, then they will be classified as worsening.

The Pain domain of the QLQ-C30 will also be summarised relative to changes in analgesic use. Patients' use of analgesics will be categorised into 2-categories (Increased or Stable) relative to their baseline use. Change in actual pain medication will be defined as (Increased/Stable) where a change (increase) is defined as a doubling of the dose of the same medication OR a switch to a more potent medication.

The EORTC QLQ-BIL21 is a validated disease-specific module for measuring QoL in patients with cholangiocarcinoma and cancer of the gallbladder that is designed to be used with EORTC QLQ-C30. The QLQ-BIL21 is self-administered and consists of 21 questions: 3 single-item assessments relating to treatment side-effects, difficulties with drainage bags/tubes, and concerns

regarding weight loss, in addition to 18 items grouped into 5 scales: eating symptoms (4 items), jaundice symptoms (3 items), tiredness (3 items), pain symptoms (4 items), and anxiety symptoms (4 items). Using an anchor-based approach, Kaupp-Roberts *et al* (2016) have reported meaningful changes in each of the domains of the QLQ-BIL21, as shown in Table 9.

Table 9 QLQ-BIL21 domain minimal clinically important differences (MCIDs)

QLQ-BIL21 Domain	Difference
Eating	18
Jaundice	7
Tiredness	22
Pain	15
Anxiety	14
Treatment side effects	16
Drains	18
Weight loss	1

Analysis of QLQ-BIL21 will be carried out in a similar manner as QLQ-C30, using the domain specific MCIDs shown in Table 9.

Perceived weight loss is an important indicator of patient well-being and is captured by the QLQ-BIL21. Actual weight patient change from baseline will also be summarised with weight loss defined as a negative change from baseline of 5% or greater.

13.6.2 EuroQoL Health Questionnaire Instrument (EQ-5D-5L)

The EQ-5D-5L questionnaire will also be administered as a part of this study to assess health-related QoL. EQ-5D is an international, validated, standardised, generic questionnaire for describing and valuing health-related QoL (Rabin & de Charro, 2001). EQ-5D was developed by the EuroQol group in order to provide a simple, generic measure of health for clinical and economic appraisal. This instrument generates a preference-based health-state utility score (EQ-5D utility index) and an overall health state score based on a visual analogue scale (EQ-5D VAS).

EQ-5D is designed for self-completion by respondents and is ideally suited for use in clinics and face to face interviews. It is cognitively undemanding, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire. The most recent version of the EQ-5D is the EQ-5D-5L, which was developed to improve the instrument's sensitivity and to reduce ceiling effects. The number of dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) has not changed; however, the new version includes 5 levels of severity in each of the existing dimensions in place of three (EuroQol Group, 2015).

13.7 Health Economics

Health economics will be assessed through collection of core health resource use information, using CRFs to capture inpatient procedure codes, total number of days in hospital and outpatient visits. Data collected on concomitant medication will also be used in this economic analysis. For the economic modelling, costs will be imputed on the basis of representative country unit costs at the point of analysis using standard fee schedules. Health outcomes will be quantified using QALYs. Quality adjustments will be based on patients' responses to the EQ-5D-5L health status measure which will be administered at baseline, before each cycle of therapy, and each point of follow up as part of the QoL questionnaire. Finally, a cost-utility analysis will be conducted by creating incremental cost-utility ratios for each of the treatment groups.

13.8 Pharmacokinetics

13.8.1 Sparse Pharmacokinetic Sub-study

Sparse PK sampling will be performed and individual exposure to NUC-1031 and dFdU will be estimated using a population PK model. Summary statistics of the observed concentrations will be reported.

A detailed description of the planned PK analyses is provided in the separate PK analysis plan.

13.9 Safety Endpoints

All safety analyses will be performed using all patients in the Safety population. No formal statistical comparison between the two treatments groups is planned.

13.9.1 Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) v20.0 (or higher), and will also be graded according to NCI CTCAE v5.0 (or higher). TEAEs will be defined as those AEs that either start after initiation of study medication (and up to 30 days after the last dose of study medication), or which are present at the time the time of starting study medication, but subsequently increase in severity.

The overall incidences of TEAEs, CTCAE Grade 3 or higher TEAEs, SAEs, TEAEs leading to study medication discontinuation, TEAEs leading to reduction in dose of study medication, TEAEs leading to interruption of study medication, and TEAEs leading to death will be produced. The following additional summaries in terms of incidences and percentages will be provided: (i) TEAEs by system organ class and preferred term; (ii) CTCAE Grade 3 or higher TEAEs by preferred term; and (iii) SAEs by preferred term. Incidence tables will also be provided for TEAEs by severity (based on individual CTCAE grades), and TEAEs by relationship to study medication. Listings will be provided for SAEs, TEAEs leading to study medication discontinuation, TEAEs leading to reduction in dose of any study medication, and TEAEs leading to death.

