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

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Gemcitabine/cisplatin 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 that this combination may represent a more efficacious therapy than gemcitabine/cisplatin 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); randomized (1:1) to NUC-1031 (725 mg/m²)/cisplatin (25 mg/m²) or gemcitabine (1000 mg/m²)/cisplatin (25 mg/m²), on days 1/8, Q21-days. Primary objectives are overall survival and objective response rate. Secondary objectives: progression-free survival, 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 identifier: NCT04163900.

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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 [1–3]. There are 11,980 estimated new cases and 4090 estimated deaths from gallbladder and BTCs (excluding intrahepatic cholangiocarcinoma) predicted in the USA in 2020 [4]. The majority of patients with BTCs present with advanced disease and potentially curative surgical resection is only possible in approximately 20% [5].
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 [6] and of 13.04 months in a more recently reported trial [7]. 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 [8], to 26.1% in the ABC-02 study [6] (both using Response Evaluation Criteria in Solid tumors [RECIST] 1.0 [9], with radiological evaluation every 6 and 12 weeks, respectively) and more recently 33% (RECIST 1.1) in a randomized Phase II study (radiological evaluation every 6 weeks until 14 months and every 12 weeks thereafter) [7].

Gemcitabine (a nucleoside analog) has a high susceptibility to cancer cell resistance [10] and the addition of a phosphoramidate motif to gemcitabine may protect it against key resistance mechanisms [11]. 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 [11,12]. In a Phase I dose-escalation first-in-human study of NUC-1031 in 68 patients with advanced solid tumors who had progressed after standard of care treatment [13], the recommended Phase II dose (RP2D) in monotherapy was 825 mg/m² on days 1, 8 and 15 of a 28-day cycle. It was well tolerated and clinically significant antitumor activity was reported, including patients previously treated with gemcitabine and in cancers not traditionally considered gemcitabine responsive [13]. The most common adverse reactions noted were reversible myelosuppression, gastrointestinal disturbance, fatigue and liver function enzyme elevation, not dissimilar to those observed with gemcitabine [13]. Seven patients with cholangiocarcinoma (primary site not specified) were included in this study, with six of these receiving ≥ 2 cycles of NUC-1031 and so were evaluable for efficacy assessment using RECIST 1.1 [14]; the best response to therapy in five of these patients was stable disease, with three showing target lesion size reduction [13].

Background & rationale
The Phase Ib ABC-08 trial (NCT02351765) was developed to determine the safety and the RP2D of NUC-1031 (starting dose 625 mg/m²) in combination with cisplatin (25 mg/m²; administered on days 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), OS and 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 [15]. There were no differences in ORR or pharmacokinetics between the two doses of NUC-1031 (625 or 725 mg/m²), thus the 725 mg/m² dose of NUC-1031 was selected as the recommended dose 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 randomized Phase III clinical study (NuTide:121) comparing NUC-1031 (725 mg/m²) and cisplatin (25 mg/m²) with gemcitabine (1000 mg/m²) and cisplatin (25 mg/m²); 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. Two on-going global studies are evaluating the addition of immunotherapy to standard of care cisplatin plus gemcitabine in unsselected patients with advanced BTC in the first-line setting (e.g., durvalumab: NCT03875235 [TOPAZ-1] and pembrolizumab: NCT04003636 [KEYNOTE-966], respectively); NuTide:121 will investigate whether the addition of NUC-1031 to cisplatin is more efficacious than the cisplatin/gemcitabine combination in the first-line advanced setting.

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, randomized Phase III study of NUC-1031 in combination with cisplatin (Arm A) compared with 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 randomized 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 (this will be the largest global Phase III randomized study of its kind in a rare disease group; ABC-02 enrolled 410 patients). Patient-reported quality of life (QoL) will be assessed using the European Organisation for Research and Treatment (EORTC) QoL Questionnaire (QLQ-
828 patients aged ≥ 18 years with histologically or cytologically proven biliary adenocarcinoma, including cholangiocarcinoma, gallbladder or ampullary cancer

Eligible patient randomisation in 1:1 ratio stratified by measurable disease at baseline (yes, no), metastatic disease (yes, no), tumour location (gallbladder, intra-hepatic, extra-hepatic/ampullary), and region (Asia, non-Asia).

