CLINICAL STUDY PROTOCOL
EudraCT Number: 2018-002647-29
US IND Number: 128897
A Multi-Centre, Randomised, Open-Label, Phase 2 Study to Assess the Safety, Tolerability and Efficacy of Fimaporfin-Induced Photochemical Internalisation of Gemcitabine Complemented by Gemcitabine/Cisplatin Chemotherapy Versus Gemcitabine/Cisplatin Alone in Patients With Inoperable Cholangiocarcinoma

PCIA 203/18

Sponsor:	PCI Biotech AS Ullernchausséen 64 0379 Oslo Norway
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]
Version of Protocol:	Final/3.0 (Global Amendment 2)
Date of Protocol:	13 Jul 2020

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6 (R2): Good Clinical Practice.

Protocol Approval – Sponsor Signatory

Study Title	A Multi-Centre, Randomised, Open-Label, Phase 2 Study to Assess the Safety, Tolerability and Efficacy of Fimaporfin-Induced Photochemical Internalisation of Gemcitabine Complemented by Gemcitabine/Cisplatin Chemotherapy Versus Gemcitabine/Cisplatin Alone in Patients With Inoperable Cholangiocarcinoma
Protocol Number	PCIA 203/18
Protocol Date	13 Jul 2020

Protocol accepted and approved by:

[redacted]

Signature Date

Protocol Approval – Principal/Coordinating Investigator

Study Title	A Multi-Centre, Randomised, Open-Label, Phase 2 Study to Assess the Safety, Tolerability and Efficacy of Fimaporfin-Induced Photochemical Internalisation of Gemcitabine Complemented by Gemcitabine/Cisplatin Chemotherapy Versus Gemcitabine/Cisplatin Alone in Patients With Inoperable Cholangiocarcinoma
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Protocol accepted and approved by:

Principal/Coordinating Investigator

[redacted]

Signature Date

Protocol Approval – Lead Statistician

Study Title	A Multi-Centre, Randomised, Open-Label, Phase 2 Study to Assess the Safety, Tolerability and Efficacy of Fimaporfin-Induced Photochemical Internalisation of Gemcitabine Complemented by Gemcitabine/Cisplatin Chemotherapy Versus Gemcitabine/Cisplatin Alone in Patients With Inoperable Cholangiocarcinoma
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Protocol accepted and approved by:

Lead Statistician

[redacted]

Signature Date

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Multi-Centre, Randomised, Open-Label, Phase 2 Study to Assess the Safety, Tolerability and Efficacy of Fimaporfin-Induced Photochemical Internalisation of Gemcitabine Complemented by Gemcitabine/Cisplatin Chemotherapy Versus Gemcitabine/Cisplatin Alone in Patients With Inoperable Cholangiocarcinoma" and the accompanying Investigator's Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 3.0, dated 13 Jul 2020, the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with PCI Biotech AS or implement protocol changes without an approval from the independent ethics committee and regulatory authorities, except to eliminate an immediate risk to patients. I agree to administer study treatment only to patients under my personal supervision or the supervision of a sub-investigator.

I will not supply the investigational drug to any person not authorised to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorisation from PCI Biotech AS.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

Summary of Changes

Protocol Amendment History and Reasons for Amendment

Version	Date	Reason for Amendment
Version 1.0	30 Aug 2018	Original Protocol
Version 2.0 (Global Amendment 1)	04 Dec 2019	• To add clarifications to the original protocol documented in the administrative letters (dated 31 Oct 2018 and 24 Jan 2019) and incorporate the content of each of the local amendments (Norway, Germany and Denmark) and requests made by the French, Italian and UK Authorities and the US Food and Drug Agency. o List of abbreviations was updated. o Exploratory objective 2 wording was clarified to distinguish between standard tumour markers and exploratory biomarkers. o Definition of any measurable disease for purposes of randomisation stratification clarified. o Hospitalisation details for patients in Arm A were added. o Stent placement - text revised for clarity. o Specific safety evaluation criteria were added that must be fulfilled before patients receive the second PCI treatment. o Updated information on the currently-ongoing Phase 1/2 study (PCIA 202/12) with fimaporfin-induced PCI of gemcitabine. o Detailed justification was provided for the chosen dose and the regimen. o Merged inclusion criterion 3 and former inclusion criterion 7 to clarify that CCA needs to be perihilar or distal, with a stenosis that has been stented or requires stenting, and that is accessible for PCI light treatment. o Inclusion criterion 4 expanded to clarify the 'inoperable' includes being considered unsuitable for 'partial liver resection or liver transplantation'. o Specified exclusion of patients with a history of frequently recurring septic biliary events caused by non-malignant strictures (exclusion criteria 3). o Excluded patients receiving prior treatment with amiodarone during the last 12 months (exclusion criterion 11). o Clarified acceptable forms of highly effective contraception and that contraception should be continued for at least 9 months after last dose of Amphinex or 6 months after last dose of chemotherapy (exclusion criterion 19). o Acceptable creatinine clearance limit in exclusion criterion 23 was clarified. Patients with inadequate renal function (defined as creatinine clearance <60 mL/min) were excluded from the study. o Specific criteria for study patient's discontinuation from treatment, or withdrawal from the study were added per ICH

	Guideline E6(R2). o Additional guidance provided on precautions to be taken by patients during and after administration of Amphinex, for the prevention of skin and eye photosensitivity reactions. o Updated the number of study sites globally. o Added dose modification criteria for Amphinex, gemcitabine, and cisplatin. o Updated and clarified information on contraception and pregnancy. o Pregnancy testing was added after the end of the active treatment period (end of treatment period Day 30). o Clarification that assessment of tumour responses for the purposes of efficacy assessment must be according to RECIST 1.1; clinical assessment of symptomatic progression not sufficient without continued follow-up for radiological RECIST progression. o Definition of progressive disease per RECIST 1.1 for non-measurable disease has been clarified. o Clarified tumour response criteria for non-target lesions, including advice on assessing non-measurable disease. o Biomarkers assessments clarified to distinguish between standard tumour markers (CA 19-9, CA-125 and CEA) and exploratory biomarkers. o Clarification that events clearly associated with the underlying disease should not be recorded as AEs was added. o Central laboratory was updated to local laboratory. o Updated reporting responsibilities for SAEs. o Reporting responsibilities and reporting timelines for SUSARs were updated. o Clarified that standard tumour markers will be analysed from serum samples collected for clinical chemistry. o Peripheral blood mononuclear cells (PBMCs) removed from exploratory biomarker assessments and exploratory biomarkers now measured in plasma only (not plasma and serum). o The PK sampling schedule has been revised; Group 1 - rich sampling - will include 20 patients randomised to Arm A, enabling non-compartmental analyses of fimaporfin PK, whereas Group 2 - sparse sampling - will provide data from the remaining Arm A pts to enable a later population PK analysis. Groups 3 and 4 have been deleted. On Day -4 and Cycle 4, Day 18, the PK samples will be time matched with ECG: For PK Group 1, PK sampling will be performed before, approximately 30 minutes after, and 4 hours after Amphinex administration, and for PK Group 2, PK sampling will be performed before Amphinex administration. o Updated blood sampling volume drawn from the patients. o Calculation of QTcB and QTcF added to ECG parameters. o ECG on Day -4 and Cycle 4, Day 18, will be performed before

Version	Date	Reason for Amendment
		and approximately 30 minutes (anticipated maximal plasma concentration) and 4 hours after Amphinex administration, to align with plasma PK sampling timepoints. o Updated definition of disease control rate (DCR). o Exploratory endpoint for standard tumour markers and exploratory biomarkers simplified for clarity. o Updated text for sample size calculations. o Distinct groups for subgroup analyses defined: primary; primary with liver metastases; primary with local lymph nodes; and primary with liver metastases and local lymph nodes. o Statistical model for analysis of the primary endpoint was updated to use the Efron approach for estimating HR and corresponding 95% CIs. o Kaplan-Meier landmark PFS estimates at 6 months and 12 months with corresponding CIs were added to the analysis method for the primary endpoint. o Revised Section 7.7.2.3 to provide comparative SAP for key secondary endpoint ORR. o Primary endpoint for interim analysis will be ORR rather than PFS. o Study to have at least 80% power to detect a clinically meaningful improvement in the key secondary endpoint of OS. o A detailed multiplicity control strategy added to Section 7.7.7.1. o Removed the need for legal guardian as the patient participating in this study will be 18 years or older and capable of understanding/providing signed and witnessed written informed consent as per inclusion criteria 1 and 2. o Clarified clinical or administrative reasons when the Sponsor reserves the right to discontinue the study at any time. o Definition of end of study amended from last patient last visit to date of final database lock. o Schedule of events (Appendix A) has been split into 2 tables, one for each treatment arm. o Pharmacokinetic sampling has now been integrated into study treatment and follow-up schedules. o Clarification that serious adverse events will be reported during the survival follow-up period was added.
Version 3.0 (Global Amendment 2)	13 Jul 2020	• To add clarifications to Version 2.0 of the protocol, to incorporate requests made by the US Food and Drug Agency, and to revise the eligibility criteria to better match the real world patient population and support patient recruitment. o Sponsor contact details (Chief Medical Officer) was updated

from [redacted].

- The Medical Monitor details were updated.
- List of abbreviations was updated.
- List of definitions was added.
- The analysis of exploratory biomarkers was removed from the exploratory objectives, exploratory endpoints and throughout the protocol.
- It was clarified that documented or objective disease progression must be determined by radiology.
- The term “background treatment” has consistently been replaced with the term “standard of care”.
- It was clarified that the second PCI treatment should be administered at least 3 months after the first PCI treatment and that patient-related factors may lead to postponement to a later cycle. The possible reasons for postponement or omission of the second PCI treatment were updated as requested by the US Food and Drug Agency.
- Hospitalisation details for patients in Arm A were clarified.
- Clarification was added regarding cycles for patients who have started gemcitabine/cisplatin treatment before screening.
- The study design figure was updated to reflect the changes to the study.
- Stent placement text was revised for clarity.
- The rationale for study design was updated with information on the recently completed study PCIA 202/12. Some paragraphs were reworded for readability.
- Safety data from studies PCI 101/06, PCIA 202/10, and PCIA 202/12 were added as part of the benefit/risk assessment.
- Inclusion criterion 6: the definition of metastatic disease allowed in the study was updated to include tissues other than bone or the central nervous system instead of liver parenchyma and/or local lymph nodes (within close proximity to the hepatoduodenal ligament). This is expected to match real world patient population and recruit additional patients, no difference in safety is expected.
- Exclusion criterion 1: added the exception of previous treatment of up to 2 cycles of gemcitabine/cisplatin. PCI treatment is expected to improve response to gemcitabine when given later than in cycle 1 of gemcitabine/cisplatin treatment. This is consistent with real world patients where chemotherapy may be initiated before further evaluation at central hospital. No difference in safety is expected.
- Exclusion criterion 3: clarified that exclusion is based on frequently recurring septic biliary events regardless of cause.
- Exclusion criterion 5: it was added that a second primary cancer that has been treated with intent to cure may be allowed after consultation with the study Medical Monitor. The risk of recurrence of a second cancer that has been properly treated

	with curative intent is, in most cases, low. Revised to better match the general population and support patient recruitment. o Exclusion criterion 16 was deleted (significant hearing impairment). This criterion is covered by exclusion criterion 13 (contraindication to the use of cisplatin). o Exclusion criterion 19 (now criterion 18): the footnote detailing the interaction of hormonal contraception with investigational medicinal product was deleted as it is not applicable. o Exclusion criterion 22 (now criterion 21): biliary drainage was specified in place of biliary tree stenting. The definition of inadequate liver function was revised: serum (total) bilirubin persisting at > 2.5 × ULN changed to > 5 × ULN. Changed to expand the target eligible population to support patient recruitment. The safety risk potentially associated with higher bilirubin level is considered negligible in the settings of the study. Considering the significant anti-tumour activity observed in earlier studies, the estimated benefit/risk ratio balance is considered ethical. o The wording regarding discontinuation from study treatment and withdrawal from study were updated for clarity. o Stratification was updated to remove the specification of 'hepatic' from the presence or absence of metastases, in accordance with revised inclusion criterion 6. o Guidance on precautions to be taken by patients during and after administration of Amphinex, for the prevention of skin and eye photosensitivity reactions was updated. o Data on photosensitivity AEs from previous studies was added. o It was clarified that estimation of GFR, according to local practice, is considered equivalent to EDTA clearance if there is a >25% increase of serum creatinine compared to the baseline. o The definitions of permitted and prohibited treatments were updated. o The male patient contraception requirements were clarified, and aligned with the end of relevant systemic exposure. o Updated and clarified information on pharmacokinetic sample collection. o The timing of electrocardiograms was clarified. o Updated blood sampling volume drawn from the patients, as samples for exploratory biomarker analysis are no longer taken. o The definition of ORR in the study was updated. ORR will be assessed in all randomised patients (ITT population), as requested by the US FDA. The Evaluable for Response analysis set was removed. o The description of the subgroups to be analysed was updated. o The exploratory endpoint for tumour response was updated. o Updated text for sample size calculations. o A detailed description of the Blinded Independent Central Review was added for clarification.

Version	Date	Reason for Amendment
		○ The interim analysis of ORR will be based on the assessment of the Blinded Independent Central Review, as requested by the US FDA. Improvement in ORR adjusted. ○ The multiple testing strategy was revised to incorporate US FDA requirement for O'Brien and Fleming boundary, and further simplified. ○ Added reference to SAP for detailed pooling strategy for handling small strata as requested by US FDA. ○ Change of analysis method for secondary endpoint ORR as requested by US FDA. Sensitivity analysis was added. ○ Schedules of events (Appendix A and Appendix B) were updated in line with changes made to the protocol. Screening period was updated from 14 to 21 days. ○ Throughout: Minor editorial revisions.

For details of Amendment 1 and 2, see Appendix E (Section 13.5).