The overall incidence of patients with a confirmed case of COVID-19 will be derived and a corresponding listing will be provided. The overall incidence of patients discontinuing study treatment due to COVID-19 will also be derived and a corresponding listing will be provided.

In addition, listings will be provided of those patients with any impact of COVID-19 on study treatment, on a study endpoint, or on the assessment of a study endpoint. This will include, but is not limited to: (i) patients delaying, interrupting, or discontinuing treatment due to the patient's confirmed or suspected COVID-19 infection; (ii) patients delaying, interrupting, or discontinuing treatment due to a COVID-19-related indirect reason; (iii) patients who missed or delayed one or

more (regularly scheduled or confirmatory) radiographic scan due to the patient's confirmed or suspected COVID-19 infection; (iv) patients who missed or delayed one or more (regularly scheduled or confirmatory) radiographic scan due to a COVID-19-related indirect reason; (v) patients taking a concomitant medication for a COVID-19 infection; and (vi) patients with a COVID-19 cause of death.

13.9.2 Laboratory Test Results

Laboratory results will be classified according to NCI CTCAE v5.0 (or higher). Incidence tables will be provided for laboratory parameters reported as TEAEs in which patient counts (and percentages) are given for each CTCAE grade separately (based on worst grade), for Grades 3-4 combined (based on worst grade), and for Grades 1-4 combined. Shift tables from baseline to each scheduled study visit will be produced for each laboratory parameter using NCI CTCAE grade. Laboratory test results that are classified as clinically significant in the opinion of the Investigator will be summarised in terms of incidence, as well as provided in listing form. Full listings of all results for laboratory parameters will also be provided.

13.9.3 Other Safety Endpoints

Vital sign results that are classified as clinically significant in the opinion of the Investigator will be summarised in terms of incidence, as well as provided in listing form. Full listings of all results for vital sign parameters (blood pressure, heart rate, respiratory rate, and temperature) and body weight will also be provided.

Incidence tables will be provided for each vital sign parameter reported as a TEAE in which patient counts (and percentages) are given for each CTCAE grade separately (based on worst grade), for Grades 3-4 combined (based on worst grade), and for Grades 1-4 combined.

The vital signs test results will also be summarised by treatment group using descriptive statistics for actual values and for changes from baseline by scheduled visit.

ECOG performance status (see Appendix 5), and physical examination findings by visit will each also be listed.

The incidence of clinically significant changes in ECG parameters will be summarised. Shift tables based on the Investigator's overall ECG assessment (normal, abnormal not clinically significant, abnormal clinically significant) will also be provided. In addition, all ECG results will be provided in listing form.

13.9.4 Exposure

The following will be summarised for the Safety population by treatment group: number of infusions received, number of cycles received, number of infusions delayed, and number of infusions missed. This information will also be provided separately for the NUC-1031 or gemcitabine component and for the cisplatin component of treatment, where in addition the total dose given during the study and the relative dose intensity will also be summarised.

13.10 Interim Analyses

Three interim efficacy analyses are planned in addition to the final analysis.

- The first interim analysis (Interim Analysis 1) will evaluate the ORR primary endpoint. It will be performed 28 weeks after 418 patients in the measurable disease stratum have been randomised. At this interim, a futility analysis will also be conducted for OS and it is estimated that approximately 258 deaths will be observed by this time.
- The second interim analysis (Interim Analysis 2) will evaluate the ORR and OS primary endpoints. It will be the final analysis for ORR and the first interim analysis (for demonstration of efficacy) on OS. It will be performed 28 weeks after 644 patients in the measurable disease stratum have been randomised. It is estimated that approximately 425 deaths will be observed by this time.
- The third interim analysis (Interim Analysis 3) will evaluate the OS primary endpoint for which it will be the second interim analysis (for demonstration of efficacy). It will take place after 541 deaths have been observed.
- The final analysis will evaluate the OS primary endpoint. It will take place after 637 deaths have been observed, and is expected to occur approximately 48.0 months after the first patient is randomised.

PFS, the key secondary endpoint, will also be assessed at Interim Analysis 2 and approximately 534 patients are expected to have a PFS event at this time.

A summary of the planned analyses for demonstration of efficacy, with timings and primary endpoints to be evaluated, is given in Table 10.

Table 10 Analyses planned, primary endpoints evaluated, approximate timing, and drivers of timing

Analysis	Primary Endpoints Assessed for Demonstration of Efficacy	Approximate Time (months)	Driver of Timing
Interim Analysis 1	ORR	~25.5[1,2]	N_{M28} = 418 patients
Interim Analysis 2	ORR, OS	~33.1[1,2]	N_{M28} = 644 patients (~425[1,3] OS events expected at this time)
Interim Analysis 3	OS	~40.0[1,3]	541 OS events
Final Analysis	OS	~48.0[1,3]	637 OS events

N_{M28} = Number of patients randomised in the measurable disease stratum with the opportunity for ≥28 weeks of follow-up.