**Treatment**

**Arm A:**
NUC-1031: 725 mg/m² + cisplatin 25 mg/m² administered intravenously on days 1 & 8 of a 21-day cycle  
**n = 414**

**Arm B:**
gemcitabine: 1000 mg/m² + cisplatin 25 mg/m² administered intravenously on days 1 & 8 of a 21-day cycle  
**n = 414**

9-weekly radiographic scan – chest abdomen pelvis – RECIST v1.1

- Progressive disease
- Unacceptable toxicity
- Patient decision to stop treatment

Stop treatment

Follow-up until death

- Response (CR or PR) or Stable disease

Continue treatment

**Primary outcomes:**
Objective response rate & overall survival

**Secondary outcomes:**
1. Progression-free survival  
2. Other efficacy measures (duration of response, 18 & 12-month survival, & disease control rate)  
3. Safety  
4. Pharmacokinetics  
5. Patient-reported quality of life

Figure 1. NuTide:121 study schema. Patients who stop treatment with no evidence of disease progression as defined by RECIST 1.1 [14] will continue to have scans every 12 weeks (±14 days) until disease progression in order to determine duration of objective response and progression-free survival.  
CR: Complete response; PR: Partial response; RECIST: Response evaluation criteria in solid tumors.
C30) [16], QLQ-BIL21 module [17] and the 5-level EuroQol 5D scale (EQ-5D-5L) [18]) at baseline, each cycle day 1 and 30 days after the last dose (end of treatment). Pharmacokinetic sampling will be on cycle 1, day 1 only. Tumor 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), tumor measurements and disease response assessments should continue every 12 weeks (±14 days) thereafter until PD is radiologically confirmed. Archived tumor specimens will be collected for biomarker analysis (nonspecified). This study will be conducted at approximately 120 sites across North America, Europe and Asia Pacific over 30 months. Target enrollment is 828 patients. There are dual primary end points: OS and ORR. The study will continue until 637 deaths have occurred, unless the results for OS meet the prespecified 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; see Figure 1 for study scheme).

Eligibility criteria
Inclusion criteria
To be enrolled in this study, patients must meet all of the following criteria during the screening period:

- Written informed consent and authorization to use and disclose health information;
- Ability to comprehend and willingness to comply with the requirements of the protocol, including the QoL questionnaires EORTC QLQ-C30 [16] with QLQ-BIL21 [17] and EQ-5D-5 questionnaire [18];
- Female or male patients aged ≥18 years;
- Histologically or cytologically confirmed adenocarcinoma of the biliary tract (including gallbladder, intra- and extra-hepatic biliary ducts and ampulla of Vater cancers) that is locally advanced, unresectable or metastatic. Patients with measurable (as per RECIST 1.1 [14]) or nonmeasurable disease are permitted;
- Life expectancy ≥16 weeks;
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1;
- 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 period;
- Adequate bone marrow, hepatic and renal function, as evidenced by:
  - Absolute neutrophil count (ANC) ≥1500/μl without colony-stimulating factor support
  - Platelet count ≥100,000/μl
  - Hemoglobin ≥10 g/dl without need for hematopoietic 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 regarding biliary drainage, patients whose bilirubin and biliary function is recovering may be re-tested during the screening period
  - ALT and/or AST <5 × ULN
  - Serum creatinine ≤1.5 × ULN or creatinine clearance ≥45 ml/min actual or calculated by the Cockcroft–Gault method
  - International normalized ratio <1.5 and partial thromboplastin time <1.5 × ULN; does not apply to patients on an anticoagulant with stable dose 28 days prior to first dose
- 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 corrected QT interval (QTc) prolongation, patients may be enrolled based on a careful risk-benefit assessment;
- Infected patients with HIV who are healthy and have a low risk of AIDS-related outcomes may be included in this study.
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 sterilization) 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;

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:

