<u>Invited Clinical trial protocol:</u> Future Oncology

Title (120 characters)

NUC-1031/cisplatin vs gemcitabine/cisplatin in patients with untreated locally advanced/metastatic biliary tract cancer (NuTide:121)

Mairéad Geraldine McNamara[1], Lipika Goyal[2], Mark Doherty[3], Christoph Springfeld[4], David Cosgrove[5], Katrin Marie Sjoquist[6], Joon Oh Park[7], Helena Verdaguer[8], Chiara Braconi[9], Paul J. Ross[10], Aimery De Gramont[11], John Raymond Zalcberg[12], Daniel H. Palmer[13], Juan W. Valle[1], Jennifer J. Knox[14].

[1]Division of Cancer Sciences, The University of Manchester and The Christie NHS Foundation Trust, Manchester M204BX, UK; [2]Massachusetts General Hospital, Boston, MA; [3]Department of Medical Oncology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada; [4]Heidelberg University Hospital, Medical Oncology, National Center for Tumor Diseases, Heidelberg, Germany; [5]Sidney Kimmel Comp Cancer Center, Baltimore, MD; [6]NHMRC Clinical Trials Centre, The University of Sydney, Sydney, Australia; [7]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic of (South); [8]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [9] Beatson West of Scotland Cancer Centre and The University of Glasgow, Glasgow, United Kingdom; [10]Guy's Hospital, London, United Kingdom; [11]Franco-British Institute, Levallois-Perret, France; [12]Peter MacCallum Cancer Centre, Melbourne, Australia; [13]University of Liverpool, Liverpool, United Kingdom; [14]Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada.

Corresponding authors

*Dr Mairéad G McNamara,

Division of Cancer Sciences, University of Manchester & Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester M20 4BX, UK.

Tel: +44-161 446 8106

Fax: +44-161 446 3468

Email: Mairead.McNamara@christie.nhs.uk

*Prof Jennifer J Knox

Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada.

Tel: +1-416-946-2399

Fax: +1-416-946-6546

Email: Jennifer.Knox@uhn.ca

Abstract (120 words)

Gemcitabine/cisplatin (GemCis) is standard of care for first-line treatment of patients with advanced biliary tract cancer (aBTC); new treatments are needed. NUC-1031 is designed to overcome key cancer resistance mechanisms associated with gemcitabine. The tolerability/efficacy signal of NUC-1031/cisplatin in the phase Ib ABC-08 study suggested this combination may represent a more efficacious therapy than GemCis for patients with aBTC, leading to initiation of the global NuTide:121 study which will include 828 patients ≥18 years with untreated histologically/cytologically-confirmed aBTC (including cholangiocarcinoma, gallbladder, or ampullary cancer); randomised (1:1) to NUC-1031 (725 mg/m^2)/cisplatin (25 mg/m^2) or gemcitabine (1000 mg/m^2)/cisplatin (25 mg/m^2), on days 1/8, Q21-days. Primary objectives are OS and ORR. Secondary objectives: PFS, safety, pharmacokinetics, patient-reported quality of life, and correlative studies.

(Investigational New Drug (IND) number: 139058, European Clinical Trials Database: EudraCT Number 2019-001025-28, ClinicalTrials.gov: NCT04163900).

Keywords

Advanced biliary tract cancer, first-line treatment, cisplatin, gemcitabine, NUC-1031, overall survival, objective response rate

Introduction

Biliary tract cancer (BTC) encompasses intrahepatic cholangiocarcinoma, originating from the bile ducts within the liver, extrahepatic cholangiocarcinoma (perihilar and distal cholangiocarcinoma), gallbladder and ampulla of Vater cancer [Nakeeb et al 1996, Valle et al 2016, Overman et al 2013]. There are 11,980 estimated new cases, and 4,090 estimated deaths from gallbladder and BTCs (excluding intrahepatic cholangiocarcinoma) predicted in the United States in 2020 [Siegel et al 2020]. The majority of patients with BTCs present with advanced disease and potentially curative surgical resection is only possible in approximately 20% [Primrose et al 2019]. Standard of care treatment for patients with advanced disease is cisplatin plus gemcitabine, with a median overall survival (OS) reported of 11.7 months for this combination in the Advanced Biliary Cancer (ABC)-02 trial [Valle et al 2010], and of 13.04 months in a more recently reported trial [Valle et al 2020]. The objective response rate (ORR) reported for this combination in the first-line advanced BTC setting varies from 19.5% in the Japanese BT22 study [Okusaka et al 2010], to 26.1% in the ABC-02 study [Valle et al 2010] (both using Response Evaluation Criteria in Solid Tumours (RECIST) 1.0 [Therasse et al 2000], with radiological evaluation every 6 and 12 weeks respectively), and more recently 33% (RECIST 1.1) in a randomised phase II study (radiological evaluation every 6 weeks until 14 months and every 12 weeks thereafter) [Valle et al 2020].