Table of Contents

List of Tables

List of Figures

Protocol Synopsis

Protocol Number:	PCIA 203/18
Title:	A Multi-Centre, Randomised, Open-Label, Phase 2 Study to Assess the Safety, Tolerability and Efficacy of Fimaporfin-Induced Photochemical Internalisation of Gemcitabine Complemented by Gemcitabine/Cisplatin Chemotherapy Versus Gemcitabine/Cisplatin Alone in Patients With Inoperable Cholangiocarcinoma
Sponsor:	PCI Biotech AS Ullernchausséen 64 0379 Oslo Norway
Study Phase:	2
Study Sites:	Approximately 50 sites in Asia, Europe and North America
Indication:	Inoperable cholangiocarcinoma (CCA)
Rationale:	The purpose of this study is to evaluate the safety and efficacy of fimaporfin-induced photochemical internalisation (PCI) of gemcitabine complemented by gemcitabine/cisplatin systemic chemotherapy in patients with advanced inoperable CCA.
Objectives:	**Primary Objective** To assess the efficacy of fimaporfin-induced PCI of gemcitabine complemented by systemic gemcitabine/cisplatin chemotherapy versus gemcitabine/cisplatin alone in patients with inoperable CCA by assessment of progression-free survival (PFS) **Secondary Objectives** • To assess the longer-term efficacy of fimaporfin-induced PCI of gemcitabine complemented by systemic gemcitabine/cisplatin chemotherapy versus gemcitabine/cisplatin alone in patients with inoperable CCA by assessment of overall survival (OS); • To further assess the efficacy of fimaporfin-induced PCI of gemcitabine complemented by systemic gemcitabine/cisplatin chemotherapy versus gemcitabine/cisplatin alone in patients with inoperable CCA by assessment of best overall response (BOR), objective response rate (ORR), duration of response (DoR), disease control rate (DCR) at 6 and 12 months, and change in tumour size per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1);

- To assess the effects of fimaporfin-induced PCI on safety in terms of loco-regional tumour-related events and biliary complications;
- To further assess the safety profile (adverse events [AEs], laboratory assessments, physical findings, and photosensitivity) of fimaporfin-induced PCI of gemcitabine complemented by systemic gemcitabine/cisplatin combination versus gemcitabine/cisplatin chemotherapy alone;
- To further characterise the pharmacokinetic (PK) profile of fimaporfin in plasma;
- To assess the health-related quality of life (HRQoL) and patient-reported outcome (PRO) measures of fimaporfin-induced PCI of gemcitabine complemented by systemic gemcitabine/cisplatin chemotherapy versus gemcitabine/cisplatin alone in patients with inoperable CCA.

Exploratory Objectives

- To assess tumour response (ORR, DCR, and PFS) by location of disease including loco-regional tumour control and metastatic lesions.
- To explore changes in standard tumour markers for the assessment of their diagnostic and prognostic relevance in the disease, and for the treatment itself.

Primary Endpoint

Progression-free survival, defined as the time from randomisation to radiological disease progression or death from any cause.

Secondary Endpoints

- Overall survival (OS), calculated as the time from randomisation to the date of death from any cause
- Best overall response (BOR), the best response recorded from the start of the treatment until disease progression/recurrence (using the smallest measurements recorded since the treatment started as reference for progressive disease)
- Objective response rate (ORR), calculated as the proportion of patients who have at least one visit response with a complete response (CR) or partial response (PR) noted

- Duration of response (DoR), defined as time from first documented tumour response until the first documented disease progression, or death in the absence of disease progression
- Disease control rate (DCR), defined as the proportion of patients with stable disease or better (ie, CR, PR or stable disease), assessed at 6 months and 12 months
- Change in tumour size, defined as the best overall percentage change in tumour size from baseline
- Toxicity profile (AEs, laboratory assessments and physical findings) of fimaporfin-induced PCI of gemcitabine with the gemcitabine/cisplatin combination, or the gemcitabine/cisplatin combination alone
- Frequency and severity of loco-regional tumour-related events and biliary complications requiring unplanned hospital visits and inpatient care
- Pharmacokinetic profile of fimaporfin
- HRQoL/PRO assessments

Exploratory Endpoints

- Tumour response (ORR, DCR and PFS) by location of disease, as pre-defined further in the statistical analysis plan (SAP), including:
  - loco-regional tumour control
  - metastatic lesions
  - local lymph nodes
- To analyse blood samples for standard tumour markers.

Study Population: The main inclusion criteria include:

- Male or female patient ≥18 years of age;
- Cholangiocarcinoma verified as adenocarcinoma by histopathology or cytology with a perihilar or distal stenosis that has been stented or will require stenting, and that is accessible for PCI light treatment;
- Cholangiocarcinoma must be considered inoperable with respect to radical resection (including partial liver resection or liver transplantation);

- At least 1 radiologically evaluable lesion (measurable and/or non-measurable) that can be assessed at baseline and is suitable for repeated radiological evaluation;
- If metastatic disease, metastasis must be limited to tissues other than bone or the central nervous system;
- Adequate biliary drainage (at least 50% of the liver volume or at least 2 sectors), with no evidence of active uncontrolled infection (patients on antibiotics are eligible);
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- Estimated life expectancy of at least 12 weeks.

Study Design:

This study is a multi-centre, randomised, open-label, Phase 2 study with conditional marketing authorisation intent, to primarily evaluate the efficacy of fimaporfin-induced PCI of gemcitabine complemented by gemcitabine/cisplatin chemotherapy versus gemcitabine/cisplatin chemotherapy alone in patients with inoperable CCA, and to further evaluate the safety and tolerability of the PCI treatment(s).

Approximately 186 patients will be randomised in a 1:1 ratio to receive:

Arm A: PCI treatment, consisting of Amphinex® (fimaporfin) given once intravenously (IV) 4 days in advance of gemcitabine administration IV and intraluminal laser light application on Day 1, Cycle 1 as part of up to 8 gemcitabine/cisplatin cycles, with a second PCI treatment procedure aimed at the initiation of Cycle 5 or, if patient-related factors demand postponement, at initiation of a later cycle. The PCI treatments must be separated by at least 3 months.

Arm B: up to 8 gemcitabine/cisplatin cycles alone.

The randomisation will be stratified by 2 factors: any measurable disease at baseline (yes versus no) and presence or absence of metastases. Patients should continue their randomised chemotherapy treatment until a maximum of 8 gemcitabine/cisplatin cycles, or until a treatment discontinuation criterion is met.

Patients will be followed for PFS until approximately 129 objective progression events (as defined by RECIST 1.1) have been observed for the primary analysis. Patients should be followed for radiological progression, regardless of whether they discontinue therapy or have symptomatic progression. After radiological progression, patients will enter the survival follow-up phase. A formal interim analysis of ORR will be performed after approximately 120 patients have been randomised and followed to their first follow-up scan to support a conditional marketing authorisation application.

Data collection for OS will continue beyond the PFS analysis and an updated OS analysis will be performed after approximately 147 death events have occurred. The exact level of maturity will be determined based on the PFS and interim OS results, in discussion with regulatory authorities.

An Independent Data Monitoring Committee (IDMC) will be enlisted to perform periodic review of accumulating safety data,

	with particular focus on biliary tract events (Note: and possibly others, as to be defined in the IDMC charter) which are defined as AEs of special interest (AESI). The study will include an initial safety review by the IDMC after the initial 8 patients in Arm A have been administered 2 PCI treatments and followed up for 21 days. The IDMC will assess whether the second PCI treatment during the chemotherapy period should continue to be administered for future patients randomised to Arm A, in addition to the first PCI. Further, based on the periodic or ad hoc safety data reviews, the IDMC can make a recommendation to continue, amend, or stop the study at any point for safety reasons. Although there are no formal futility stopping rules in the study, the IDMC will review the results of the interim ORR analysis and provide a recommendation as to whether the study demonstrates a positive risk benefit that is clinically meaningful and meets the pre-defined statistical boundary for efficacy.
Estimated Study Duration:	In this rare disease, and with a variety of factors limiting final eligibility, recruitment rate per site is anticipated to be relatively low. The time from first patient, first visit, to the interim analysis (approximately 120 patients randomised) is estimated to be approximately 39 months. The study duration up to the PFS analysis (129 events/186 patients) is estimated to be 48 to 51 months. The total study duration up to the final OS analysis (147 events/186 patients) is estimated to be 63 to 66 months. The study duration for a patient will be approximately 6 months during the active treatment period, with an additional number of assessments occurring every 3 months until progression, as individually applicable.
Efficacy Assessments:	Tumour response will be assessed, according to RECIST 1.1, every 12 weeks (±1 week) from randomisation until disease progression and should NOT follow delays incurred in the treatment period. The study will evaluate tumour responses as determined by the Investigator according to RECIST 1.1. The primary PFS analysis will be based on the local radiological assessment, which will be used to guide clinical management decisions. Note: In cases of symptomatic progression, patients will continue to be followed for radiological progression. A blinded independent central radiological review (BICR), blinded to treatment and to the local efficacy assessment, will also be performed for the tumour response data.

	A supportive analysis of PFS will be performed based on data from the BICR. For the interim analysis of ORR, the BICR assessment will be considered the primary analysis.
Pharmacokinetic, Pharmacodynamic, and Other Assessments:	In order to evaluate the PK of fimaporfin in plasma, blood samples will be obtained from all patients in Arm A at the time points specified in PK sampling schedule. Quality of life will be measured by use of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and the EORTC QLQ-B21 questionnaire. The standard tumour markers carbohydrate antigen 19-9 (CA 19-9), cancer antigen-125 (CA-125) and carcinoembryonic antigen (CEA) will be analysed from blood samples collected for safety laboratory assessments throughout the study.
Safety Assessments:	Safety will be assessed by AEs, serious AEs, deaths, loco-regional tumour-related events and biliary complications, clinical laboratory assessments, physical examinations, vital signs, electrocardiograms, and photosensitivity measures and skin reactions.
Study Treatment, Dosage, and Route of Administration:	The Arm A PCI treatment consists of IV administration of Amphinex solution for injection (investigational product) at 0.22 mg/kg dose of fimaporfin, followed 4 days later by a standard dose of gemcitabine infusion (1000 mg/m^2) and intraluminal laser light application (30 J/cm). The light source used to activate fimaporfin is a medical laser system (CE marked), emitting red light at 652 nm. Gemcitabine is currently not licensed for the treatment of patients with advanced inoperable CCA. All patients will receive the recognised standard of care for this indication (in addition to the PCI treatment for patients in Arm A); systemic chemotherapy consisting of 8 cycles of cisplatin, 25 mg/m^2 plus gemcitabine, 1000 mg/m^2. In Arm A, cisplatin will be omitted on days when PCI treatment is given (on Day 1 of Cycle 1, and on Day 1 of Cycle 5). Biliary stenting (plastic stents) is to be performed on all patients.
Sample Size:	Approximately 186 patients
Statistical Methods:	Approximately 186 patients with inoperable CCA will be randomised in a 1:1 ratio (fimaporfin-induced PCI of gemcitabine complemented by gemcitabine/cisplatin

chemotherapy versus gemcitabine/cisplatin chemotherapy alone) to this study.

Primary Analysis: The primary endpoint is PFS and a hierarchical approach to the primary analysis will be employed. The primary analysis of PFS, as assessed by local radiological assessment, will be conducted when approximately 129 progression events (69% maturity) have been observed. If the PFS result is statistically significant at the 3.95% 2-sided alpha level (adjusted for the interim analysis of ORR) an interim analysis of OS will be assessed.

If the true PFS hazard ratio (HR) for the comparison of fimaporfin-induced PCI of gemcitabine complemented by gemcitabine/cisplatin chemotherapy versus gemcitabine/cisplatin chemotherapy alone is 0.6, 129 progression events will provide approximately 80% power to demonstrate a statistically significant difference in PFS at a 3.95%, 2-sided significance level (this may translate to an improvement in median PFS from 7.4 to 12.3 months, if PFS is exponentially distributed). A minimum or critical HR of 0.69 (eg, 7.4 to 10.7 months) will be statistically significant, if observed.

Progression-free survival will be analysed in the Intent-to-Treat (ITT) analysis set, using a log-rank test stratified by any measurable disease at baseline (yes versus no) and presence or absence of metastases. In the event of low numbers within a stratum, the data will be pooled across strata in the stratified analyses. Further details will be provided in the SAP.

The primary analysis of PFS will be based on the local evaluation and will also be tested using the blinded independent central review (BICR) data. Summaries of secondary endpoints assessed by RECIST v1.1 will also be repeated using the BICR data.

Interim Analyses: A formal interim analysis of ORR will be performed after approximately 120 patients (65%) have been randomised and followed to their first 12-week follow-up scan. Analysis will be based on BICR assessment. There will be >80% power to detect an improvement in ORR from 15% to 45% with 2-sided $p<0.0105$ (O'Brien and Fleming boundary based on 65% information). A minimum improvement from 15% to 38% will be statistically significant, if observed. If the comparison of the interim ORR data between the arms based on a Cochran-Mantel-Haenszel test is statistically significant, it will

	be summarised together with OS to support a conditional marketing authorisation application. Progression-free survival and DoR will be summarised descriptively with no formal comparison of PFS. A second interim analysis of OS will be performed in line with the PFS analysis when approximately 108 patients are predicted to have died. A 2-sided $p<0.0173$ will be required to demonstrate statistical significance. **Updated OS Analysis:** An updated (third) OS analysis will be performed with further survival follow-up after the PFS analysis. The final OS analysis will be triggered after approximately 147 death events. There will be 80% power to detect an OS HR of 0.63 (eg, improvement in median OS from 11.7 to 18.7 months) with 2-sided $p<0.0447$ (O'Brien and Fleming boundary adjusted for 2 interim analyses of OS). A minimum or critical HR of 0.72 (eg, 11.7 to 16.3 months), if observed, would be statistically significant. The exact level of maturity will be determined based on the PFS and interim OS results, in discussion with regulatory authorities. Overall survival will be analysed in the same manner as PFS. The secondary endpoints of ORR, BOR, DCR, and DoR will be summarised for the ITT analysis set (ie, all randomised patients). Summaries and waterfall plots indicating best percentage change from baseline in the sum of the diameters of target lesions will be produced. Kaplan-Meier plots will be produced to assess PFS and OS. Safety, including the incidence and characteristics of biliary/loco-regional tumour-related events leading to hospitalisation and/or interventions, will be summarised descriptively. Pharmacokinetic data will also be summarised descriptively.
Version and Date of Protocol:	Final/Version 3.0, 13 Jul 2020

List of Abbreviations

Abbreviation	Definition
AE(s)	adverse event(s)
AESI(s)	adverse event(s) of special interest
AI(s)	adverse incident(s)
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BICR	blinded independent central review
BOR	best overall response
CA-125	cancer antigen 125
CCA	cholangiocarcinoma
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CI	confidence interval
CR	complete response
CRC	Cohort Review Committee
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLTs	dose-limiting toxicities
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EDR	early discrepancy rate
EDTA	ethylenediamine tetraacetic acid
EORTC	European Organisation for Research and Treatment of Cancer
ERCP	endoscopic retrograde cholangio-pancreatography
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice

Abbreviation	Definition
GMP	Good Manufacturing Practice
HNSCC	head and neck squamous cell carcinoma
HR	hazard ratio
HRQoL	health-related quality of life
HUS	haemolytic uraemic syndrome
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous(ly)
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LDR	late discrepancy rate
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NE	not evaluable
ORR	objective response rate
OS	overall survival
PCI	photochemical internalisation
PD	progressive disease
PDT	photodynamic therapy
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome
PSC	primary sclerosing cholangitis

Abbreviation	Definition
QLQ	Quality of Life Questionnaire
RECIST	Response Evaluation Criteria in Solid Tumours
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD	stable disease
SLT	schedule-limiting toxicity
SmPC	summary of product characteristics
SoC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent AE
UADE	unanticipated adverse device effect
ULN	upper limit of normal
WOCBP	women of childbearing potential

List of Definitions

PCI treatment	In the present protocol, a single PCI treatment consists of IV administration of Amphinex solution for injection (dose 0.25 mg/kg fimaporfin-di-olamine, equivalent to 0.22 mg/kg fimaporfin), followed 4 days later by gemcitabine IV infusion (1000 mg/m^2) and bile duct intraluminal laser light application (light dose 30 J/cm).
Amphinex®	Amphinex solution for injection is a sterile solution containing active substance fimaporfin di-olamine; 30 mg/mL (equals 26 mg/mL of fimaporfin), [redacted]
Fimaporfin	Active substance (salt form: fimaporfin di-olamine)

1 Introduction

1.1 Cholangiocarcinoma

Cholangiocarcinoma (CCA) is an uncommon adenocarcinoma arising from the neoplastic transformation of cholangiocytes, the epithelial cells lining the intrahepatic and extra-hepatic bile ducts (Anderson et al 2004). Cholangiocarcinoma may arise anywhere in the biliary tree, from the small, peripheral hepatic ducts to the distal common bile duct. The term CCA includes all bile duct cancers (intrahepatic, perihilar and distal extrahepatic). Cholangiocarcinoma is the second most frequent type of primary liver cancer and accounts for about 3% of all digestive tumours (Global Burden of Disease Cancer Collaboration et al 2015). It has an annual incidence of less than 6 cases per 100,000 in the western world, higher in some countries and regions such as South Korea and North Thailand, but rates of intra-hepatic CCA have been steadily rising over the past 3 decades while the incidence of peri-hilar and distal CCA has remained stable (Blechacz et al 2008) or seems to be decreasing (Banales et al 2016). Patients with these tumours have poor overall survival (OS) with a 5-year survival rate of about 5% (Vauthey and Blumgart 1994). Over 50% of patients present with advanced-stage disease, and the prognosis is poor with survival time of between 6-12 months for unresected patients, even after biliary decompression.