- Combined or mixed hepatocellular/cholangiocarcinoma;
- Prior systemic therapy for advanced or metastatic BTC. 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 enrollment is permitted. The following prior interventions are allowed, provided the patient has fully recovered:
  - Surgery: noncurative resection with macroscopic residual disease or palliative bypass surgery. Patients who have previously undergone curative surgery must now have evidence of nonresectable disease requiring systemic chemotherapy
  - Radiotherapy: prior radiotherapy (with or without radio-sensitising low-dose chemotherapy) for localized disease and there is now clear evidence of disease progression requiring systemic chemotherapy
  - Photodynamic therapy: prior photodynamic therapy for localized disease with no evidence of metastatic disease or for localized 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
  - 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, Kolliphor ELP, Tween 80);
  - Symptomatic central nervous system or leptomeningeal metastases;
  - 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 tumors curatively treated with no evidence of disease for ≥3 years;
  - 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;
  - 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;
  - Prior exposure to another investigational agent within 28 days prior to randomization;
  - Major surgery within 28 days prior to randomization; patient must have completely recovered from any prior surgical or other procedures;
  - Pregnant or breastfeeding;
  - 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;
  - Concomitant use of drugs at doses known to cause clinically relevant prolongation of QT/QTc interval (see Supplementary Information 1);
  - Administration of a live vaccination within 28 days prior to randomization;
  - Ongoing or recent (≤6 months) hepatorenal syndrome.
Planned sample size & study period
For OS, a hazard ratio (HR) of 0.76 has been assumed. With three 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 $\alpha$-spending function [19], an overall $\alpha = 0.020$ one-sided and 1:1 randomization, then a total of 637 OS events gives 90.9% power (after allowing for the small power loss from having the futility boundary). Initially, $\alpha = 0.020$ one-sided is assigned to OS and $\alpha = 0.005$ one-sided is assigned to ORR.

A 30-month duration of enrollment 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 an 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 [6]. The HR 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 randomized.

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 [20], 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 [6], BT-22 [8] and ABC-03 [21] studies (allowing for the requirement of confirmation, based on patients with ECOG performance status 0 or 1 only, including all randomized patients in the denominator, excluding patients with nonmeasurable disease at baseline and adjusting for use of blinded independent central review (BICR) rather than investigator assessment) will be 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 two looks for ORR (at 65 and 100% as described in Supplementary Table 2), use of the Lan-DeMets O’Brien-Fleming-like $\alpha$-spending function [19] and with an overall $\alpha = 0.005$ 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 postbaseline radiographic scans plus a one week visit window) after the last of these required numbers of patients have been randomized. The number of randomized patients in the stratum for nonmeasurable disease at baseline is capped at 82 patients (~10%), which therefore gives at least 746 randomized patients in the measurable disease at baseline stratum.

There are dual primary end points: OS and ORR.

Subgroup analyses
For OS, numbers of events by treatment group, together with HRs (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 tumor 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, $\geq$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 tumor 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 randomized in this study from approximately 120 sites in North America, Europe and Asia Pacific.

Patients may be randomized up to one working day prior to cycle 1, day 1 using an independent Interactive Voice/Web Response System (IxRS). At this time, the investigator will enter into the IxRS system their site information, metastatic disease at baseline (yes, no) and the primary tumor location (gallbladder, intra-hepatic, extra-hepatic or ampulla of Vater cancer). The BICR will be already entered into the IxRS system and so it will be known whether the patient has measurable disease at baseline (yes, no). The IxRS will then indicate to which treatment group the patient has been randomized and the study site will obtain the patient's identification number from the IxRS.

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

• Measurable disease at baseline (yes, no) as determined by BICR;
• Metastatic disease at baseline (yes, no);
• Tumor location (gallbladder, intra-hepatic, extra-hepatic/ampulla of Vater cancer);
• Region (Asia, non-Asia).