Gemcitabine (a nucleoside analogue) has a high susceptibility to cancer cell resistance [Nakano et al 2007], and the addition of a phosphoramidate motif to gemcitabine may protect it against key resistance mechanisms [Slusarczyk et al 2014]. One of these phosphoramidate prodrugs is NUC-1031, and compared with gemcitabine is significantly less dependent on deoxycytidine kinase and nucleoside transporters and is resistant to cytidine-mediated

degradation [Slusarczyk et al 2014, Sarr et al 2019]. In a phase I dose escalation first-in-human study of NUC-1031 in 68 patients with advanced solid tumours who had progressed after standard of care treatment [Blagden et al 2018], the recommended phase II dose (RP2D) in monotherapy was 825mg/m^2 on days 1, 8 and 15 of a 28 day cycle. It was well tolerated and clinically-significant anti-tumour activity was reported, including patients previously treated with gemcitabine and in cancers not traditionally considered gemcitabine-responsive [Blagden et al 2018]. The most common adverse reactions noted were reversible myelosuppression, gastrointestinal disturbance, fatigue and liver function enzyme elevation, not dissimilar to those observed with gemcitabine [Blagden et al 2018]. Seven patients with cholangiocarcinoma (primary site not specified) were included in this study, with 6 of these receiving ≥2 cycles of NUC-1031, and so were evaluable for efficacy assessment using RECIST 1.1 [Eisenhauer et al 2009]; the best response to therapy in 5 of these patients was stable disease (SD), with 3 showing target lesion size reduction [Blagden et al 2018].

Background and rationale

The phase Ib ABC-08 trial (NCT02351765) was developed to determine the safety and the RP2D of NUC-1031 (starting dose 625mg/m^2) in combination with cisplatin (25mg/m^2) (administered day 1 and 8 of a 21 day cycle) in patients with advanced BTC in the first-line setting; secondary objectives included evaluation of ORR, progression-free survival (PFS) and OS and to undertake pharmacokinetic analyses. In the interim analysis of ABC-08, the combination of NUC-1031 and cisplatin was well-tolerated over multiple cycles, with no unexpected adverse events, no dose-limiting toxicities, no discontinuations due to NUC-1031-associated toxicity and no Grade 4 adverse events [McNamara et al 2018]. There were no differences in ORR or pharmacokinetics between the two doses of NUC-1031 (625 or 725 mg/m^2), thus the 725mg/m^2 dose of NUC-1031 was selected as the RP2D in combination

with cisplatin in patients with advanced BTC for phase III evaluation in the first-line advanced setting, additionally allowing greater scope for dose reduction, if required.

Based on data from the ABC-08 study, the global randomised phase III clinical study (NuTide:121) comparing NUC-1031 (725mg/m^2) and cisplatin (25mg/m^2) with gemcitabine (1,000mg/m^2) and cisplatin (25mg/m^2) (days 1 and 8 of a 21 day cycle) for the first-line treatment of patients with advanced BTC was initiated (NCT04163900) and further details will now follow.

Design

Study design

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

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 intravenously on days 1 and 8 of a 21 day cycle, in previously untreated patients with locally advanced or metastatic BTC. 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 documentation of disease progression, evidence of unacceptable treatment-related Adverse Events (AEs) despite optimal medical management and/or dose modification, or withdrawal of consent. Tumour measurements and disease response assessments are to be performed every 9 weeks (±7 days) (approximating three cycles) from Cycle 1, Day 1 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 every 12 weeks (±14 days) thereafter until PD is radiologically confirmed. This study will be conducted at approximately 120 sites across North America, Europe, and Asia-Pacific over 30 months. Target enrolment is 828 patients. The study will continue until 637 deaths have occurred, unless the results for overall survival (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).