1. Approximate times for all 4 looks and approximate number of OS events at Interim Analysis 2 assume a 30-month duration of enrolment with gradual ramp-up (as described in the SAP) over the first 12 months, and a constant rate of enrolment for the next 18 months.

2. Approximate times for the first 2 looks also assume that the percentage of patients with non-measurable disease at baseline is exactly 10%.

3. Approximate times for the last 2 looks and the approximate number of OS events at Interim Analysis 2 further assume that:

(i) OS events follow an exponential distribution with a 11.7-month median for the control arm (Arm B) as well as a median of 11.7/0.76 months in Arm A;

(ii) The rate of discontinuation of treatment and the rate of discontinuation from the study (for Arm A and for Arm B) are both comparable to the rates seen in the gemcitabine plus cisplatin arm of ABC-02; *and*

(iii) A total of 2% of patients will be lost to follow-up for OS.

Note: PFS, the key secondary endpoint will also be assessed at Interim Analysis 2.

If ORR crosses its efficacy boundary at Interim Analysis 1, and provided that a further assessment of ORR is not required by regulators, then the driver of timing for Interim Analysis 2 will instead be the occurrence of 425 OS events.

13.10.1 Type 1 Error Control across the Interim Analyses and across the Multiple Endpoints

The Maurer & Bretz method is used to provide strong control of Type 1 error across the two primary endpoints and the key secondary endpoint, as well as across the interim analyses (Maurer & Bretz, 2013). Figure 3 shows the initial one-sided α allocated to each of these three endpoints, and the arrows indicate how α is recycled between the endpoints.

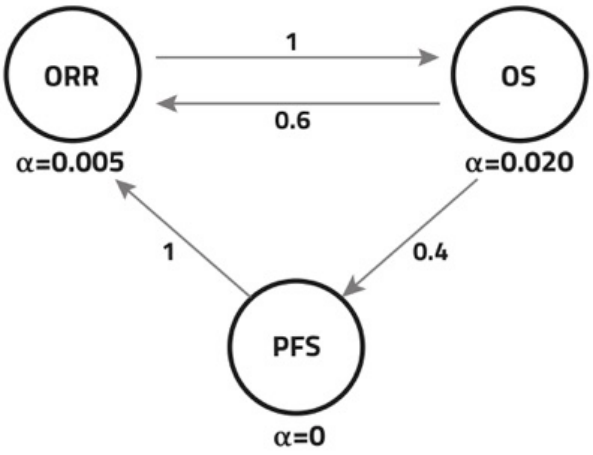

Figure 3 Type 1 error recycling between the two primary endpoints and the key secondary endpoint

Further details are provided below for each of the primary endpoints and for the key secondary endpoint.

ORR

ORR will be tested using an overall α=0.005 one-sided initially. If the null hypothesis for OS is rejected (at Interim Analysis 2, Interim Analysis 3, or at the Final Analysis), then ORR can be tested using an overall α=0.017 one-sided. If, in addition, the null hypothesis for PFS is rejected (at Interim Analysis 2), then ORR can be tested using an overall α=0.025 one-sided. The Lan-DeMets O'Brien-Fleming-like α-spending function (Lan & DeMets, 1983) will be used to control the Type 1 error across the two looks for ORR, and Table 11 gives the bounds and boundary properties for ORR testing.

If ORR has not already obtained statistical significance (using the overall α=0.005 one-sided) at either Interim Analysis 1 or Interim Analysis 2, then if the null hypothesis for OS is rejected (at Interim Analysis 2, Interim Analysis 3, or at the Final Analysis), but the null hypothesis for PFS is not rejected (at Interim Analysis 2), then the p-value for ORR at Interim Analysis 2 can be compared to the updated alpha value of 0.0160 one-sided (from the α=0.017 one-sided column in Table 11) to determine statistical significance for the ORR primary endpoint. However, if the null hypothesis for OS and the null hypothesis for PFS are both rejected, then the p-value for ORR at Interim Analysis 2 can be compared to the updated alpha value 0.0233 one-sided (from the α=0.025 one-sided column in Table 11) to determine statistical significance for the ORR primary endpoint.

Table 11, including the required critical values, will be updated using the actual numbers of patients (in the stratum corresponding to measurable disease at baseline who have the opportunity for ≥28 weeks of follow-up), if these differ from those given.