In Arm A, cisplatin will be administered by intravenous (iv.) infusion at 25 mg/m² over 60 min followed by iv. infusion of NUC-1031 at 725 mg/m² 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/m² over 60 min followed by iv. infusion of gemcitabine at 1000 mg/m² over 30 minutes on days 1 and 8 of each 21-day cycle. Tumor 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. 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 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 PD, 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 deriving 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 tumor 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 anticancer therapies. Following discontinuation of study treatment, patients will receive treatment in accordance with local standard of care.

Study objectives & end points
Primary objectives
• Overall survival;
• ORR based on BICR in patients with measurable disease at baseline.

Secondary objectives
• PFS based on BICR;
• Duration of response based on BICR;
• 18- and 12-month survival;
• Disease control rate based on BICR;
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- Safety;
- Pharmacokinetics of NUC-103;
- Patient-reported QoL.

**Tertiary objectives**
- Health economics;
- Assessment of archival tumor sample characteristics that may further an understanding of the mechanism(s) through which the clinical activity of NUC-1031 is achieved.

**Primary end points**
- OS, defined as the time from randomization to the time of death from any cause;
- ORR, defined as the percentage of patients achieving a confirmed CR or PR to treatment, as assessed by BICR according to RECIST 1.1 [14]. This will be assessed only in patients with measurable disease at baseline.

**Secondary end points**

**Key secondary end point**
- PFS, based on BICR according to RECIST 1.1 [14] defined as the time from randomization to the first observation of objective tumor 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 [14].

**Other secondary end points**

**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 tumor progression or death from any cause;
- 18-month survival;
- 12-month survival;
- Disease control rate, based on BICR according to RECIST 1.1 [14], defined as the percentage of patients demonstrating a best objective response of CR, PR or stable disease.

Objective disease assessment will be performed radiologically and assessed according to RECIST 1.1 [14]. 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 CTCAE v5.0;
- Serious TEAEs;
- Deaths due to TEAEs;
- Treatment discontinuations due to TEAEs;
- Clinically significant changes in laboratory parameters;
- Changes in ECOG performance status, physical exam, ECG and vital signs.

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

**Pharmacokinetics of NUC-1031**
Sparse pharmacokinetic sampling will be taken on cycle 1, day 1 at the end of infusion, 2 h after the end of infusion and 6 h after the end of infusion, to capture C_{trough} and C_{max} plasma levels.

**Patient-reported QoL**
Patient-reported QoL will be assessed using the EORTC QoL Questionnaire (QLQ-C30) [16], QLQ-BIL21 module [17] and the EQ-5D-5L [18].
Tertiary end points
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 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 tumor 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 [22] and US FDA Guidance for Industry: Clinical Trial End points for the Approval of Cancer Drugs and Biologics (2018) [23].

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

Intention-to-treat population
The intention-to-treat (ITT) population will consist of all patients who are randomized, regardless of whether any study medication was received. Patients will be summarized on the basis of the treatment group to which they were randomized.

Intention-to-treat with measurable disease at baseline population
The intention-to-treat with measurable disease at baseline (ITTMD) population will consist of all patients who are randomized 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 summarized on the basis of the treatment group to which they were randomized.

Modified intention-to-treat population
The modified intention-to-treat population will consist of all patients who are randomized and received any study medication. Patients will be summarized on the basis of the treatment group to which they were randomized.

Safety population
The safety population will consist of all patients who are randomized and receive any study medication. Patients will be summarized on the basis of the actual study medication received, in other words, 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 summarized under Arm A.

Primary analysis populations
The ITTMD will be the primary analysis population for evaluating ORR and disease control rate. Duration of Response will be analysed in the subset of patients (ITTMD), who have confirmed response. For evaluating all other efficacy end points, the primary analysis population will be the ITT population. The modified intention-to-treat population will be used only for a secondary analysis of the OS primary end point. The safety population will be the primary analysis population for evaluating all safety end points.

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 summarized. Major protocol deviations (as defined in a separate Protocol Deviation Management Plan) will also be summarized by reason and overall.
Demographics & baseline characteristics
Demographic and baseline characteristics will be summarized by treatment group for the ITT, ITTMD and safety populations. Full details on the variables summarized will be provided within the SAP.