Up to 20% of all CCAs are intrahepatic, whereas 50% to 60% are perihilar, involving the bifurcation of the ducts. Peri-hilar CCAs are a subset of extrahepatic CCAs. Up to 20% of CCAs are distal extrahepatic tumours and 5% of tumours are multifocal (Khan et al 2002). Intra-hepatic CCA develops in the smaller bile duct branches inside the liver. Peri-hilar CCA develops at the hilum, where the left and right hepatic ducts have joined and are just leaving the liver. The distal CCA appears further down the bile duct, closer to the small intestine. There has a been a growing recognition that hilar CCA disease has a distinct biological behaviour and natural history compared to (distal) extrahepatic CCA, and an increasing acknowledgment that different therapeutic strategies are required (Wiedmann et al 2004). At initial presentation of patients with extrahepatic CCA, 30 to 50% have local lymph node involvement and 10 to 20% have metastatic spread typically to the liver and peritoneum. With hilar CCA, due to the long asymptomatic course, only 20% are resectable at the time of diagnosis (Henson et al 1992).

1.2 Current Standard Treatment for Patients with Cholangiocarcinoma

Cholangiocarcinomas are generally asymptomatic in the early stages and are usually diagnosed when the disease has already metastasised, by combining non-specific biomarkers in serum and/or biopsy samples, as well as imaging methods. Late diagnosis compromises the effective therapeutic options, which are based on surgical resection and/or liver transplantation, whereas chemotherapies are virtually palliative given the marked chemoresistance of this cancer. Standard treatment options for CCA include surgery, radiotherapy and chemotherapy, dependent upon if the CCA is intra- or extrahepatic. Tumour resection is the only potential cure for CCA. Recent advances in transplantation using stringent selection criteria and utilisation of neoadjuvant chemoradiation have demonstrated encouraging results with 5-year survival rates of over 70% (Singal et al 2009), with even one series from the Mayo Clinic yielding a 5-year survival rate of 82% (Rea et al 2005). For the 80% who present with unresectable disease, the utility of these modalities combined with biliary decompression interventions only provided a median survival time of 3-6 months from the time of diagnosis (Ito et al 2009). For these patients with inoperable advanced CCA, the main treatment aim is palliative to relieve local symptoms such as pain and jaundice. Surgery for these patients is primarily for creating a bypass in patients who cannot be stented. Cholangiocarcinoma is highly resistant to pharmacological therapy, but activity has been seen using chemotherapy.

For patients who are unsuitable for curative resection, the current systemic combination chemotherapy is with cisplatin plus gemcitabine. This was established in the largest randomised Phase 3 study to date in non-operable biliary tract cancer which demonstrated a response rate of 26.1% and a disease control rate of 81.4%. The median progression-free survival (PFS) was 8.0 months (95% confidence interval [CI], 6.6 – 8.6) and OS was 11.7 months (95% CI, 9.5 - 14.3); notably there was no statistically significant increase in toxicity when compared to gemcitabine monotherapy (Valle et al 2010). Unpublished data obtained from the authors of this study, showed that 33 patients with extrahepatic CCA treated with cisplatin plus gemcitabine had a response rate of 8.7%, median PFS of 7.89 months (95% CI, 3.2 – 9.0) and a median OS of 8.8 months (95% CI, 5.8 – 16.1).

In a recently published retrospective analysis of first line cisplatin plus gemcitabine treatment of biliary tract cancers, a response rate of 8.9%, median PFS of 6.4 months

(95% CI, 5.4 - 7.3) and median OS of 12.7 months (95% CI, 10.6 – 14.9) was reported for a subgroup of 79 patients with extrahepatic CCA (Kim et al 2017).

1.3 Photodynamic Therapy

Majority of patients with CCA (70%-80%) present with advanced stage and non-resectable tumours due to locally advanced disease or presence of distant metastases (Nathan et al 2009). Palliative biliary stenting to alleviate obstructive cholestasis is the primary standard of care (SoC) (Moole and Puli 2015). With the development of improved interventional and endoscopic technologies, techniques aimed at gaining control of local disease have evolved, including local ablation, embolisation, brachytherapy, radio-frequency ablation and, most significantly, photodynamic therapy (PDT) (Kiesslich et al 2009). PDT is a local-ablative, tumour-specific treatment that involves administration of a photosensitising drug with affinity for neoplastic tissue. Photosensitisers are non-cytotoxic drugs that are activated following their administration by selective illumination with light at the defined wavelength matching their absorption. The resulting interaction between light and the photosensitising agent causes formation of oxygen free radicals (Henderson and Dougherty 1992), inducing death of tumour and neovascular cells by apoptosis, necrosis or autophagy, vascular shutdown, and may induce T-cell mediated immune response (Dolmans et al 2003).

McCaughan et al (1991) described the first successful case of PDT for nonresectable CCA. Since then, the benefit of using PDT in patients with nonresectable CCA has been demonstrated in many studies, and with more than 2 decades of experience, local CCA treatment with PDT is part of the therapy options for nonresectable CCA patients in many specialised centres today (Zoepf et al 2005). Since PDT studies in CCA have often been small and included patients that additionally received other palliative treatments (surgery, radiotherapy, chemotherapy), a recent systematic review and meta-analysis (Moole et al 2017) exclusively investigated studies of PDT with biliary stenting versus biliary stenting alone. PDT appeared to be relatively safe and was superior to palliative stenting alone in terms of survival, successful biliary drainage, and Karnofsky performance scores.

1.4 Photochemical Internalisation

Photochemical internalisation (PCI) is a novel photochemical technology. With PCI, photochemical reactions are used to enhance the effect of drugs in illuminated areas of the body, by increasing the ability of such drugs to interact with their targets inside the cells. A common feature of candidate drugs that may be used in PCI is that they have an intracellular molecular target. For many drugs that do not readily pass the plasma membrane, cellular uptake may be limited. One way that such drugs could be taken up by the cells is by the normal cellular process of endocytosis. However, for many existing and potential therapeutic molecules this uptake leads to degradation or loss of the biological activity before it can reach its intracellular target.

The molecular mechanism behind the PCI technology is based on the use of a photosensitising molecule (photosensitiser) localising specifically to the membranes in endocytic vesicles. Upon activation by light, the photosensitiser will induce photochemical reactions leading to damage to these membranes and to the rupture of the endocytic vesicles, thereby leading to the release of entrapped drugs into the cytosol.

2 Study Objectives

2.1 Primary Objective

The primary objective of this study is to assess the efficacy of fimaporfin-induced PCI of gemcitabine complemented by systemic gemcitabine/cisplatin chemotherapy versus gemcitabine/cisplatin alone in patients with inoperable CCA by assessment of PFS.

2.2 Secondary Objectives

The secondary objectives of this study are:

1. To assess the longer-term efficacy of fimaporfin-induced PCI of gemcitabine complemented by systemic gemcitabine/cisplatin chemotherapy versus gemcitabine/cisplatin alone in patients with inoperable CCA by assessment of OS;
2. To further assess the efficacy of fimaporfin-induced PCI of gemcitabine complemented by systemic gemcitabine/cisplatin chemotherapy versus gemcitabine/cisplatin alone in patients with inoperable CCA by assessment of best overall response (BOR), objective response rate (ORR), duration of response (DoR), disease control rate (DCR) at 6 and 12 months, and change in tumour size per Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST 1.1);
3. To assess the effects of fimaporfin-induced PCI on safety in terms of loco-regional tumour-related events and biliary complications;
4. To further assess the safety profile (adverse events [AEs], laboratory assessments, physical findings, and photosensitivity) of fimaporfin-induced PCI of gemcitabine complemented by systemic gemcitabine/cisplatin combination versus gemcitabine/cisplatin chemotherapy alone;
5. To further characterise the pharmacokinetic (PK) profile of fimaporfin in plasma;
6. To assess the health-related quality of life (HRQoL) and patient-reported outcome (PRO) measures of fimaporfin-induced PCI of gemcitabine complemented by systemic gemcitabine/cisplatin chemotherapy versus gemcitabine/cisplatin alone in patients with inoperable CCA.

2.3 Exploratory Objectives

The other objectives of this study are:

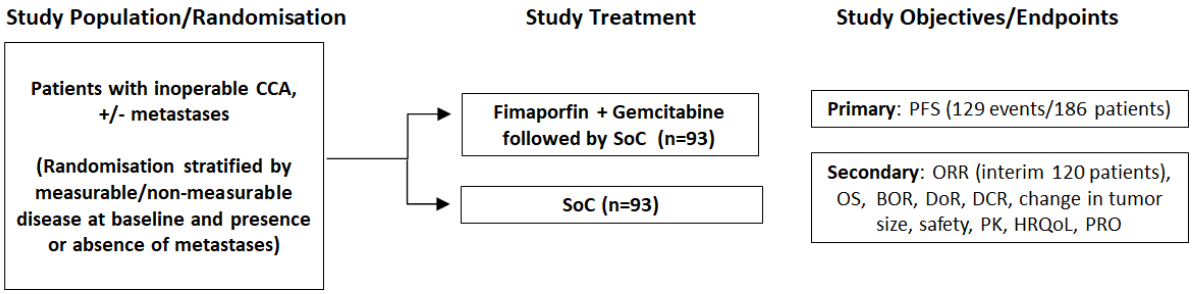
1. To assess tumour response (ORR, DCR, and PFS) by location of disease including loco-regional tumour control and metastatic lesions.
2. To explore changes in standard tumour markers for the assessment of their diagnostic and prognostic relevance in the disease, and for the treatment itself.

3 Investigational Plan

3.1 Study Design

This study is planned to be a multi-centre, randomised, open-label, Phase 2 study with conditional marketing authorisation intent, to evaluate the efficacy of fimaporfin-induced PCI of gemcitabine complemented by gemcitabine/cisplatin chemotherapy versus gemcitabine/cisplatin chemotherapy alone in patients with inoperable CCA. It will also evaluate the safety and tolerability of the PCI treatment(s).

Figure 1 Overall Study Design



Abbreviations: BOR, best overall response; CCA, cholangiocarcinoma; DCR, disease control rate; DoR, duration of response; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PRO, patient-reported outcome; SoC, standard of care.

3.2 Treatment Assignment

Patients will be randomly assigned in a 1:1 ratio to either Arm A or Arm B. All patients in both arms will be stented (Section 3.3.1). It is expected that approximately 93 patients will be randomly assigned to Arm A and approximately 93 patients will be randomly assigned to Arm B.

Patients will be stratified at randomisation according to whether they have any measurable disease at baseline (as assessed by the Investigator) versus no measurable disease, and according to presence or absence of metastases. It is expected that approximately two-thirds of patients will have measurable disease at baseline.

3.2.1 Arm A

Patients randomised to Arm A will be treated with PCI, integrated into 21-day cycles of gemcitabine/cisplatin combination chemotherapy (SoC treatment).

Patients who have started gemcitabine/cisplatin treatment before the screening period should continue their treatment as scheduled. PCI treatment should be synchronised with the schedule of the ongoing gemcitabine/cisplatin treatment. Study cycles will be counted from enrolment – as for all patients in the study; however, the number of chemotherapy cycles with gemcitabine/cisplatin will be counted from first treatment. For clarification, treatment with gemcitabine/cisplatin cannot exceed 8 treatment cycles.

Treatment schedule as follows:

Cycle 1: Amphinex® (fimaporfin) will be administered on Day -4 (4 days before gemcitabine administration), followed by gemcitabine administration and laser light application on Day 1, and gemcitabine/cisplatin on Day 8. Note: Cisplatin is omitted from Cycle 1 Day 1 treatment.

Cycles 2 to 3: Gemcitabine/cisplatin will be administered on Days 1 and 8.

Cycle 4: Gemcitabine/cisplatin will be administered on Days 1 and 8. A second dose of Amphinex will be administered on Day 18 (4 days prior to Day 1 of Cycle 5).

Cycle 5: Gemcitabine administration and laser light application will be given on Day 1, and gemcitabine/cisplatin on Day 8. Note: Cisplatin is omitted from Cycle 5 Day 1 treatment.

Cycles 6 to 8: Gemcitabine/cisplatin will be administered on Days 1 and 8.

Patient-related factors may demand postponement of the second PCI treatment to a later cycle. Please see Section 3.3.2 for more detailed information.

Patients in Arm A may be admitted for overnight follow-up after laser light application and related procedures on Day 1 of Cycle 1 and on Day 1 of Cycle 5.

3.2.2 Arm B

Patients randomised to Arm B (control arm) will be administered SoC treatment (gemcitabine/cisplatin chemotherapy) only, on Days 1 and 8 of each 21-day cycle, for up to 8 cycles.

Patients who have started gemcitabine/cisplatin treatment before the screening period should continue their treatment as scheduled. Cycle 1, Day 1 visit should be synchronised with the schedule of the ongoing gemcitabine/cisplatin treatment. Study cycles will be counted from enrolment – as for all patients in the study; however, the number of chemotherapy cycles with gemcitabine/cisplatin will be counted from first treatment. For clarification, treatment with gemcitabine/cisplatin cannot exceed 8 treatment cycles.