Eligibility criteria:

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 the protocol, including the Quality of Life (QoL) questionnaires (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 [Aaronson et al 1993] with QLQ-BIL21 [Friend et al 2011] and EQ-5D-5 questionnaire [EQ-5D-5L Ref]).

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. Patients with measurable (as per RECIST 1.1 criteria [Eisenhauer et al 2009]) or non-measurable disease are permitted.

5. Life expectancy ≥16 weeks.

6. Eastern Cooperative Oncology Group (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 ≥10 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.

• Serum creatinine ≤1.5 × ULN or creatinine clearance ≥45 mL/min actual or calculated by the Cockcroft-Gault method.

• International normalised ratio (INR) <1.5 and partial thromboplastin time (PTT) <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. Infected patients with Human Immunodeficiency Virus who are healthy and have a low risk of Acquired Immune Deficiency 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

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 the excipients contained in NUC-1031 or diluent solution (dimethylacetamide [DMA], Kolliphor ELP, Tween 80).

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, low grade prostate cancer not requiring treatment or other solid tumours curatively treated with no evidence of disease for ≥3 years.

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. 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.

8. Prior exposure to another investigational agent within 28 days prior to randomisation.

9. Major surgery within 28 days prior to randomisation; patient must have completely recovered from any prior surgical or other procedures.

10. Pregnant or breastfeeding.

11. Residual toxicities from prior treatments or procedures which have not regressed to Grade ≤1 severity (Common Terminology Criteria for Adverse Events (CTCAE) v5.0), except for alopecia or ≤Grade 2 peripheral neuropathy.

12. Concomitant use of drugs at doses known to cause clinically relevant prolongation of QT/QTc interval (see Appendix 1).

13. Administration of a live vaccination within 28 days prior to randomisation.

14. Ongoing or recent (≤6 months) hepatorenal syndrome.

Planned sample size and study period:

For overall survival (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 Supplementary Table 1), 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 Statistical Analysis Plan (SAP)). Overall survival 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 (Supplementary Table 1), 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 experiment wise Type 1 error will still be controlled at the required level. The SAP will provide 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 [Valle et al 2010], BT-22 [Okusaka et al 2010], and ABC-03 [Valle et al 2015] studies (allowing for the requirement of confirmation, based on patients with ECOG 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 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 Supplementary Table 2), 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.

There are dual primary endpoints: OS and ORR. 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.

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, ampulla of Vater cancer

• **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 years, ≥65 years

• **Measurable disease at baseline**: yes, no

For ORR, analyses in terms of estimates (of ORR, as well as counts for complete response (CR) and for partial response (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, ampulla of Vater cancer

• **Stage of disease at baseline**: metastatic disease, locally advanced disease

Study procedures:

Patients will be randomised in this study from approximately 120 sites in North America, Europe, and Asia Pacific. 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 over 60 minutes 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 over 60 minutes followed by IV infusion of gemcitabine at 1000 mg/m^2 over 30 minutes on days 1 and 8 of each 21 day cycle. Tumour measurements and disease response assessments

are to be performed every 9 weeks (±7 days) (approximating three cycles) from Cycle 1 Day 1 until disease progression. Objective disease assessment will be performed by radiologic evaluation and assessed according to RECIST 1.1 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.

Patients may continue to receive study treatment until 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 will be captured in the patient medical record and on the treatment discontinuation page of the case report form (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 every 12 weeks (±14 days) until such time as progression can be documented or new treatment is initiated. 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.

Study objectives and endpoints:

Primary Objectives

• Overall Survival.

• Objective Response Rate 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) based on BICR.

• Safety.

• Pharmacokinetics of NUC-103.

• Patient-reported Quality of Life.

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.

Primary Endpoints:

• Overall survival, defined as the time from randomisation to the time of death from any cause.

• Objective Response Rate, defined as the percentage of patients achieving a confirmed CR or PR to treatment, as assessed by BICR according to RECIST 1.1 criteria [. This will be assessed only in patients with measurable disease at baseline.