Table 11 Efficacy boundaries and properties for ORR

Analysis	Value	α=0.005 (1-sided)	α=0.017 (1-sided)	α=0.025 (1-sided)
Interim Analysis 1: 65% N_{M28} = 418[1]	Critical p-value (1-sided)	0.0005	0.0031	0.0054
	Cumulative α (1-sided)	0.0005	0.0031	0.0054
	Odds Ratio at boundary[2]	~2.11	~1.88	~1.80
	Difference in proportions at boundary[2]	~14.1%	~11.6%	~10.7%
	Cumulative Power[3]	29.6%	50.7%	58.3%
Interim Analysis 2: 100% N_{M28}: 644[1]	Critical p-value (1-sided)	0.0048	0.0160	0.0233
	Cumulative α (1-sided)	0.0050	0.0170	0.0250
	Odds Ratio at boundary[2]	~1.63	~1.50	~1.46
	Difference in proportions at boundary[2]	~8.6%	~7.1%	~6.5%
	Cumulative Power[3]	80.0%	90.2%	92.6%

1. N_{M28} denotes the number of patients in the stratum corresponding to measurable disease at baseline who have the opportunity for ≥28 weeks of follow-up.
2. The approximate odds ratio and approximate difference in proportions at the boundary assume that ORR=19% is observed in the control arm.
3. The cumulative power is based on assumed true proportions of 31% vs. 19%.

OS

OS will be tested using an overall α=0.020 one-sided. If the null hypothesis for ORR is rejected (at either Interim Analysis 1 or Interim Analysis 2), then OS can be tested using an overall α=0.025 one-sided. The Lan-DeMets O'Brien-Fleming-like α-spending function (Lan & DeMets, 1983) is used to control the Type 1 error across the three looks for OS, and Table 12 gives the bounds and boundary properties for OS testing.

Table 12, including the required critical values, will be updated using the actual number of OS events if these differ from the counts given.

Table 12 Efficacy boundaries and properties for OS

Analysis	Value	α=0.020 (1-sided)	α=0.025 (1-sided)
Interim Analysis 2: 67% N ~ 828 ~ 425 OS events	Z-statistic	2.6198	2.5082
	Critical p-value (1-sided)	0.0044	0.0061
	Cumulative α (1-sided)	0.0044	0.0061
	Hazard Ratio at boundary[1]	~ 0.776	~ 0.784
	Difference in medians at boundary (months)[1,2]	~ 3.39	~ 3.22
	Cumulative Power[3]	58.3%	62.6%
Interim Analysis 3: 85% N = 828 541 OS events	Z-statistic	2.3164	2.2204
	Critical p-value (1-sided)	0.0103	0.0132
	Cumulative α (1-sided)	0.0116	0.0150
	Hazard Ratio at boundary[1]	~ 0.819	~ 0.826
	Difference in medians at boundary (months)[1,2]	~ 2.58	~ 2.46
	Cumulative Power[3]	81.4%	83.8%
Final Analysis: 100% N = 828 637 OS events	Z-statistic	2.1366	2.0490
	Critical p-value (1-sided)	0.0163	0.0202
	Cumulative α (1-sided)	0.0200	0.0250
	Hazard Ratio at boundary[1]	~ 0.844	~ 0.850
	Difference in medians at boundary (months)[1,2]	~ 2.16	~ 2.06
	Cumulative Power[3]	90.9%	92.2%

1. The approximate hazard ratio and the approximate difference in medians at the boundary assumes proportional hazards.
2. The approximate difference in medians at the boundary also assumes an 11.7 month observed control arm median.
3. Cumulative power is based on an assumed true hazard ratio of 0.76. These power values allow for the possibility that the study could stop for futility at Interim Analysis 1.

PFS

If the null hypothesis for ORR (at Interim Analysis 1 or Interim Analysis 2) and the null hypothesis for OS (at Interim Analysis 2, Interim Analysis 3, or at the Final Analysis) are both rejected using the Maurer & Bretz procedure then PFS can be tested at the α=0.025 one-sided significance level. However, if only the null hypothesis for OS is rejected then PFS can be tested at the α=0.008 one-sided significance level.

PFS will be analysed at Interim Analysis 2 only, at which point 534 patients are expected to have had a PFS event. This number of patients with a PFS event is based on a control median of 7.6 months, a hazard ratio of 0.74, a 30-month duration of enrolment with gradual ramp-up (as described in the SAP) over the first 12 months, and a constant rate of enrolment for the next 18 months.

13.10.2 Interim Analysis for Futility

At Interim Analysis 1, a futility analysis will take place based on the OS endpoint. A total of approximately 258 OS events are expected to have occurred, which represents approximately 41% of the required number (637) of OS events. The futility boundary is $Z_1 \leq ZFUT$, where Z_1 is derived from a log-rank test stratified by primary tumour location (gallbladder, intra-hepatic, extra-hepatic/ampullary) and extent of disease (locally advanced, metastatic), where ZFUT = 0.0. This boundary can be viewed as corresponding to an effect size favouring the control arm. Kaplan-Meier plots will be produced for OS at Interim Analysis 1 to determine if there is any evidence of delayed onset of efficacy. The IDMC will indicate whether or not they recommend stopping the trial for futility, and such a recommendation to stop for futility should be made only if the futility boundary is crossed and there is no indication of delayed onset of OS efficacy.