3.3 Treatment Schedule

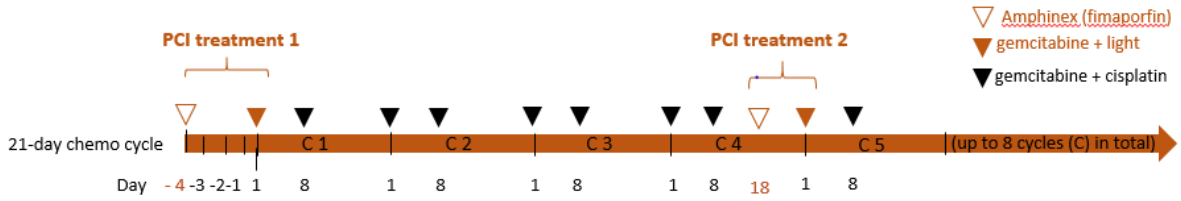
3.3.1 Stent Placement

Biliary stenting is to be performed on all patients according to local practice; however, the chosen stent must be of an exchangeable plastic type until radiological progression. Stenting must be performed at the latest before first study treatment (Arm B) or immediately after the first laser light application (Arm A). Patients who have already undergone stenting before screening should be reviewed to ensure the stent is of plastic type, correctly positioned and adequate liver drainage confirmed; at least 50% of liver volume, or at least 2 sectors, should be drained. Stents must be removed for the laser light application, and a new stent must be placed immediately after light application. Stent removal, laser light application, and stent replacement will take place during the same one procedure.

3.3.2 Arm A

Patients randomised to Arm A will receive up to 2 PCI treatments, separated by at least 3 months, together with up to 8 cycles of gemcitabine/cisplatin combination chemotherapy (Figure 2).

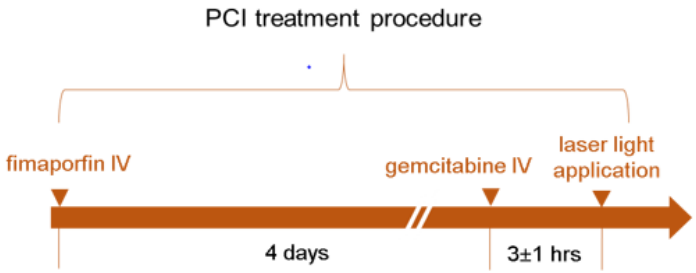
Figure 2 Photochemical Internalisation (PCI) Treatment Schedule



First PCI treatment:

A 0.22 mg/kg dose of fimaporfin will be administered intravenously (IV) on Day -4 followed 4 days later by a standard dose of gemcitabine infusion (1000 mg/m^2) and intraluminal laser light application (30 J/cm) on Day 1, as shown in Figure 3.

Figure 3 PCI Treatment Sequence



This regimen replaces the gemcitabine/cisplatin administration of Day 1 in the first chemotherapy cycle. Patients will thereafter receive the remaining treatments as per SoC gemcitabine/cisplatin combination chemotherapy in Cycle 1 (Day 8) to Cycle 4 with cisplatin at 25 mg/m^2 and gemcitabine at 1000 mg/m^2, administered on Day 1 and Day 8 of each 21-day cycle.

Second PCI Treatment

A second PCI treatment following the same schedule will be performed at the start of Cycle 5 (Amphinex injection on Cycle 4, Day 18) followed by gemcitabine infusion and intraluminal laser light application on Cycle 5, Day 1. The second PCI treatment should be separated by at least 3 months from the first PCI treatment.

Patients will thereafter receive the gemcitabine/cisplatin standard combination chemotherapy (cisplatin at 25 mg/m^2 and gemcitabine at 1000 mg/m^2) on Day 8 of Cycle 5 and then on Day 1 and Day 8 of each 21-day treatment cycle for up to 8 cycles.

If delays in the chemotherapy schedule have occurred or the schedule has been altered for any reason; or if a second PCI treatment in Cycle 5 is deemed medically inappropriate, temporarily unsafe, presents with an increased risk related to the endoscopy or PCI treatment; or if the patient strongly prefers its postponement for other reasons, or the patient has had chemotherapy before enrolment, the second PCI can be conducted in any of the later cycles at the discretion of the treating physician. However, the general goal should be to schedule the second PCI treatment at the start of Cycle 5 and avoid postponements unless an event or cause as outlined above is present to justify it.

The second PCI treatment may be postponed if:

- In the opinion of the Investigator, the single dose of gemcitabine cannot be given at the full 1000 mg/m^2 dose due to residual toxicity
- The Investigator determines that the patient will not tolerate a second PCI treatment at the scheduled time based on the patient's poor tolerability of the first PCI treatment
- In the view of the Investigator, there is evidence of ongoing inflammation within the PCI illumination area
- In the opinion of the Investigator, the patient shows significant signs of photosensitivity
- If one of the following criteria is present:
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) or alkaline phosphatase (ALP) >5 × the upper limit of normal (ULN)
    - ALT or AST or ALP >3 × ULN with the appearance of symptoms associated with a clinical diagnosis of hepatitis including right upper quadrant pain or tenderness, fever, rash or eosinophilia (>5%)

- ALT or AST >3 × ULN and total bilirubin >2.5 × ULN or international normalised ratio >1.5[1] or other evidence of impairment to the synthesis function of the liver
- Total bilirubin >2.5 × ULN

In contrast to postponing the second PCI, this treatment will not be given at all if any of the following criteria are fulfilled:

- The patient experienced a PCI treatment-related schedule-limiting toxicity (SLT) defined as:
  - A clinically significant toxicity or abnormal laboratory value occurring after PCI treatment and during the first chemotherapy cycle, assessed as unrelated to the underlying disease, or concomitant medications, where there is a reasonable possibility that it is related to either PCI treatment or to the combination of PCI treatment with the cisplatin/gemcitabine systemic chemotherapy and meets any of the following criteria, based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0:
    - Photosensitivity Grade 3 outside the treatment area, except for areas exposed for skin sensitivity tests and areas exposed for re-introduction to normal light (patient compliance with light protection guidelines MUST be followed; non-compliance will be taken into account when determining SLT)
    - Phototoxicity Grade 4 inside the treatment area (eg, duodenal ulceration)
    - Non-haematological toxicity (excluding nausea and vomiting) ≥Grade 3
    - Neutropenia or thrombocytopenia Grade 4
    - All other Grade 3 toxicities that are clinically unexpected and considered related to the PCI treatment

[1] Unless on anti-coagulants

- The patient is expected not to be able to receive the single dose of gemcitabine at a dose of 1000 mg/m^2 at any time

Furthermore, if the patient is unwilling to undergo a second PCI treatment, the second PCI can be omitted; however, the patient can continue to receive the gemcitabine/cisplatin standard combination chemotherapy.

If treatment is delayed, computed tomography (CT)/magnetic resonance imaging (MRI) scans should still be conducted at the scheduled time point relative to randomisation. This is to avoid the risk of a difference between arms in the primary endpoint of PFS that can be attributed to changes in scanning frequency rather than treatment.

The second PCI treatment will continue to be included in the Arm A treatment schedule only if the first PCI treatment is found to be tolerable and recommended to be continued by an Independent Data Monitoring Committee (IDMC) based on an initial safety review of the first 8 patients treated with 2 PCI treatments; otherwise, only a single PCI administration schedule integrated in Cycle 1 will be employed.

In patients on study treatment, the reason(s) for delays, postponement, or omitting of the second PCI must be adequately documented and recorded in the electronic case report form (eCRF).

Patients should continue their randomised chemotherapy treatment until a maximum of 8 gemcitabine/cisplatin cycles or until a treatment discontinuation criterion is met.

3.3.3 Arm B

Patients randomised to Arm B (control arm) will receive SoC treatment only, gemcitabine/cisplatin combination chemotherapy for nonresectable or metastatic CCA as follows:

Cisplatin IV infusion at 25 mg/m^2 plus gemcitabine IV infusion at 1000 mg/m^2 on Days 1 and 8 of each 21-day treatment cycle for up to 8 cycles.

If treatment is delayed, CT/MRI scans should still be conducted at the scheduled time point relative to randomisation. This is to avoid the risk of a difference between arms in the

primary endpoint of PFS that can be attributed to changes in scanning frequency rather than treatment.

Patients should continue their randomised chemotherapy treatment until a maximum of 8 gemcitabine/cisplatin cycles or until a treatment discontinuation criterion is met.

3.4 Rationale of Study Design

The purpose of this study is to evaluate the safety and efficacy of fimaporfin-induced PCI of gemcitabine complemented by gemcitabine/cisplatin systemic chemotherapy in patients with advanced inoperable CCA.

3.4.1 Rationale for Patient Population

Local control of perihilar disease has been shown to be a major influencing factor for both OS and quality of life (Mihalache et al 2010) in CCA. Patients are at a high risk of dying early from complications of local tumour infiltration (eg, cholestasis, septic cholangitis, empyema, or liver failure) rather than systemic disease. In most cases, treatment consists of biliary stenting followed by systemic chemotherapy. Thus, it is proposed that PCI of gemcitabine complemented by gemcitabine/cisplatin chemotherapy in patients with inoperable extrahepatic CCA should demonstrate an advantage in this subset of patients.

3.4.2 Rationale for Study Endpoints

The primary endpoint for the study is PFS, which is a commonly used surrogate for OS (Fleming 2005). An analysis of 104 chemotherapy trials in 2810 patients with advanced biliary tract carcinoma, demonstrated a strong association between time to tumour progression and OS (correlation coefficient [r]=0.73, $p<0.001$). A 1 month increase in time to tumour progression corresponded to a 1.3 month increase of OS (Eckel and Schmid 2007).

In a second publication, 17 randomised trials with a total of 2148 patients were analysed. Of all the evaluated efficacy endpoints, the strongest correlation was observed between median OS and median PFS hazard ratios (HRs) (Moriwaki et al 2016). In trials with gemcitabine-containing therapies and targeted agents, the coefficient of determination (r^2) value was 0.78 and the surrogate threshold effect was estimated at 0.81. Surrogate threshold effect is defined as the minimum treatment effect on the surrogate endpoint (ie, PFS) that is

necessary to predict a non-zero effect on the true endpoint (ie, OS HR<1). Therefore, based on the study by Moriwaki et al, a PFS HR<0.81 is necessary to predict for OS HR<1.

The authors discussed that a PFS HR<0.7 observed in a randomised clinical trial of advanced biliary tract cancer treatment with a superiority design could translate to a 20% improvement in OS.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] Pisello et al 2009 Talreja et al 2013 [redacted]

[redacted]

[redacted]

3.4.4 Rationale for Dose

In terms of safety, Amphinex has been well tolerated in doses up to the maximum tolerated dose of 0.87 mg/kg as established in the Phase 1 study PCI 101/06 and as shown by the absence of DLTs in the Phase 1 dose escalation part of the study PCIA 202/12 in CCA. Overall, Amphinex shows a suitable safety and tolerability profile for the treatment of advanced CCA. [redacted]

[redacted]

[redacted]

[redacted] Section 3.4.3 [redacted]

3.4.5 Rationale for Treatment Regimen

A single treatment schedule of Amphinex-induced PCI of gemcitabine has been found to be both well-tolerated and clinically active in Cohorts 3 and 4 of the Phase 1 dose escalation part of study PCIA 202/12. This has raised the question as to whether a 2-administration schedule would increase the clinical effectiveness of Amphinex-induced PCI of gemcitabine by further treating any residual tumour while maintaining the tolerability profile.

In the extended part of Phase 1 in study PCIA 202/12, the 2-administration schedule was to be considered non-tolerated if 2 or more of the first 6 evaluable patients experienced an SLT. If none or 1 of the first 6 evaluable patients experienced an SLT (see definition in Section 3.3.2), the 2-administration schedule was to be considered tolerated.

A total of 5 patients underwent the 2 PCI treatment procedures and completed the required 21-day safety window following the second procedure as per protocol. All SLT criteria were assessed and no SLTs were reported in these 5 eligible patients. The CRC concluded that the procedure was tolerable based on the fact that no SLTs were observed in the 5 eligible patients. Therefore, the 2-administration schedule can be considered tolerated.

[redacted]

[redacted]

In this study (PCIA 203/18), an IDMC will be convened to perform periodic reviews of accumulating safety data, with focus on biliary tract events which are defined as AEs of special interest (AESIs). The study will include an initial safety review by the IDMC after the initial 8 patients in Arm A have been administered 2 PCI treatments and followed up for 21 days. The IDMC will assess whether the second PCI treatment during the chemotherapy period should continue to be administered for future patients randomised to Arm A.

[redacted]

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[redacted]

[redacted] Nakeeb et al 1996 [redacted] (Sakamoto et al 1998 [redacted]

[redacted]

[redacted]

[redacted]

4 Patient Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 186 patients with inoperable CCA will be enrolled at approximately 50 sites in Asia, Europe and North America. Patients will be assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

4.1.1 Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in this study:

1. Capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements;
2. Male or female patient ≥18 years of age;
3. Cholangiocarcinoma verified as adenocarcinoma by histopathology or cytology with a perihilar or distal stenosis that has been stented or will require stenting, and that is accessible for PCI light treatment;
4. Cholangiocarcinoma must be considered inoperable with respect to radical resection (including partial liver resection or liver transplantation);
5. At least 1 radiologically evaluable lesion (measurable and/or non-measurable) that can be assessed at baseline and is suitable for repeated radiological evaluation;
6. If metastatic disease, metastasis must be limited to tissues other than bone or the central nervous system;
7. Adequate biliary drainage (at least 50% of the liver volume or at least 2 sectors), with no evidence of active uncontrolled infection (patients on antibiotics are eligible);
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1;
9. Estimated life expectancy of at least 12 weeks.

4.1.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Previously received any anti-tumour (either local or systemic) treatment for CCA, except for previous treatment of up to 2 cycles of gemcitabine/cisplatin;

2. Severe visceral disease other than CCA;
3. A history of frequently recurring septic biliary events;
4. Porphyria or hypersensitivity to porphyrins;
5. A second primary cancer with a disease-free interval of <5 years. A second primary cancer that has been treated with intent to cure may be allowed after consultation with the study Medical Monitor. Adequately treated basal cell carcinoma, squamous cell carcinoma or other non-melanomatous skin cancer, in-situ carcinoma of the uterine cervix, or prostate cancer that is controlled by hormone therapy (patients may continue hormone therapy while on study) are allowed;
6. Unable to undergo contrast-enhanced CT or MRI;
7. Currently participating in any other interventional clinical study;
8. Planned surgery, endoscopic examination, or dental treatment in the first 30 days after PCI treatment;
9. Co-existing ophthalmic disease likely to require slit-lamp examination within the first 90 days after PCI treatment;
10. Clinically significant and uncontrolled cardiac disease including unstable angina, acute myocardial infarction within 6 months prior to baseline, congestive heart failure, and arrhythmia requiring therapy, except for extra systoles or minor conduction abnormalities and controlled and well treated chronic atrial fibrillation;
11. Known allergy or sensitivity to photosensitisers, (the active substance and/or any of the excipients); or chronic use of other photosensitising therapies (Section 5.5.3); treatment with amiodarone during the last 12 months;
12. Known hypersensitivity to or contraindication to the use of gemcitabine (the active substance and/or any of the excipients);
13. Known hypersensitivity, or contraindication to the use of cisplatin (the active substance and/or any of the excipients);
14. Ataxia telangiectasia;

15. Upon the Investigator's discretion, evidence of any other medical conditions (such as psychiatric illness, physical examination or laboratory findings) that may interfere with the planned PCI treatment, affect patient compliance or place the patient at high risk from treatment-related complications;
16. Plans to have, or has recently had, vaccination with a live vaccine, including for yellow fever;
17. Concurrently receiving treatment with phenytoin;
18. Male patients unwilling to use highly effective contraception, or women of childbearing potential (WOCBP) (see definition in Section 5.6) unwilling to use a highly effective form of contraception such as the following:
    - Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal and transdermal)
    - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
    - Intrauterine devices
    - Intrauterine hormone-releasing system
    - Bilateral tubal ligation
    - Vasectomised partner[2] (Section 5.6)
    - Sexual abstinence[3]

    Patients must continue the use of contraception during PCI treatment and subsequent chemotherapy, and for at least 9 months after last dose of Amphinex or 6 months after last dose of chemotherapy, whichever is the latest.