Three interim efficacy analyses are planned according to the statistical analysis plan
• The first interim analysis (Interim Analysis 1) will evaluate the ORR primary end point. It will be performed 28 weeks after 418 patients in the measurable disease stratum have been randomized. 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 end points. 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 randomized. 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 end point 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 end point. It will take place after 637 deaths have been observed and is expected to occur approximately 48 months after the first patient is randomized.

PFS, the key secondary end point, 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 end points 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. The statistical analysis plan will provide information on Type 1 error control across the Interim Analyses and across the multiple end points.

Institutional review boards/ethics committees
The applicable institutional review boards (IRBs)/ethics committees (ECs) will review all appropriate study documentation in order to safeguard the rights, safety and well being of the patients. The final study protocol and informed consent form will be approved in writing by the applicable IRBs/ECs for each site. Authorization 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 randomization and the trial will be conducted in accordance with the Declaration of Helsinki.

Conclusion
The Phase III open-label, multicenter, randomized 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 end points: OS and ORR.

Supplementary data
An infographic accompanies this paper at the end of the references section. To download the infographic that accompanies this paper and view the supplementary data, please visit the journal website at: www.future-science.com/doi/suppl/10.2217/fon-2020-0247

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Executive summary

Background
- 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 approximately 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 seven patients with cholangiocarcinoma, single-agent NUC-1031 was well tolerated and demonstrated clinically significant antitumor activity in patients with previously treated advanced solid tumors.

Background & rationale
- The ABC-08 study determined that the recommended dose of NUC-1031 in combination with cisplatin in the first-line setting in patients with advanced biliary tract cancer was 725 mg/m².
- This resulted in the development of the global randomized Phase III clinical study (NuTide:121) comparing NUC-1031 (725 mg/m²) and cisplatin (25 mg/m²) with gemcitabine (1000 mg/m²) and cisplatin (25 mg/m²; days 1 and 8 of a 21-day cycle) for the first-line treatment of patients with advanced biliary tract cancer.

References
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• Confirms the findings of the ABC-02 clinical trial (cisplatin/gemcitabine is efficacious in the first-line treatment of patients with
advanced biliary tract cancer).
10. Nakano Y, Tanno S, Koizumi K et al. Gemcitabine chemoresistance and molecular markers associated with gemcitabine transport and

- Describes the application of protide technology which led to the development of NUC-1031.


- Establishes that the dose of 825 mg/m² of NUC-1031 was the recommended Phase II dose in monotherapy.


- Establishes the dose of NUC-1031 to be used in combination with cisplatin in the first-line treatment of patients with advanced biliary tract cancer.


NUC-1031/cisplatin vs gemcitabine/cisplatin in untreated locally advanced/metastatic BTC Clinical Trial Protocol

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

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**Article URL**

**Study registration number**
NCT04163900

**Objectives**

**Primary objectives**
- OS
- ORR based on BICR in patients with measurable disease at baseline

**Secondary objectives**
- PFS based on BICR
- 18-month survival
- Safety
- Patient-reported 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 and treatment**

**Treatment**

**Arm A:**
- NUC-1031: 725 mg/m² + cisplatin 25 mg/m² administered intravenously on days 1 & 8 of a 21-day cycle
- n = 414

**Arm B:**
- gemcitabine: 1000 mg/m² + cisplatin 25 mg/m² administered intravenously on days 1 & 8 of a 21-day cycle
- n = 414

**30-month duration of enrollment**

**Key eligibility criteria**

**Aged ≥18 years**

Histologically- or cytologically proven biliary adenocarcinoma, including cholangioadeno, gallbladder or ampullary cancer

**Life expectancy ≥16 weeks**

ECOG performance status 0 or 1

**Objective disease assessment will be performed by radiologic evaluation and assessed according to RECIST 1.1.**

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.

**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).**

**82 patients aged ≥ 18 years with histologically or cytologically proven biliary adenocarcinoma, including cholangioadeno, gallbladder or ampullary cancer**

**82 patients aged ≥ 18 years with histologically or cytologically proven biliary adenocarcinoma, including cholangioadeno, gallbladder or ampullary cancer**