The futility boundary is non-binding and so it is ignored in all calculations of Type 1 error. However, for OS power calculations the impact of the futility boundary is taken into account.

The time of Interim Analysis 1 is based on ORR and the exact number of OS events may differ from 258. If the number of OS events at Interim Analysis 1 is ≤248 then ZFUT will be re-calculated using a method described in the SAP.

13.11 Sample Size and Power Calculation

For OS a hazard ratio of 0.76 has been assumed. With 3 looks (at 67%, 85%, and 100% of the required number of OS events as described in Table 12), use of the Lan-DeMets O'Brien-Fleming-like α-spending function (Lan & DeMets, 1983), an overall α=0.020 one-sided, and 1:1 randomisation, then a total of 637 OS events gives 90.9% power (after allowing for the small power loss from having the futility boundary). Initially, α=0.020 one-sided is assigned to OS and α=0.005 one-sided is assigned to ORR.

A thirty-month duration of enrolment is assumed with gradual ramp-up over the first 12 months (as described in the SAP). OS events are assumed to follow an exponential distribution, and a 11.7 month median has been assumed for the control arm as seen in the gemcitabine in combination with cisplatin arm in the ABC-02 trial (Valle *et al*, 2010). The hazard ratio of 0.76 then gives a median of approximately 15.4 months in the NUC-1031 in combination with cisplatin arm (Arm A). If the rate of discontinuation of treatment and the rate of discontinuation from the study (for Arm A and for Arm B) are both assumed to be comparable to the gemcitabine in combination with cisplatin arm from ABC-02, then 811 patients would result in the last of the 637 events occurring at approximately 48 months. It is also assumed that 2% of patients will be

lost to follow-up for OS (with unknown status of dead/alive) and so 828 patients will be randomised.

If the study has not stopped with demonstration of efficacy then a power reassessment will be carried out at Interim Analysis 3, which is scheduled to occur after 541 OS events. This power reassessment will use the CHW method (Cui *et al*, 1999), which guarantees that the maximum experimentwise Type 1 error will still be controlled at the required level. The SAP provides additional details on the procedure that will be used to implement the CHW method, including details on the maximum increase in number of OS events.

For ORR, a 19% rate is assumed for the control arm. The derivation of this rate from the gemcitabine in combination with cisplatin arms within ABC-02, BT-22, and ABC-03 studies (allowing now for the requirement of confirmation, based on patients with performance status 0 or 1 only, including all randomised patients in the denominator, excluding patients with non-measurable disease at baseline, and adjusting for use of BICR rather than Investigator assessment) is provided in Appendix 1 of the SAP. For the NUC-1031 in combination with cisplatin arm (Arm A) a 31% ORR is assumed, which gives an assumed true odds ratio of 1.92.

With 2 looks for ORR (at 65% and 100% as described in Table 11), use of the Lan-DeMets O'Brien-Fleming-like α-spending function (Lan & DeMets, 1983), and with an overall α=0.005 one-sided, then a total of 644 patients with measurable disease at baseline (together with 418 at the interim analysis) gives 80% power. The two looks will take place 28 weeks (corresponding to three scheduled post-baseline radiographic scans plus a one week visit window) after the last of these required numbers of patients have been randomised. The number of randomised patients in the stratum for non-measurable disease at baseline is capped at 82 patients (~10%), which therefore gives at least 746 randomised patients in the measurable disease at baseline stratum.

13.12 Subgroup Analyses

For OS, numbers of events by treatment group, together with hazard ratios (derived from an unstratified Cox proportional hazards model with a single term for treatment within the model) will be provided separately for each of the following subgroups:

- Primary tumour site: gallbladder, intra-hepatic, extra-hepatic, ampullary
- Stage of disease at baseline: metastatic disease, locally advanced disease
- ECOG Performance Status (at baseline): 0, 1
- Region: Asia, Non-Asia (with non-Asia also subdivided and provided separately for North America/Western Europe/Australasia combined, and for Central/Eastern Europe/Rest of the World combined)
- Gender: Male, Female
- Age (at baseline): <65, ≥65
- Measurable disease at baseline: yes, no

For ORR, analyses in terms of estimates (of ORR, as well as counts for CR and for PR) by treatment group, together with odds ratios, difference in proportions of patients with ORR will be given for each of the following subgroups:

- Primary tumour site: gallbladder, intra-hepatic, extra-hepatic, ampullary

- Stage of disease at baseline: metastatic disease, locally advanced disease

For OS as well as for ORR, the statistical methods to derive CIs for the individual subgroups are provided within the SAP.