[2] Vasectomised partner is a highly effective birth control method only if the partner is the sole sexual partner of the WOCBP study participant and if the vasectomised partner has received medical assessment of the surgical success.
[3] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.

19. Breastfeeding women or women with a positive pregnancy test at baseline;
20. Inadequate bone marrow function as evidenced by one of the following:
    - Absolute neutrophil count (ANC) $<1.5 \times 10^9$/L
    - Platelet count $<100 \times 10^9$/L
    - Haemoglobin <6 mmol/L (transfusion allowed);
21. Inadequate liver function despite satisfactory biliary drainage, defined as:
    - Serum (total) bilirubin persisting at >5 × the ULN for the institution
    - AST or ALT >3.0 × ULN (>5 × ULN if liver metastases are present)
    - ALP levels >5.0 × ULN;
22. Inadequate renal function, as determined by local practice for patients on fractionated platinum-based chemotherapy. Patients with creatinine clearance <60 mL/min must not be included.

4.2 Discontinuation/Withdrawal of Patients From Study Treatment and/or the Study

4.2.1 Discontinuation From Study Treatment

Study treatment will continue until a maximum of 8 gemcitabine/cisplatin chemotherapy cycles or criteria for discontinuation of treatment are met. A study patient is free to discontinue study treatment prematurely at any time. If so, the patient shall always be asked about the reason(s) for treatment discontinuation, and the presence of SAEs and AEs. If AEs are ongoing, these will be followed up as detailed in the study plan.

A patient may discontinue study treatment in any of the following situations:

- Severe non-compliance to study protocol
- Incorrect enrolment and randomisation
- Progressive disease
- Development of toxicity
    - Arm A patients after first PCI treatment: the development of toxicity, which precludes further treatment with both:

- PCI treatment, see SLT definition in Section 3.3.2 and
- standard gemcitabine/cisplatin combination chemotherapy, as per local practice

  Note: If a patient can no longer receive PCI treatment due to toxicity but can continue on the standard gemcitabine/cisplatin combination chemotherapy, or vice versa, then the patient will not be considered as discontinued from treatment.

- Arm A patients after second PCI treatment and Arm B patients: the development of toxicity, which precludes further treatment with standard gemcitabine/cisplatin combination chemotherapy, as per local practice

- Patient refusal to receive further study treatment

  Note: If a patient no longer wishes to receive PCI treatment but can continue on the standard gemcitabine/cisplatin combination chemotherapy, or vice versa, then the patient will not be considered as discontinued from treatment.

- Lost to follow-up
- Intercurrent illness precluding further study treatment
- Pregnancy
- Any other reasons not listed above as per Investigator discretion

The reason for treatment discontinuation must be adequately documented and recorded in the eCRF.

4.2.2 Withdrawal From Study

In case of death, the randomised patient will be considered withdrawn from the study.

Further, a patient will be withdrawn from the study in any of the following situations:

- Patient is lost to follow-up
- Patient decides to withdraw consent from participating in the study

- Screen failure
- Study terminated by Sponsor
- Other

The reason for withdrawal from the study must be adequately documented and recorded in the eCRF.

Patients who choose to withdraw from the study shall always be asked about the reason(s) for withdrawal from study. Patients should always be asked specifically whether they consent to be contacted for determination of survival follow-up. If patients who withdraw do not consent to survival follow-up, no further study procedures or follow-up assessments will be performed following withdrawal, and no further data will be collected through patient interactions.

For patients whose reason for withdrawal is not death, if permitted, determination of survival may be collected through publicly available death registry information.

4.2.3 Handling of Discontinuations/Withdrawals

Patients are free to withdraw from the study or discontinue study treatment at any time upon request. Patient participation in the study may be stopped at any time at the discretion of the Investigator or at the request of the Sponsor.

Patients who discontinue study treatment or active participation in the study will no longer receive study treatment from the Sponsor. When a patient withdraws from the study treatment or active participation in the study, the reason(s) for withdrawal shall be recorded by the Investigator on the relevant page of the eCRF. Patients who discontinue study treatment prematurely will continue to be followed for radiological progression and survival. Patients who fail to return for final assessments will be contacted by the site (eg, 2 documented phone calls followed by 1 registered letter) in an attempt to have them comply with the protocol.

To achieve the goals of the study and maintain patient safety, it is vital to obtain follow-up data on any patient withdrawn from the study. In every case, efforts must be made to undertake protocol-specified, safety, follow-up procedures.

All randomised patients will be included in the primary Intent-to-Treat (ITT) analysis set regardless of treatment received.

4.2.4 Replacements

Randomised patients who discontinue treatment or withdraw from the study will not be replaced. If a randomised patient is withdrawn, the patient identifier number will not be reused.

5 Study Treatments

5.1 Method of Assigning Patients to Treatment Arms

Upon completion of all screening evaluations to confirm eligibility to participate in the study, eligible patients will be randomised via the Interactive Web Response System (IWRS). The randomisation will be stratified by 2 factors: any measurable disease at baseline (yes versus no) and presence or absence of metastases. Once the patient is randomised through the IWRS, the patient will be considered enrolled in the study. Specific instructions for the central enrolment and registration/randomisation procedures will be provided to the centre in a separate IWRS Procedure Manual. Approximately 186 patients will be enrolled at approximately 50 sites and randomised in a 1:1 ratio (fimaporfin-induced PCI of gemcitabine complemented by gemcitabine/cisplatin chemotherapy versus gemcitabine/cisplatin chemotherapy alone).

Sites will be required to complete a Screening Log of all screened patients, regardless of whether the patient is randomised in the study. Randomised patients will be assigned a unique patient identifier number. If a randomised patient is withdrawn, the patient identifier number will not be reused.

5.2 Identity of Investigational Products/Standard of Care Treatment

A single PCI treatment consists of IV administration of Amphinex solution for injection (dose 0.25 mg/kg fimaporfin-di-olamine, equivalent to 0.22 mg/kg fimaporfin), followed 4 days later by gemcitabine IV infusion (1000 mg/m^2) and bile duct intraluminal laser light application (light dose 30 J/cm).

Gemcitabine is currently not licensed for the treatment of patients with advanced inoperable CCA, but it is part of the current recognised SoC therapy. All patients will also receive SoC treatment (Arm A: SoC treatment plus PCI treatment, Arm B: SoC treatment alone). The current recognised SoC for nonresectable or metastatic CCA is cisplatin IV infusion, dose 25 mg/m^2 on Days 1 and 8, plus gemcitabine IV infusion, dose 1000 mg/m^2 on Days 1 and 8, in up to 8 cycles of 21 days (Valle et al 2016; National Comprehensive Cancer Network 2020).

5.2.1 Amphinex

Amphinex solution for injection is a sterile solution containing the following:

- Active substance fimaporfin di-olamine; 30 mg/mL (equals 26 mg/mL of fimaporfin)

[redacted]

5.2.1.1 Fimaporfin-Associated Photosensitivity

All patients who receive Amphinex (fimaporfin) are expected to become temporarily photosensitive and must take precautions to protect the skin and the eyes in order to prevent photosensitivity reactions.

Data from clinical studies (studies PCI 101-06, PCIA 202-10 and PCIA 202-12) showed that all photosensitivity-related AEs were mild or moderate. [redacted]

Based on non-clinical data (Gederaas et al 2017) it is expected that fimaporfin photoactivation properties are diminished upon exposure to light ("bleaching" effect) and

therefore a gradual return to normal light conditions is recommended to shorten the time of light sensitivity.

Luxmeters will be provided to the patients to enable them to measure light in their surroundings and to guide the gradual increase in exposure. The duration and degree of photosensitivity varies between patients, and patients must be encouraged to follow guidance and test for skin sensitivity.

Photosensitivity precautions to be taken before, during and immediately after administration of Amphinex include the following:

- As there is a potential for exacerbation of skin photosensitivity if Amphinex is used with other medicinal products known to induce skin-photosensitising reactions, precautions should be applied if these medications are being taken while Amphinex is being administered. A list of common photosensitising agents is provided in Table 4.
- Patients must wear glasses that protect against laser emission wavelength, and all wavelength that activates fimaporfin, ie, ultravisible and visible light (dark glasses). The eyewear will be provided by the Sponsor.
- As some pulse oximeters produce red light of a wavelength close to 652 nm, oximeters must be repositioned at least every 10 to 15 minutes to avoid the risk of local skin burns. Any non-compliance with regard to light protection should be adequately documented and recorded in the eCRF.
- Immediately after administration of Amphinex, the injection site should be protected from light by a dressing.

Following Amphinex injection, precautions should be taken for at least 4 weeks to avoid exposure of skin and eyes to direct sunlight or bright indoor light. Procedures for gradual re-introduction to light are provided in Table 1. Investigator must inform the patient of these procedures and document this counselling in the eCRF. In addition, all patients who receive Amphinex will receive a patient leaflet with information on how to protect from light, how to test for light sensitivity and how to gradually increase exposure to light.

Table 1 Precautions for the Prevention of Skin and Eye Photosensitivity Reactions

Time after Amphinex (fimaporfin) injection	Precautions to prevent skin and eye photosensitivity reactions
Patients should be made aware that there can be marked variation in sensitivity and duration of sensitivity between people.	
Day 1 (0–24 hours)	**Patients should avoid direct exposure of eyes to any light sources and avoid direct and indirect daylight exposure.** • The patient should stay indoors with low intensity (dim) indoor light (max 100 lux). • Patients should avoid watching television or using computers, tablets, or smart phones. • To avoid exposure to daylight from the window, curtains and blinds should be closed. Lighting choice: warm white light bulbs (not more than 800 lumen: max 60W tungsten filament warm light bulb, 13W energy saver, or 6W LED)
Day 2-7:	**Indoors: Patients should avoid direct daylight coming through the window** or direct light from household appliances such as reading lamps. Beginning at 100 lux on Day 1, patients may gradually return to normal indoor lighting by a stepwise increase in the light of 100 lux per day, to reach 700 lux by Day 7. **Outdoors:** Patients may go outdoors after dusk. If need to travel during the day, such as to hospital appointments, the patient must sit away from windows and **cover all skin including face and hands, and wear the dark glasses provided by Sponsor.** The type of clothes and accessories the patient must wear are: • Wide-brimmed hat: for head, neck, face, nose and ears • Scarf: for head and neck • Dark glasses with side panels: for eyes and skin around eyes • Long sleeved top: for upper body/arms • Long trousers: for lower body/legs • Gloves: for hands, wrist and fingers • Socks: for feet and ankles • Closed shoes: for feet • An umbrella/parasol can give additional protection Skin photosensitivity reactions are caused by visible light. Sunscreens that protect from ultraviolet light will not protect from visible light. Dark, tightly woven clothing should be worn. Very thin clothing will not protect from strong light. **If exposed to excessive bright light, the patient may feel a burning sensation on the skin. The patient must move away from the light source. If a photosensitivity reaction develops, contact the Clinical Investigator for**

Time after Amphinex (fimaporfin) injection	Precautions to prevent skin and eye photosensitivity reactions
	advice (see below).
Day 8-15:	**<u>Indoors:</u> Patients should avoid direct daylight coming through the window** or direct light from household appliances such as reading lamps. Continue to gradually return to normal indoor lighting by a stepwise increase in the light (by 100 lux per day, ie, from 800 lux on Day 8 to 1500 lux on Day 15). **<u>Outdoors:</u>** Patients may go outdoors but only if it is cloudy, shaded and not sunny. If need to travel during the day, such as to hospital appointments, the patient must sit away from windows and **cover all skin including face and hands, and wear the dark glasses provided by Sponsor.** Skin test: Patient should try cautious exposure only to back of hands over 5-15 minutes on non-sunny days. If any prickling or discomfort occurs then patient should stop exposure immediately, cover up and go indoors. If there is no reaction 24 hours later, patient can continue to extend and gradually build up exposure time. **If exposed to excessive bright light, the patient may feel a burning sensation on the skin. The patient must move away from the light source. If a photosensitivity reaction develops, contact the Clinical Investigator for advice (see below).**
After 2 weeks:	**A gradual increase in exposure to light should be encouraged, and the patient should continue to test for skin photosensitivity as described above.** If there are no reactions 24 hours after the exposure, the duration of light exposure can be increased by 15 minutes per day. **<u>Indoors:</u> gradually build up to normal levels of exposure.** Patients should still take precautions to avoid exposure of skin to direct sunlight or bright indoor light for at least 4 weeks following administration of Amphinex. Eyes can remain sensitive to bright light for 3 months. **<u>Outdoors:</u>** During the first days of outdoor exposure the patient should stay in shaded areas or go out only when cloudy. The patient should continue to wear dark glasses and dark, tightly woven clothing. Two weeks after Amphinex injection, the patient should start to gradually return to normal levels of direct sunlight exposure. The patient's eyes may be very sensitive to bright light during the first 3 months; therefore, when outdoors, the patient should continue to wear the dark glasses provided by the Sponsor. **If at any time the patient experiences symptoms – prickling, discomfort or redness – then he/she should cover up and go indoors and let the symptom settle fully before repeating exposure.**
Surgery:	Surgery or dental treatment involving the use of light for visualisation or

Time after Amphinex (fimaporfin) injection	Precautions to prevent skin and eye photosensitivity reactions
	treatment should be avoided during the first 4 weeks following Amphinex administration, unless it is absolutely necessary and only if the potential benefits for the patient outweigh the risks. Direct illumination of the patient with the operating room lights, including the surgeon's headlamp, should be avoided. If an acute surgical intervention is needed, yellow or green light should be used. Ideally this could come from a sodium lamp but it may be more practical to use green filters that absorb wavelengths that activate fimaporfin (around 415 nm and 652 nm, contact Sponsor for advice). All incisions should be shielded from light. Some pulse oximeters may produce red light of a wavelength close to that used for the photoactivation of fimaporfin. To avoid the risk of local skin burns, pulse oximeters must be repositioned every 10 minutes and must not be used for longer than needed.
Up to 3 months:	For at least 3 months following PCI treatment: Eye tests that use bright lights should be avoided. Patients should contact their Investigator if eye tests using bright light are planned. Patients should avoid ultraviolet tanning beds and should not sunbathe.
After 3 months	Some patients may experience photosensitivity reactions beyond 3 months. Hence, the precautionary measures may be required for longer. Liver or renal impairment may prolong the elimination of fimaporfin, requiring longer periods of light protection. Patients should continue to test for photosensitivity periodically as described above until such time that no reactions are observed.
Treatment of photosensitivity reactions	If patients experience skin photosensitivity reactions, they can be treated in the same way as sunburn: Use of cooling emollients, skin moisturiser, topical corticosteroids. Analgesics can be considered for symptomatic relief. Extra care must be taken to protect skin while it heals.