Secondary Endpoints:

Key Secondary Endpoint

• Progression-free survival, based on BICR according to RECIST 1.1 criteria [Eisenhauer et al 2009] defined as the time from randomisation to the first observation of objective tumour progression or death from any cause. Assessment of progression for the purposes of measuring PFS in patients with non-measurable disease will be performed according to RECIST 1.1 recommendations [Eisenhauer et al, 2009].

Other Secondary Endpoints:

Efficacy

• Duration of Response, 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.

• Disease Control Rate, based on BICR according to RECIST 1.1 criteria [Eisenhauer et al, 2009], defined as the percentage of patients demonstrating a BOR of CR, PR, or stable disease (SD).

Objective disease assessment will be performed radiologically and assessed according to RECIST 1.1 criteria [Eisenhauer et al, 2009]. 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:

• Treatment emergent adverse events (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 performance 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 (PK) 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 Ctrough and Cmax plasma levels.

Patient-Reported Quality of Life

Patient-reported QoL will be assessed using the European Organisation for Research and Treatment (EORTC) QoL Questionnaire (QLQ-C30) [Aaronson et al 1993] QLQ-BIL21 module [Friend et al 2011] and the 5-level EuroQol five-dimension scale (EQ-5D-5L) [EQ-5D-5L Ref]).

Tertiary Endpoints:

Health economics

Health economics will be assessed through collection of core health resource use information using 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.

Statistics

Full details of the planned analyses will be provided in a separate SAP. The statistical principles applied in the design and planned analyses of this study are consistent with ICH E9 [Ref] and FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018) [Ref].

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

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.

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.

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.

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.

Primary Analysis Populations

The ITTMD will be the primary analysis population for evaluating ORR and DCR. Duration of Response 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.

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.

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 will be provided within the SAP.

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) of 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.

Progression-free survival, 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 Supplementary Table 3.

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. For further information on Type 1 error control across the Interim Analyses and across the multiple endpoints, see supplementary material 1.

Institutional Review Boards (IRBs)/ Ethics Committees (ECs)

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 informed consent form will be approved in writing by the applicable IRBs/ECs for each site. Authorisation to conduct the study will be obtained from the applicable Regulatory

Authorities prior to initiating the study in each participating country. All patients are required to give written informed consent before randomisation and the trial will be conducted in accordance with the Declaration of Helsinki.

Conclusion

The 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 (NuTide:121) is open to recruitment. This study will be conducted at approximately 120 sites across North America, Europe, and Asia-Pacific over a 30 month duration, recruiting 828 patients. There are dual primary endpoints: OS and ORR. 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.

Executive summary

- Standard of care first-line treatment for patients with advanced biliary tract cancer is the gemcitabine/cisplatin combination, resulting in a median overall survival of less than 1 year.
- New therapeutic combinations are required.
- Efficacy of gemcitabine is limited by cancer cell resistance mechanisms.
- A phosphoramidate modification of gemcitabine, NUC-1031 was designed to overcome these key gemcitabine resistance mechanisms.
- In a first-in-human study, including 7 patients with cholangiocarcinoma, NUC-1031 was well tolerated and demonstrated clinically significant anti-tumour activity in patients with previously treated advanced solid tumours.
- The ABC-08 study determined that the recommended phase 2 dose of NUC-1031 in combination with cisplatin in the first-line setting in patients with advanced biliary tract cancer was 725mg/m^2.
- This resulted in the development of the global randomised phase III clinical study (NuTide:121) comparing NUC-1031 (725mg/m^2) and cisplatin (25mg/m^2) with gemcitabine (1,000mg/m^2) and cisplatin (25mg/m^2) (days 1 and 8 of a 21 day cycle) for the first-line treatment of patients with advanced biliary tract cancer.

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Figure legends

Figure 1

NuTide:121 study schema

CR; Complete response, **PR**: Partial response, **RECIST:** Response evaluation criteria in solid tumours. Patients who stop treatment with no evidence of disease progression as defined by RECIST 1.1 criteria [Eisenhauer et al 2009] will continue to have scans every 12 weeks (±14 days) until disease progression in order to determine duration of overall response and progression-free survival.

Supplementary Figure 1

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

ORR: Overall response rate, **PFS:** Progression-free survival, **OS:** Overall survival