Additional power calculations are provided in the SAP for subgroup analyses.

13.13 Changes to the Planned Statistical Methods

Any changes to the planned statistical methods from those specified in the final SAP will be documented in the clinical study report (CSR).

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, but are not limited to, laboratory reports and objective disease assessment scans.

An 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 centre can enter a patient into the study, a representative of NuCana or designee will visit the study centre 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, representatives from NuCana and/or its designee will have regular contacts with the study centre, 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.,* charts or records)
- Record and report protocol deviations
- Confirm AEs and SAEs have been identified and 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. Note, during the COVID-19 pandemic, remote visits may replace on-site visits for as short a period of time as possible.

14.3 Patient Confidentiality

Personal data recorded on all documents will be regarded as highly confidential. To preserve each patient's anonymity, only the patient study number, initials and date of birth, as appropriate to country regulations, will be recorded on the eCRFs.

The Investigative 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, REGULATORY AND RISK CONSIDERATIONS

15.1 Good Clinical Practice Compliance

NuCana, designees, 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 Boards/ Ethics Committees

The applicable IRBs/ECs will review all appropriate study documentation in order to safeguard the rights, safety, and wellbeing 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 the appointed CRO before a study centre can enrol any patients into the study. In addition, the IRB/EC must approve all advertising used to recruit patients for the study.

In some countries, 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

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

15.4 Risk Management Considerations

This study will enrol patients with advanced or metastatic BTC, a disease for which there are currently no approved therapies. Given the limited treatment options and poor prognosis, this patient population is considered appropriate for enrolment to a Phase III study of chemotherapy combination treatment. The sites that have been selected for participation in this study have experience in treating this patient population and in conducting Phase III clinical studies.

As described in Section 3.2, the dose and schedule of NUC-1031 has been appropriately determined from the ongoing ABC-08 study, in which the combination of NUC-1031 and cisplatin has been well-tolerated in patients with advanced or metastatic BTC.

To ensure patient safety, the IDMC will review the safety, dosing intensity and clinical activity data during the study. As described in Section 12.16, an initial safety check will be performed after the first 50 patients have been randomised (approximately 25 in each treatment group) and a futility analysis will be performed after approximately 258 OS events have occurred to ensure patients are not exposed to sub-optimal therapies. In addition, dose modification criteria and suggested management procedures for drug-related toxicities are provided in Section 9.

ECGs are being routinely monitored throughout the study for any acute cardiac effects (see Summary Schedule of Events). As outlined in Section 3.5, a robust QT analysis is being conducted as part of a sub-study in 74 patients (approximately 37 each arm) to assess any potential effect of the NUC-1031 + cisplatin combination on the QT interval.

Patient safety will be monitored closely on an ongoing basis through recording and reporting of AEs, routine laboratory tests, and physical examination/vital signs monitoring. Procedures for safety reporting are clearly outlined in Section 12 and post-study follow-up of patients is described in Section 4.4.

15.5 Protocol Amendments

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

15.6 Protocol 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 NuCana 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 major protocol deviation (sometimes referred to as a protocol violation) occurs when there is nonadherence to the protocol that results in a significant, additional risk to the patient, when the patient has failed to adhere to significant protocol requirements, or when there is nonadherence to the FDA or other applicable ICH-GCP guidelines.

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

15.7 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 NuCana or its designee within one working day if any serious breach of ICH-GCP or the protocol is suspected. Upon confirmation of a serious breach, NuCana or its designee will notify the applicable Regulatory Authorities. Typically, serious breach notifications

should be made within seven days of NuCana or its designee becoming aware; however, this timeline may differ as specified by applicable local regulatory requirements.

15.8 Study Reporting Requirements

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

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

15.10 Investigator Documentation

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

15.11 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 and ECG endpoints and the disposition of samples donated via the study must also comply with applicable legislation.

15.12 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 designated 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 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. Mechanisms for publicly disclosing study results include posting on ClinicalTrials.gov, the European Clinical Trials Database (EudraCT) and/or 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

Investigators may not publish or disclose results until the study is completed. In addition, Investigators shall acknowledge that, due to the limited patient numbers in their individual group, the data generated from their individual participation in the study and evaluation of individual results, may not be sufficient from which to draw any meaningful scientific conclusion.

Authorship rights will generally be allocated to Investigators in order of greatest contribution of evaluable patients to the study. NuCana may form a publication committee to evaluate and give approval of any submission for publication or presentation.

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 recognised ethical publications and authorship standards, including Section II of the 'Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals' (ICMJE, 2018).