5.2.2 Gemcitabine

Gemcitabine will be provided from the pharmacy stock. The gemcitabine bag used for administration will be labelled according to the local routines and regulatory requirements. The investigational site will be responsible for ordering gemcitabine. In the event that the investigational site cannot source gemcitabine locally for any reason, the Sponsor may provide gemcitabine centrally. The manufacturer and batch numbers will be documented. Refer to the Summary of Product Characteristics (SmPC)/Prescribing Information for further information on gemcitabine.

5.2.3 Cisplatin

Cisplatin will be provided from the pharmacy stock. The cisplatin bag used for administration will be labelled according to the local routines and regulatory requirements. The investigational site will be responsible for ordering cisplatin. In the event that the investigational site cannot source cisplatin locally for any reason, the Sponsor may provide cisplatin centrally. The manufacturer and batch numbers will be documented. Refer to the SmPC/prescribing information for further information on cisplatin.

5.2.4 Stenting

Refer to Section 3.3.1.

5.2.5 Light Source

Laser light is used to activate fimaporfin. The light source used in this study will be supplied by the Sponsor and is a CE-marked medical laser system, emitting red light at 652 nm. [redacted]

[redacted]

5.2.6 Dose Modifications

5.2.6.1 Dose Modifications for Amphinex and PCI treatment

No dose modifications are allowed for Amphinex or gemcitabine given as part of the PCI treatment. See Section 3.3.2 regarding postponements or omissions of PCI treatment.

5.2.6.2 Dose Modifications for Systemic Chemotherapy Cycles

The investigator site is expected to follow local practice for dose modification of the standard gemcitabine/cisplatin combination chemotherapy; however, the following information is provided for guidance.

Haematological Toxicity

The absolute neutrophil count must be ≥1,500 × 10^6/L and the platelet count must be ≥100,000 × 10^6/L in order to administer full doses of gemcitabine and cisplatin in combination. Patients should be monitored prior to each dose for platelet, leucocyte and granulocyte counts, and, if necessary, the dose of gemcitabine and cisplatin may be either reduced or withheld in the presence of haematological toxicity according to the following scale (Table 2).

Table 2 Dose Modifications for Haematological Toxicities

Day 1				
Absolute neutrophil count (× 10^6 /L)		**Platelet count (× 10^6 /L)**	**Percent (%) of full dose gemcitabine**	**Percent (%) of full dose cisplatin**
≥1,500	and/or	≥100,000	100	100
≥500 - <1,000	and/or	≥50,000 - <100,000	delay dose until recovery, then 75	100
<500	and/or	<50,000	omit dose until recovery, then 75	omit dose until recovery, then 75
Day 8				
Absolute neutrophil count (× 10^6 /L)		**Platelet count (× 10^6 /L)**	**Percent (%) of full dose gemcitabine**	**Percent (%) of full dose cisplatin**
≥1,000	and/or	≥100,000	100	100
≥500 - <1,000	and/or	≥50,000 - <100,000	omit dose until recovery, then 75	100
<500	and/or	<50,000	omit dose until recovery, then 75	omit dose until recovery, then 75

Non-Haematological Toxicity

Renal toxicity: The creatinine clearance must be ≥ 60 mL/min in order to administer the full dose of cisplatin. Serum creatinine should be checked before each cycle of treatment. If there is a >25% increase of serum creatinine compared to the baseline, then the ethylenediamine tetraacetic acid (EDTA) clearance (or equivalent, including estimation of GFR, according to local practice) must be performed.

Pulmonary toxicity: Transient dyspnoea occurs in <10% of patients after gemcitabine, secondary to mild bronchospasm. Rarely, more severe pulmonary toxicity characterised by tachypnoea, hypoxia diffuse interstitial infiltrates, acute respiratory distress syndrome and respiratory failure may also occur. The patient should be withdrawn from treatment.

Table 3 Dose Modifications for Non-Haematological Toxicities

	Percent (%) of Full Dose Gemcitabine	Percent (%) Full Dose Cisplatin
Renal Function		
≥60 mL/min	100	100
40–59 mL/min	100	50
<40 mL/min	Omit	Omit
Biliary Tract Obstruction		
Bilirubin >2.5 × ULN	Omit	Omit
AST/ALT/ALP >5.0 × ULN	Omit	Omit
Peripheral Neuropathy		
Grade 1–2	100	Delay until recovery, then 100
Grade 3–4	100	Discontinue
Tinnitus		
If full recovery between cycles	100	100
If no full recovery between cycles	100	Omit
Lethargy		
Grade 3–4	75 (if no response, stop treatment)	100
Oedema		
Grade 3–4	75 (if no response, stop treatment)	100

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST; aspartate aminotransferase; ULN, upper limit of normal.

Gemcitabine-Specific Non-Haematological Toxicity

Posterior Reversible Encephalopathy Syndrome: Reports of posterior reversible encephalopathy syndrome (PRES) with potentially severe consequences have been reported in patients receiving gemcitabine as a single agent or in combination with other chemotherapeutic agents. Acute hypertension and seizure activity were reported in most gemcitabine patients experiencing PRES, but other symptoms such as headache, lethargy, confusion and blindness could also be present. Diagnosis is optimally confirmed by MRI. Posterior reversible encephalopathy syndrome was typically reversible with appropriate supportive measures. Gemcitabine should be permanently discontinued and supportive

measures implemented, including blood pressure control and anti-seizure therapy, if PRES develops during therapy.

Haemolytic Uraemic Syndrome: Clinical findings consistent with the haemolytic uraemic syndrome (HUS) were rarely reported (postmarketing data) in patients receiving gemcitabine. Haemolytic uraemic syndrome is a potentially life-threatening disorder. Gemcitabine should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, and/or elevation of serum bilirubin, serum creatinine, blood urea nitrogen or lactate dehydrogenase. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.

5.3 Management of Clinical Supplies

5.3.1 Study Drug Packaging and Storage

Amphinex will be labelled, packaged and stored by:

[redacted]

5.3.2 Test Article and Device Accountability

The Investigator and/or Pharmacist will be responsible for drug and device accountability. The study medication and laser will be kept in a secure place with limited access and will only be supplied to patients in the study under the supervision of the Investigator. The Investigator and the pharmacy (if applicable) are responsible for maintaining accurate records of the dispensing of study medication and use of the laser. Provision will be made in

the eCRF and drug accountability section of investigator site file to verify that laser use and dosing has taken place in accordance with this protocol, respectively. Used study medication will be stored safely until destruction and must be accounted for by the Investigator. Any study medication accidentally or deliberately destroyed will be accounted for. Any discrepancies between study medication amounts dispensed and returned will be explained. The Monitor will check drug accountability during the monitoring visits. After study termination, all unused (and used, if applicable) study medication and clinical supplies at a site will be sent to an authorised institution for destruction. The procedures for destruction of clinical supplies will be described in the study-specific Pharmacy Manual.

5.3.3 Other Supplies

Study sites will be provided with protective eyewear for the operators (ie, glasses protecting against the laser emission wavelength [652 nm]). Study sites will also be provided with protective eyewear for patients, protecting against the laser emission wavelength (652 nm) and all other ultravisible and visible light that activate fimaporfin, and optical fibres and catheters for the laser light application.

Only the supplies provided by the Sponsor should be used. Additional items supplied by the Sponsor are described in the Procedure Manual and Laboratory Manual.

5.4 Treatment Compliance

The details of the study treatment will be adequately documented and recorded in the eCRF and drug accountability forms as applicable. All study treatment-related procedures will be performed at the investigational site by qualified health care personnel. All instances of non-compliance and all resulting protocol deviations will be adequately documented and recorded in the eCRF.

5.4.1 Light Protection Compliance

Investigators must counsel patients to observe the light protection precautions described in Table 1 to prevent photosensitivity reactions. It should be adequately documented and recorded in the eCRF that the patient was thoroughly informed on the light protection precautions. Any non-compliance with regard to light protection should also be adequately documented and recorded in the eCRF.

5.5 Concomitant Treatments

5.5.1 Permitted Treatments

Any medication except those as noted in Section 5.5.2, which are considered necessary for the patient's welfare, and which will not interfere with the study treatment, may be given at the discretion of the Investigator.

Patients will be allowed to receive supportive care therapies (including cytokine growth factors) concomitantly during the study. Other than the chemotherapy given during the course of the study, the use of any other chemotherapy, immunotherapy, radiation therapy, or experimental medications is prohibited during the study treatment period. Patients with prostate cancer that is controlled by hormone therapy may continue that therapy while on study. Disease progression requiring other specific anti-tumour therapy will be cause for discontinuation from the study treatment.

Prophylactic anti-emetic and antibiotic therapy is permitted where indicated. During stent placement and the light application procedure, sedation with adequate analgesic cover is preferred; however, general anaesthesia is also permitted.

Any prior, concurrent, or procedural medications or therapy given to or taken by the patient will be recorded in the eCRF along with the indication for its use. All concomitant medication taken from the time that the informed consent form (ICF) is signed, until 30 days after end of treatment, will be recorded in the eCRF. The date of first administration and reason for use will be recorded in the eCRF. Major changes in dose, schedule, or reason for use will also be recorded in the eCRF.

After this period, only relevant medication (eg, medication in patients with treatment-related AEs including antibiotic treatment in biliary events, any anti-cancer therapy) will be recorded in the eCRF. Both generic and trade names may be recorded. However, the generic name is generally preferred because of its specificity, whereas trade names are preferred for combination products.

5.5.2 Prohibited Therapies

The following therapies are prohibited during the study treatment period:

- **Clozapine**: The use of clozapine is not permitted during the study due to an increased risk for agranulocytosis.
- **Live vaccines**: Vaccination with a live vaccine, such as the vaccine against yellow fever, has resulted in severe and fatal infections when used in combination with immunosuppressive chemotherapeutics. This risk increases in patients with existing immune suppression because of the underlying disease. If possible, use of an inactivated vaccine (poliomyelitis) is recommended.
- **Cyclosporine, tacrolimus**: prohibited due to a risk of excessive immune suppression with risk of lymphoma proliferation.
- **Phenytoin**
- Anti-cancer treatment other than the study treatments. Hormone therapy for prostate cancer that started before randomisation is allowed to continue during the study.
- Any experimental treatment other than PCI treatment.

5.5.3 Photosensitising Drugs

There may be a potential for exacerbation of skin photosensitivity if Amphinex is used with other photosensitising drugs. Precautions should therefore be applied if medicinal products known to induce skin-photosensitising reactions are to be administered together with Amphinex. A list of common medications with photosensitising potential is provided in Table 4. Due to the long half-life of amiodarone, Amphinex must not be administered in patients treated with amiodarone during the last 12 months. For other listed compounds in Table 4 that are exchangeable or can be terminated, termination should allow for a completed systemic clearance before Amphinex administration, usually corresponding to the respective half-life times 5.

Table 4 Medications with Photosensitising Potential

Psoralenes	**Phenothiazines**	**Tetracyclines**	**Quinolones**
8-Methoxypsoralene 5-Methoxypsoralene Trimethylpsoralene	Chlorpromazine Promethazine	Demeclocycline Doxycycline Tetracycline	Norfloxacin Ciprofloxacin
Potential Inducers of Photosensitivity	**PDT Photosensitisers**	**Miscellaneous**	
Fibrates NSAIDs	5-aminolevulinic acid Methyl-5-aminolevulinic acid Hexaminolevulinate Photofrin	Musk fragrances Amiodarone[a] St. John's wort Furosemide Sulfonylureas Antifungals Sunscreens (PABA-esters, benzophenones)	

Abbreviation: NSAIDs, non-steroidal anti-inflammatory drugs; PABA, p-aminobenzoic acid; PDT, photodynamic therapy.

a. Due to the long half-life of amiodarone, Amphinex must not be administered in patients treated with amiodarone during the last 12 months.

5.6 Contraception

A woman is considered of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. A WOCBP must continue the use of contraception during treatment and until the end of relevant systemic exposure (at least 9 months after last dose of Amphinex or 6 months after last dose of chemotherapy, whichever is the latest).

Only men with pregnant or non-pregnant partners considered of childbearing potential will need to follow contraception requirements. A condom is also required to be used by vasectomised men to prevent delivery of the drug via seminal fluid. As the treatment includes

genotoxic investigational medicinal products, the male patient should use condoms during treatment and until the end of relevant systemic exposure in the male patient (at least 9 months after last dose of Amphinex or 6 months after last dose of chemotherapy, whichever is the latest).

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence will need to be evaluated by site personnel in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.

Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together.

6 Study Assessments and Procedures

All study assessments will be performed at the visits indicated in the study plan in the schedule of events for the active treatment period (Table 10 and Table 11) and the schedule of events for the follow-up period (Table 12).

Prior to performing any study procedures, all potential patients will sign an ICF. Patients will have the opportunity to have any questions answered before signing the ICF. The Investigator must address all questions raised by the patient. The Investigator or designee will also sign the ICF.

6.1 Efficacy Assessments

6.1.1 Tumour Assessment

The study will evaluate tumour responses as determined by Investigator according to RECIST 1.1. The primary PFS analysis will be based on the local radiological assessment, which will be used to guide clinical management decisions. Note: In cases of symptomatic progression, patients will continue to be followed for radiological RECIST progression.

From the Investigator's review of the imaging scans, the RECIST tumour response data will be used to determine each patient's visit response according to RECIST v1.1. At each visit, patients will be programmatically assigned a RECIST v1.1 visit response of CR, PR, SD, or progressive disease (for measurable/target lesions) or CR, progressive disease, or non-CR/non-PD (for non-measurable/non-target lesions) depending on the status of their disease compared with baseline and previous assessments. If a patient has had a tumour assessment which cannot be evaluated, then the patient will be assigned a visit response of not evaluable (NE).

Radiological assessments use images from contrast-enhanced CT or MRI scans, collected during screening/baseline and at regular follow-up intervals following study treatment. The RECIST 1.1 guidelines (link in Appendix C) provide a method of assessment of change in tumour burden in response to treatment. Screening/baseline imaging should be performed no more than 28 days before the randomisation. The RECIST 1.1 assessments of baseline images identify target (measurable), and non-target (non-measurable) lesions, and each lesion is evaluated in subsequent follow-up images. The same imaging modality and contrast protocol used at baseline must be used for all subsequent follow-up imaging. This allows

follow-up determination of target lesion response, non-target lesion response, and overall time point tumour responses (CR, PR, SD, non-CR/non-PD, progressive disease, or NE).

Table 5 and Table 6 provide a definition of the different response criteria for tumour evaluation of target and non-target lesions.

Table 5 Tumour Response Criteria for Target Lesions

Response	Evaluation of Target Lesions
Complete Response	Disappearance of all target lesions. Any pathological lymph nodes should be reduced to <10 mm in the short axis.
Partial Response	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.
Progressive Disease	At least a 20% relative and a 5 mm absolute increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters recorded on study (including baseline) or the appearance of 1 or more new lesions.
Stable Disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum of diameters while on study.

Abbreviation: LD, longest diameter

Table 6 Tumour Response Criteria for Non-target Lesions

Response	Evaluation of Non-target Lesions
Complete Response	Disappearance of all non-target lesions. All lymph nodes should be non-pathological in size (<10 mm in the short axis)
Non-CR/Non-PD	Persistence of 1 or more non-target lesion(s)
Progressive Disease	Appearance of 1 or more new lesion(s) and/or unequivocal progression of existing non-target lesions

Abbreviations: CR, Complete response; PD, progressive disease.

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 progressive disease for measurable disease, ie, 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) or an increase that is sufficient to require a change in therapy.

If a patient has a response of SD or PR for target lesions, a modest 'increase' in size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

Tumour response will be assessed according to RECIST 1.1 every 12 weeks (±1 week), from randomisation until disease progression and should NOT follow delays incurred in the treatment period. Patients will be followed for radiological progression, regardless of whether they discontinue therapy or have symptomatic progression.

It is important to follow the imaging assessment schedule as closely as possible. If an unscheduled imaging assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at the next scheduled imaging visit. Computed tomography and/or MRI scans should be performed of the abdomen/pelvis only, unless clinically indicated or if disease progression is suspected.

The local radiological assessment will be used to guide clinical management decisions and will be the basis for the primary analysis of PFS. In addition, a blinded independent central radiological review (BICR), blinded to the assessment of the local radiologist and/or oncologist, will be performed for the tumour response data. The data from the BICR will provide data for a supportive analysis of PFS. For the interim analysis of ORR, the assessment made by the BICR will be considered the primary analysis.

Survival follow-up phase

Survival status will be documented for all patients in an extended follow-up phase. Patients who have progressed will enter the survival follow-up phase of the study, and otherwise be managed according to standard clinical practice.

At the time of the data cut-off for the primary PFS analysis, further data collection of RECIST data will stop. Patients who have not yet progressed will enter the survival follow-up phase of the study and will continue to receive randomised treatment. Following discontinuation of randomised treatment, patients will be followed up for survival and information on any subsequent anti-cancer treatments as detailed in the study plan, unless they have withdrawn their consent.

Additional survival contacts (ie, outside of the 12-weekly calls) may be conducted around the time of interim ORR analysis and PFS analysis at data cut-off to ensure that the survival

information is as up to date as possible for the analysis of OS. Determination of survival may be collected through publicly available death registry information, where permitted locally.

6.1.2 Quality of Life Measurements

Health-related quality of life (HRQoL) is a multi-dimensional construct of an individual's subjective assessment of the impact of an illness or treatment on their physical, psychological, social, and somatic functioning and general well-being.

In this study, HRQoL will be measured by use of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and the EORTC QLQ-BIL21 questionnaire (Appendix D). Patients will complete the questionnaires at the time points specified in Table 10, Table 11 and Table 12, preferably before any other study assessments are performed. To obtain feedback on the suggested questionnaire's feasibility, an exercise of patient/carer opinion and assessment of feasibility was conducted at an annual CCA patient conference (UK, May 2018). This included an 8-question survey followed by one-to-one interviews on the selected compiled questionnaire, timing of measurements, and other patient feedback. The suggested instrument was overall confirmed as relevant and the feasibility of PRO completion at multiple time points and at follow-up endorsed.

6.2 Pharmacokinetic Assessments

In order to evaluate the PK of fimaporfin in plasma, blood samples will be obtained from all patients in Arm A as specified in Table 10. The actual time points of the blood sample collections will be captured to the nearest minute and will be recorded in the eCRF.

[redacted]

6.3 Standard Tumour Markers

The standard tumour markers cancer antigen 125 (CA-125), carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) will be analysed from blood samples collected for safety laboratory assessments throughout the study.

The dynamics of tumour markers, alone or combined, are routinely followed as a measurement of recurrence and method to predict the disease process. CA 19-9, CEA and CA-125 are the most investigated tumour markers in patients with hilar CCA. Combined CA 19-9 and CEA levels are widely used in the diagnosis of hilar CCA and have been reported to be associated with advanced tumour stage and poor survival outcome (Juntermanns et al 2010).

CA-125 is a member of the mucin family glycoproteins, secreted by epithelial cells in various organs. It is clinically most used in ovarian cancer but is also recognised as a prognostic marker in various gastrointestinal cancers. In a study of perihilar CCA, the cut-off value for CA-125 to predict resectability was 25.9 U/mL with a sensitivity of 78.6% and specificity of 67.5%. It has also been demonstrated that preoperative serum CA-125 level can be used to predict recurrence in all forms of CCA (Hu et al 2016).

CA 19-9, the most commonly used serum marker in clinical practice, is a sialylated Lewis blood group antigen targeted by the monoclonal antibody described in 1979 as a tumour-associated antigen in a colorectal cancer cell line. CA 19-9 has a wide variation in sensitivity (50%-90%) and specificity (54%-98%) (Patel et al 2000). It is elevated in approximately 75% to 85% of patients with CCA and has a specificity of 50-80%. Very high levels of CA 19-9 (≥1000 U/mL) have been associated with metastatic intrahepatic CCA; significantly elevated postoperative CA 19-9 levels are associated with early recurrence (LaFemina and Jarnigan 2012).

CEA is a set of glycoproteins involved in cell adhesion, found in healthy subjects at around 20 ng/mL, and initially detected in colon cancer cells. It can be elevated in a variety of tumour types, but with variable sensitivity, and a specificity affected by other factors (eg, smoking). In intrahepatic CCA, CEA has been found to be significantly associated with OS (Ishimoto et al 2018). In one of the larger studies that included all types of CCA, the data showed no correlation between tumour location and serum level of CEA and the sensitivity

and specificity of CEA for diagnosis of CCA was found to be 66.0% and 81.5%, respectively (Deng et al 2017).

6.4 Safety Assessments

6.4.1 Adverse Events

6.4.1.1 Definitions of Adverse Events

The Investigator is responsible for reporting all treatment-emergent AEs (TEAEs) that are observed or reported during the study, regardless of their relationship to study treatment 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 treatment. Patients will be instructed to contact the Investigator at any time after randomisation if any symptoms develop.

A TEAE is defined as any event not present before exposure to study treatment or any event already present that worsens in either intensity or frequency after exposure to study treatment.

6.4.1.2 Serious Adverse Events

An SAE is defined as any event that

- 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

Important medical events that may not result in death, be life threatening, or require hospitalisation may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or 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 or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse.

6.4.1.3 Eliciting and Documenting Adverse Events

Adverse events will be recorded from the time of the patient signing the ICF up to 30 days after the last administration of any study treatment.

Serious AEs that occur more than 30 days after the last dose of study treatment need not be reported unless the Investigator considers them related to study treatment and/or procedures.

At every study visit, patients will be asked a standard nonleading question 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 identified from any study data (eg, laboratory values, physical examination findings, electrocardiogram [ECG] changes) or identified from review of other documents (eg, patient diaries) that are relevant to patient safety will be documented on the AE page in the eCRF.

6.4.1.4 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes the following:

- event term
- time of onset
- Investigator-specified assessment of severity and relationship to study treatment
- time of resolution of the event
- seriousness
- any required treatment or evaluations
- outcome

Adverse events 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 to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST 1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression radiologically. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

6.4.1.5 Reporting Serious Adverse Events

The Investigator must report any AE that meets SAE criteria (Section 6.4.1.2) to [redacted], using the electronic data capture (EDC) system, immediately (ie, within 24 hours) after the time the site personnel first learn about the event.

In the event the EDC entry is not possible (eg, system failure or access problems), the study site should complete the paper SAE report form and fax the form to [redacted] within 24 hours of awareness. The EDC system should be updated as soon as it is available.

A full description of every SAE will need to be provided to [redacted] (this may be supported by source documentation such as discharge summary or laboratory report should the patient be hospitalised).

The following contact information is to be used for SAE reporting:

[redacted]

[redacted]

6.4.1.6 Suspected Unexpected Serious Adverse Reactions and Adverse Events of Special Interest

The Sponsor will promptly evaluate all SUSARs and AESIs against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, Independent Ethics Committees/Institutional Review Boards (IECs/IRBs), and applicable health authorities based on applicable legislation.

The Sponsor will ensure that all relevant information about SUSARs that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the Member States concerned, and to the IECs/IRBs, and in any case no later than 7 calendar days after knowledge by the Sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional 8 calendar days.

All other SUSARs will be reported to the competent authorities concerned in accordance with their specific requirement and to the IECs/IRBs concerned as soon as possible but within a maximum of 15 calendar days of first knowledge by the Sponsor. The Sponsor will also inform all Investigators.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Amphinex (fimaporfin) IB
- SmPC and prescribing information for gemcitabine

The Sponsor will compare the severity of each SUSAR and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

[redacted]

All AESIs will be assessed by the IDMC as specified / laid out in the IDMC charter.

6.4.1.7 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the patient's daily activities. The intensity of all AEs will be graded in accordance with the current version of NCI CTCAE. Guidance for events that cannot be graded according to the NCI CTCAE is provided below:

Mild:	An AE that is usually transient in nature and generally does not interfere with normal activities.
Moderate:	An AE that is sufficiently discomforting to interfere with normal activities.
Severe:	An AE that interrupts a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterised as intermittent do not require documentation of onset and duration of each episode.

6.4.1.8 Assessment of Causality

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

The Investigator's opinion of the relationship of the AE to the study treatment and procedures (ie, Amphinex administration, gemcitabine administration, cisplatin administration, stent placement and laser light application procedure) will be collected for all AEs.

The relationship or association of the study treatment/procedure in causing or contributing to the AE will be characterised using the following classification and criteria:

Unrelated: This relationship suggests that there is no association between the study treatment/procedure and the reported event.

Possible: This relationship suggests that study treatment/procedure caused or contributed to the AE, ie, the event follows a reasonable temporal sequence from the time of study treatment administration or follows a known response pattern to the study treatment but could also have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with study treatment administration/procedure exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the Investigator's clinical experience, the association of the event with the study treatment/procedure seems likely. The event disappears or decreases on cessation or reduction of the dose of study treatment.

Definite: This relationship suggests that a definite causal relationship exists between study treatment administration/procedure and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study treatment is re-administered.

If relationship of the AE is categorised as 'possible', 'probable', or 'definite', the Investigator should specify in the eCRF/SAE form whether relationship is described with respect to Amphinex, gemcitabine, cisplatin, stent placement or laser light application procedure. For reporting purposes 'possible', 'probable', and 'definite' will be considered as related.

6.4.1.9 Follow-Up of Patients Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the Investigator deems the event to be chronic or not clinically significant, or until the patient is considered to be stable.

6.4.2 Adverse Incidents/Unanticipated Adverse Device Effects

An adverse incident (AI) (or Incident) is “any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, user, or other person, or to a serious deterioration in their state of health.” (Definition of an Adverse Incident from the Medical Device Directive 93/42/EEC, Art. 10).

A “malfunction or deterioration” should be understood as a failure of the device to perform in accordance with its intended purpose when used in accordance with the manufacturer’s instructions.

Per US Title 21 Code of Federal Regulations (21 CFR) Part 812.3 (s), unanticipated adverse device effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

Please note that for this study light emanating from the laser should be considered separate to the laser device itself. Thus, an AE related to the laser light should not be considered an UADE, but an AE related to study treatment.

An AI/UADE that results in:

1. Death of a patient, user or other person
2. Serious deterioration in state of health of a patient, user or other person

will need to be reported as both an AI/UADE and an SAE.

A serious deterioration in state of health can include:

a) life-threatening illness

b) permanent impairment of a body function or permanent damage to a body structure

c) a condition necessitating medical or surgical intervention to prevent a) or b)

Examples:

- Clinically relevant increase in the duration of a surgical procedure
- A condition that requires hospitalisation or significant prolongation of existing hospitalisation

d) any indirect harm as a consequence of an incorrect diagnostic or intravenous test result, when used within manufacturer's instructions for use

e) foetal distress, foetal death or any congenital abnormality or birth defects

A deterioration in state of health is considered unanticipated if the condition leading to the event was not considered in the device risk analysis.

6.4.2.1 Reporting of Adverse Incidents/Unanticipated Adverse Device Effects

The Investigator must report all AIs/UADEs involving the laser/study device, occurring in the period of observation (see Section 6.4.1.3).

All AIs require the completion of a study-specific AI/UADE Form. For AIs/UADEs involving patient harm, the AE page in the eCRF must also be completed and where the event meets any serious criteria a separate SAE report form must be completed. Information not available at the time of the initial report (eg, device analysis) must be documented in a follow-up form.

The Investigators are responsible for reporting of any AIs/UADEs occurring during the study to the Sponsor and to the reviewing IECs/IRBs. The Sponsor shall conduct an evaluation of any AI/UADE and shall ensure reporting of the results of such evaluation to the regulatory agencies and to all reviewing IECs/IRBs and participating Investigators. [redacted] will be responsible for submission of such reports to the regulatory agencies.

6.4.3 Laboratory Analyses

6.4.3.1 Safety Laboratory Analyses

Blood and urine samples will be collected at times specified in the schedule of events (Table 10, Table 11 and Table 12) and sent to a local laboratory for analysis. Details of

sample collection, processing, shipping and storage will be described in the Laboratory Manual. The following laboratory variables should be measured:

Clinical Chemistry

S/P – alanine aminotransferase
S/P – aspartate aminotransferase
S/P – alkaline phosphatase
S/P – gamma-glutamyltransferase
S/P – bilirubin, total
S/P – calcium
S/P – creatinine[a]
S/P – C-reactive protein
S/P – glucose (fasting)
S/P – magnesium
S/P – phosphate
S/P – potassium
S/P – sodium
S/P – urea or blood urea nitrogen
S/P – amylase
S/P – lipase
S/P – chloride
S/P – protein, total
S/P – lactate dehydrogenase

Haematology

B – haemoglobin
B – white blood cell count
B – absolute leukocyte count
Neutrophils
Lymphocytes
Monocytes
Basophils
Eosinophils
B – platelet count
B – haematocrit

Coagulation

B – international normalised ratio
B – activated partial thromboplastin time

Urinalysis

U – albumin or total protein
U – glucose
U – blood
U - bilirubin

Standard Tumour Markers

S – CA-125, CA 19-9, CEA

Abbreviations: B, blood; CA-125, cancer antigen-125; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; P, plasma; S, serum; U, urine.
[a] Serum creatinine should be checked before each cycle of treatment. If there is a >25% increase compared to the baseline, then the ethylenediamine tetraacetic acid (EDTA) clearance or equivalent, including estimation of GFR, according to local practice, must be performed and cisplatin dosing modified accordingly.

Standard tumour markers will be analysed from serum samples collected for clinical chemistry.

Additionally, a urine or blood serum sample will be collected from all WOCBP at screening, on the first day of each cycle of chemotherapy, and at the end of treatment (Day 30), for a highly sensitive pregnancy test.

Laboratory values that meet the criteria for CTCAE Grade 3 or have changed significantly from baseline and are considered to be of clinical concern will be repeated/confirmed within 7 days and followed up as appropriate.

For blood volumes to be drawn, see Table 7.