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18 APPENDICES

Appendix 1: EORTC QLQ-C30 with QLQ-BIL21 Module

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: b b b b
Your birthdate (Day, Month, Year): c e c e c d d e
Today's date (Day, Month, Year): 31 c e c e c d d e

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Biliary Tract Cancer QoL Validation Study

(Ethics Ref: 11/SC/0241)

EORTC QLQ – BIL21

Site ID: ……..……...…… **…nt Study ID:** ……

Today's date (Day, Month, Year): __ _

Patients sometimes report that they … …r problems. Please indicate the extent to which you have experi… …during the past week. Please answer by circling the number…

During the past w…			**Quite bit**	**Very much**
31.	Have v…			4
32.	Have …			
33.	Have you…			
34.	Were you re… as a result of y…			
35.	Have your skin o…			
36.	Have you had itchin…			
37.	Have you been worried…			
38.	Have you been l…			
39.	Have you fe…			
40.	Have you fe…			
41.	Did you have pai…			
42.	Have you had pain in y…			4
43.	Have you had pain in your back?			4
44.	Did you have a bloated feeling in your abdom…		3	4
45.	Have you felt stressed?		3	4
46.	Have you felt less able to enjoy yourself?	2	3	4
47.	Have you worried about your health in the future?	1 2	3	4
48.	Were you worried about your family in the future?	1 2	3	4
49.	To what extent have you been troubled with side-effects from your treatment?	1 2	3	4
50.	Have you had difficulties with drainage tubes/ bags?	1 2	3	4
51.	Have you worried about losing weight?	1 2	3	4

Appendix 2: EQ-5D-5 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 ACTIVITIES *(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 ❑

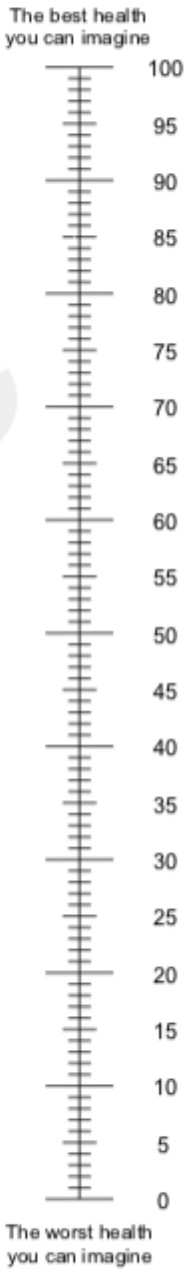
ANXIETY / DEPRESSION

- 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 ❑

2

- 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 3: 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 3. Table 1. Drugs known to prolong QT/QTc interval

Generic Name	Brand Names (Partial List)
Aclarubicin (only on non-US market)	Aclacin®, Aclacinomycine®, Aclacinon®, Aclaplastin®, Jaclacin®
Amiodarone	Cordarone®, Pacerone®, Nexterone®
Anagrelide	Agrylin®, Xagrid®
Arsenic trioxide	Trisenox®
Astemizole (removed from US market)	Hismanal®
Azithromycin	Zithromax®, Zmax®
Bepridil (removed from US market)	Vascor®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®, Largactil®, Megaphen®
Chlorprothixene	Truxal®
Cilostazol	Pletal®
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®
Cisapride (removed from US 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®

Generic Name	Brand Names (Partial List)
Gatifloxacin (removed from US market)	Tequin®
Grepafloxacin (removed from US market)	Raxar®
Halofantrine (only on non-US market)	Halfan®
Haloperidol	Haldol® (US & UK), Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol® (Germany), Einalon S®, Eukystol®, Halosten®, Keselan®, Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®
Hydroquinidine (Dihydroquinidine) (only on non-US market)	Serecor
Hydroxychloroquine	Plaquenil®, Quineprox®
Ibogaine (only on non-US market)	None
Ibutilide	Corvert®
Levofloxacin	Levaquin®, Tavanic®
Levomepromazine (Methotrimeprazine) (only on non-US market)	Nosinan®, Nozinan®, Levoprome®
Levomethadyl acetate (removed from US market)	Orlaam®
Levosulpiride (only on non-US market)	Lesuride®, Levazeo®, Enliva® (with rabeprazole)
Mesoridazine (removed from US market)	Serentil®
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®, Physeptone®, Heptadon®
Moxifloxacin	Avelox®, Avalox®, Avelon®
Nifekalant (only on non-US market)	Shinbit®
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®, Setronax®
Oxaliplatin	Eloxatin®
Papaverine HCl	None
Pentamidine	Pentam®
Pimozide	Orap®
Probucol (removed from US 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®

Generic Name	Brand Names (Partial List)
Sparfloxacin (removed from US 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 US 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®

If clinically relevant or urgent medical intervention is required with a drug known to prolong the QT/QTc interval, study treatment must be paused and options for re-starting the study drugs should be discussed with the Medical Monitor.

Note: Medicines on the above 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, AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755, USA.

https://www.crediblemeds.org/#sthash.vzyRSgay.dpuf. Accessed 11 October 2020.

Appendix 4: Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1

The following paragraphs provide a detailed description of the implementation of RECIST criteria (v1.1; Eisenhauer *et al,* 2009), with slight modifications and additional clarifying text to highlight what is required for this study.

MEASURABILITY OF TUMOUR AT BASELINE DEFINITIONS

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows.

a. Measurable Tumour Lesions

Tumour Lesions. Tumour lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resolution imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

b. Non-Measurable Tumour Lesions

Non-measurable tumour lesions encompass small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), as well as trulynon-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

c. Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered

measurable lesions if the soft tissue component meets the definition of measurability described above
- Blastic bone lesions are non-measurable

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions

Lesions with prior local treatment:

- Tumour 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.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

a. Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 21 days before the beginning of the treatment.

b. Method of Assessment

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during study. Imaging-based evaluation (CT scan, MRI, or PET-CT) should always be used in this study.

Clinical Lesions. Clinical lesions will be considered measurable only when they are superficial and ≥10 mm in diameter as assessed using calipers (*e.g.,* skin nodules). For the case of skin lesions, documentation by colour photography, including a ruler to estimate the size of the lesion, is suggested.

Chest X-Ray. Chest X-ray should not be used in assessment of lesion size or for detecting new lesions. If, however, a new lesion is detected by X-ray then it should be confirmed by CT scan, MRI, or PET-CT.

CT, MRI, PET-CT. 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 on the basis of 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 and PET-CT are also acceptable. 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).

If prior to enrolment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT scan or MRI

scan (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumour type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after a baseline contrast CT scan is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) scan will be performed should also be based on the tumour type and the anatomic location of the disease and should be optimised to allow for comparison with the prior studies if possible.

Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumour Markers, Cytology, Histology. The utilisation of these techniques for objective tumour evaluation cannot generally be advised.

TUMOUR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOUR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumour burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-target lesions (even if the size is >10 mm by CT, MRI, or PET-CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs but, additionally, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumour. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI scan the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example,

an abdominal node that is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

Lesions irradiated within 3 weeks prior to Cycle 1 Day 1 may not be counted as target lesions.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the CRF (*e.g.,* "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

RESPONSE CRITERIA

a. Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumour response for target lesions.

- Complete response (CR): disappearance of all target lesions
    - Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm
- Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline
    - In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm
    - The appearance of one or more new lesions is also considered progression.
- Stable disease (SD): neither sufficient shrinkage (compared to baseline) to qualify for PR nor sufficient increase (taking as reference the smallest sum of diameters while on study) to qualify for PD

b. Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to <10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis <10 mm.

Target Lesions That Become Too Small to Measure. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (*e.g.,* 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure.

When this occurs, it is important that a value be recorded on the CRF as follows:

- 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 and BML (below measurable limit) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and, in that case, BML should not be ticked.

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

c. Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumour response for the group of non-target lesions. Although some non-target lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

- CR: disappearance of all non-target lesions
    - All lymph nodes must be non-pathological in size (<10 mm short axis)
- Non-CR/Non-PD: persistence of one or more non-target lesion(s)
- PD: unequivocal progression of existing non-target lesions
    - The appearance of one or more new lesions is also considered progression

d. Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial

worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non--measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease; that is, an increase in tumour burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localised to widespread or may be described in protocols as "sufficient to require a change in therapy." If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. Although it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

e. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumour (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

EVALUATION OF RESPONSE

a. Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 1 Timepoint response: patients with target lesions (with or without non-target lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2 Timepoint response: patients with non-target lesions only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some studies; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and, during the study, only two lesions were assessed, but those gave a sum of 80 mm; the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess," except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.

Table 3 Best overall response allowing for the requirement of confirmation for PR and CR

Overall Response at First Response Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR. Note: For a BOR of SD, the timepoint on which this is based must be at least 8 weeks after C1D1.

c. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 1-Table 3.

For equivocal findings of progression (*e.g.,* very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment unless there are other indications for discontinuation, such as AEs or co-morbidities. If at the next scheduled assessment progression is confirmed, the date of progression should be the earlier date when progression was suspected.

If a patient undergoes an excisional biopsy or other appropriate approach (*e.g.,* multiple passes with large core needle) of a new lesion or an existing solitary progressive lesion that following serial sectioning and pathological examination reveals no evidence of malignancy (*e.g.,* inflammatory cells, fibrosis, *etc.*), then the new lesion or solitary progressive lesion will not constitute disease progression.

The present study is one in which patients with advanced disease are eligible (*i.e.,* primary disease still or partially present), the primary tumour should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of CR if the primary tumour is still present but not evaluated as a target or non-target lesion.

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**