Table 7 Blood Sampling Volume

Tests **Patients**	**Blood volume each patient and each sampling point**	**Sampling points** **Number of samples**	**Total blood volume** **Arm A**	**Total blood volume** **Arm B**
Amphinex pharmacokinetics **Arm A patients**	5 mL	Up to 19 sampling points	95 mL	NA
Clinical chemistry (including standard tumour markers in serum)	20 mL for serum	22 sampling points in Arm A 20 sampling points in Arm B	440 mL	400 mL
Haematology	3.5 mL (EDTA plasma)	22 sampling points	77 mL	77 mL
Coagulation	3.5 mL (citrate plasma)	10 sampling points in Arm A 9 sampling points in Arm B	35 mL	31.5 mL
Total[a]			**647 mL**	**508.5 mL**

Abbreviations: EDTA, ethylenediamine tetraacetic acid; NA, not applicable.

[a] The total volume that will be drawn from each patient in this study will vary depending on how long the patient stays on study

6.4.3.2 Hepatotoxicity

In the event that a patient shows AST or ALT ≥3 × ULN or total bilirubin ≥2 × ULN indicative of hepatotoxicity related to chemotherapy (ie, with an ensured proper biliary drainage in place and a clinical picture indicative of a correlation to chemotherapy treatments), the delay, postponement or omission of the following chemotherapy

administration is to be decided at the discretion of the treating physician as per local standard procedures applicable to gemcitabine/cisplatin treatment.

If, however, symptoms indicative of cholangitis are concurrently present (fever/septicaemia with or without chills; pain or tenderness in the right upper quarter of the abdomen, the chest, the upper back or the right shoulder), with or without jaundice, the patient is to be hospitalised with prompt measures to confirm the diagnosis by clinical and radiological investigations and by bacterial culturing. Antibiotic treatment is to be immediately administered and emergency endoscopic or transhepatic biliary drainage optimised.

6.4.4 Loco-Regional Tumour-Related Events and Biliary Complications

Unless caused by a terminal, intractable overgrowth of the loco-regional tumour in patients with established progressive disease, unplanned or emergency hospital visits caused by clinical signs of sudden bile duct obstruction, including but not limited to malaise, pain, jaundice, septicaemia, or several symptoms combined, and with clinical, laboratory and radiological findings confirmatory of unexpected, biliary obstruction leading to unplanned hospitalisation will be recorded and reported as SAEs (see Section 6.4.1.5). The nature of the event (diagnosis and MedDRA classification), duration of hospital stay, need for endoscopic or other intervention, and antibiotic treatment days shall be captured in the eCRF. Also, the time elapsed since the last endoscopic ERCP intervention and PCI treatment (if relevant) must be recorded.

6.4.5 Vital Signs

Systolic and diastolic blood pressure and pulse rate will be measured in the sitting position after at least 10 minutes rest. Body temperature will be measured in degrees Celsius. Any changes in vital signs should be recorded as an AE if deemed clinically significant by the Investigator.

Vital signs on Day -4 and Cycle 4, Day 18 must be collected both before and after Amphinex administration.

6.4.6 Electrocardiograms

Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes. A standardised ECG machine will be used and the patient should be examined using the same machine throughout the study, where feasible.

After paper ECGs have been recorded, the Investigator or designated physician will review each of the ECGs and may refer to a local Cardiologist if appropriate. A signed and dated copy, with relevant results noted by the Investigator, should be filed in the patient's medical records. If an abnormal ECG finding at screening is considered to be clinically significant by the Investigator, it should be reported as a concurrent condition. For all ECGs, details of rhythm, PR, R-R, QRS and QT intervals and an overall evaluation will be recorded. Corrected QT intervals will be calculated using Bazett's formula (QTcB) and Fridericia's formula (QTcF).

The ECG on Day -4 and on Cycle 4, Day 18 must be performed before and approximately 30 minutes and 4 hours after Amphinex administration.

6.4.7 Photosensitivity and Skin Reactions

In both study arms, skin reactions and photosensitivity reactions will be documented as AEs in the eCRF and coded using MedDRA and followed to adequate resolution.

6.4.8 Medical History

Medical history to be collected at the pre-treatment evaluation includes evaluation of the history of the patient's CCA and method of confirmation, its previous therapy, pre-existing diseases, and current medication.

6.4.9 Physical Examinations

A complete physical examination with weight will be performed. Height will be recorded at screening only. Body surface area will be calculated.

Performance status will be assessed at the visits as indicated in the study plan according to US ECOG criteria as follows:

0 = Fully active, able to carry out all pre-disease activities without restrictions

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature eg, light housework, office work

2 = Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours

3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4 = Completely disabled, cannot carry on self-care, totally confined to bed or chair

6.5 Independent Data Monitoring Committee

An IDMC will be employed during the course of the study to periodically assess safety. Further details are provided in Section 11.1.1.

6.6 Pregnancy

Pregnancy is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. The Investigator must report any pregnancies which come to the attention of the Investigator during the study and up to 30 days after completion of the study to the Sponsor. Pregnancies of both female patients and partners of male patients should be reported. Patients who become pregnant will be followed until completion of pregnancy.

Any pregnancy that occurs during study participation must be reported using the same procedures as an SAE (Section 6.4.1.5). To ensure patient safety, each pregnancy must be reported within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the patient was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the Investigator's attention after the patient has completed the study, and considered by the Investigator as possibly related to the study treatment, must be promptly reported.

7 Statistical and Analytical Plan

7.1 Primary Endpoint

7.1.1 Progression-Free Survival

Progression-free survival is defined as the time from randomisation until the date of radiological disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anti-cancer therapy prior to progression.

7.2 Secondary Endpoints

7.2.1 Overall Survival

Overall survival (OS) is calculated as the time from randomisation to the date of death from any cause.

7.2.2 Best Overall Response

The BOR is the best response recorded from the start of the treatment until disease progression/recurrence.

7.2.3 Objective Response Rate

The ORR is calculated as the proportion of patients who have at least one visit response with a CR or PR noted.

7.2.4 Duration of Response

The DoR is defined as the time from the first documented tumour response until radiological disease progression, or death in the absence of disease progression.

7.2.5 Disease Control Rate

The DCR is defined as the proportion of patients with stable disease or better (ie, CR, PR or SD); it will be assessed at 6 and 12 months.

7.2.6 Change in Tumour Size

Change in tumour size, defined as the best overall percentage change in tumour size from baseline. Tumour size is defined as the sum of the lengths of the longest diameters of the RECIST 1.1 target lesions.

7.2.7 Safety

Safety will be assessed using the Safety Analysis Set and will include assessment of AEs, SAEs, and deaths, clinical laboratory assessments, physical findings, vital signs, ECGs and photosensitivity assessments. Data from all cycles of treatment will be combined and used for the reporting of AE summary tables. The effects of fimaporfin-induced PCI on safety in terms of loco-regional tumour-related events and biliary complications will also be assessed.

Secondary endpoints for safety include the following:

- Toxicity profile (AEs, laboratory assessments and physical findings) of fimaporfin-induced PCI of gemcitabine with the gemcitabine/cisplatin combination, or the gemcitabine/cisplatin combination alone.
- Frequency and severity of loco-regional tumour-related events and biliary complications requiring unplanned hospital visits and inpatient care.

7.2.8 Pharmacokinetics

In order to characterise the PK profile of fimaporfin in plasma, PK samples will be analysed to obtain plasma fimaporfin concentration-time data. Fimaporfin PK parameters (area under the plasma concentration-time curve [AUC], maximum observed concentration [C_{max}], time to C_{max} [T_{max}], etc) will be determined using standard non-compartmental methods and actual PK sampling times. The fimaporfin plasma concentration-time data and PK parameters will be summarised descriptively. A population PK approach may be adopted to explore the influence of covariates on PK. Further details will be provided in the statistical analysis plan (SAP).

7.2.9 Quality of Life Assessment

An evaluation and comparison of HRQoL/PRO associated with the fimaporfin-induced PCI of gemcitabine complemented by gemcitabine/cisplatin chemotherapy versus gemcitabine/cisplatin alone, will be conducted by use of EORTC QLQ-30 and QLQ-BIL21.

7.3 Exploratory Endpoints

The following exploratory endpoints will be evaluated in this study:

- Tumour response (ORR, DCR, and PFS) by location of disease, as pre-defined further in the SAP, including:
    - Loco-regional tumour control
    - Metastatic lesions
    - Local lymph nodes
- To analyse blood samples for standard tumour markers.

7.4 Sample Size Calculations

Sample size calculations will be performed using nQuery Advanced Version 8.

Approximately 186 patients with inoperable CCA will be randomised in a 1:1 ratio (fimaporfin-induced PCI of gemcitabine complemented by gemcitabine/cisplatin chemotherapy versus gemcitabine/cisplatin chemotherapy alone) to this study. The primary analysis of PFS, as assessed by local radiological review, will be conducted when approximately 129 progression events (69% maturity) have been observed. If the PFS result is statistically significant at the 3.95% 2-sided alpha level (adjusted for interim analysis of ORR), an interim analysis of OS will then be assessed, as detailed in Section 7.7.7.

If the true HR for the comparison of fimaporfin-induced PCI of gemcitabine complemented by gemcitabine/cisplatin chemotherapy versus gemcitabine/cisplatin chemotherapy alone is 0.6, 129 progression events will provide approximately 80% power to demonstrate a statistically significant difference in PFS at a 3.95% 2-sided significance level (this may translate to an improvement in median PFS from 7.4 to 12.3 months, if PFS is exponentially distributed). A minimum or critical HR of 0.69 (eg, 7.4 to 10.7 months), if observed, would give a 2-sided $p<0.0395$, but there is only 50% power associated with the critical HR.

Assuming linear recruitment of 186 patients over 48 months with a site set-up period of approximately 6 months, 129 PFS events are expected to occur between approximately 48 and 51 months (4 to 4.3 years) from the date on which the first patient was randomised.

In addition to the interim analysis of OS at the time of the PFS analysis (approximately 58% of patients are predicted to have died at this point), data collection for OS will continue beyond the PFS analysis and an updated OS analysis will be performed. The final OS analysis will occur after approximately 147 death events have been observed in 186 patients (>75% maturity). Assuming a true OS HR of 0.63, there will be 80% power to detect an improvement in median OS from 11.7 to 18.7 months with 2-sided p<0.0447 (O'Brien and Fleming boundary adjusted for 2 interim analyses of OS). A minimum or critical HR of 0.72 (eg, 11.7 to 16.3 months), if observed, would be statistically significant. The exact level of maturity will be determined based on the PFS and interim OS results, in discussion with the regulatory authorities. The 147 death events are expected to occur at approximately 63 to 66 months from first patient randomised.

Further details on the interim analyses are provided in Section 7.7.7.

7.5 Analysis Sets

The following analysis sets will be used in the statistical analyses.

- The ITT analysis set will include all randomised patients. The ITT analysis set will be used for efficacy analyses and treatment arms will be compared on the basis of randomised study treatment, regardless of the treatment actually received.
- The modified ITT (mITT) analysis set will include all randomised patients who have received at least one dose of study treatment and have a RECIST assessment at baseline. The mITT analysis set will be used to assess the impact on the primary PFS results of any patients who are randomised but not treated, or who are not assessed for RECIST at baseline.
- The PK analysis set will include all patients who receive at least 1 dose of fimaporfin and have at least 1 measured concentration at a scheduled PK time point postdose with no important AEs or protocol deviations that may impact PK.

- The Safety Analysis Set will consist of all patients who received at least one dose of study treatment and for whom postdose data are available. Safety data will not be formally analysed but summarised using the Safety Analysis Set according to the treatment received; ie, erroneously treated patients (eg, those randomised to Arm A treatment but actually given treatment for Arm B) will be summarised according to the treatment they actually received.

7.6 Description of Subgroups to be Analysed

Subgroup analyses will be performed for the stratification factors used at the point of randomisation (measurable disease – yes versus no and presence or absence of metastases). Exploratory subgroup analyses will also be performed to assess key endpoints by loco-regional tumour control, metastatic lesions and local lymph nodes. Four distinct groups will be explored: primary; primary with metastases; primary with local lymph nodes; and primary with metastases and local lymph nodes. An additional subgroup analysis will be performed to compare patients with and without primary sclerosing cholangitis (PSC) at study entry. If there are too few events available for a meaningful analysis of a particular subgroup, the relationship between that subgroup and PFS/OS will not be assessed. In this case, only descriptive summaries will be provided. Further details and any other exploratory subgroups of interest will be provided in the SAP.

7.7 Statistical Analysis Methodology

Statistical analysis will be performed using SAS software Version 9.3 or later. Continuous variables will be summarised using the mean, the standard deviation, median, minimum value, and maximum value. Categorical variables will be summarised using frequency counts and percentages. Data will be listed in data listings.

Details of the statistical analyses, methods, and data conventions are described in the SAP.

Given the open-label design, measures will be taken to minimise bias. These include:

- Blinding of Sponsor and Investigators to study results ie, no aggregate summaries of efficacy data by treatment will be shared during the study. Only the IDMC will receive aggregated summaries of efficacy data.
- Ensuring that appropriate measures are in place to control access to unblinded data.

- Not loading blinded independent central review (BICR) data into the clinical database during the study.

7.7.1 Analysis of Primary Endpoint

The primary endpoint for this study is PFS. Progression-free survival will be analysed using the ITT analysis set and supportive analyses will be performed using the BICR data and also the mITT analysis set.

Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment. Participants lacking an evaluation of tumour response after randomisation will have their PFS time censored on the date of randomisation with the duration of 1 day. Participants with documentation of progressive disease or death after a long interval (2 or more incomplete or non-evaluable assessments) since the last tumour assessment will be censored at the time of last objective assessment that did not show progressive disease.

The length of PFS will be calculated as:

PFS time (months) = progression/death date (censor date) - randomisation date + 1.

The PFS time for each patient will always be derived based on the scan/assessment dates and not visit dates.

Progression is defined using RECIST-1.1; a 20% increase in the sum of diameters of target lesions and the sum must also demonstrate an absolute increase of at least 5 mm, or unequivocal progression of existing non-target lesions or the appearance of new lesions.

RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- Date of progression will be determined based on the earliest of the dates of the component that triggered the progression.
- When censoring a patient for PFS, the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

Progression-free survival, as assessed by local radiological review, will be analysed using a log-rank test stratified by any measurable disease at baseline (yes versus no), and presence or

absence of metastases. If these 2 stratification factors lead to low numbers (eg, <5 progression events) within a single stratum, data will be pooled across strata in the stratified analyses. The criteria for pooling will be pre-defined in the SAP.

The HR will be estimated using a stratified Cox-proportional hazards model using the Efron approach for handling ties (Efron 1977), together with the associated 95% CI for the HR based on the Wald method.

The effect of treatment will be estimated by the HR together with its corresponding 95% CI and p-value for the ITT analysis set.

The primary analysis of PFS based on the local evaluation will be repeated using the BICR data as a supportive analysis.

A Kaplan-Meier (KM) plot of PFS will be presented by treatment group. Median PFS with 95% CIs will be presented. In addition, KM landmark PFS estimates at 6 months and 12 months with corresponding CIs will also be presented using KM methodology. KM estimates may be presented for other timepoints of interest. The assumption of proportionality will be assessed. In the event of non-proportionality, the HR will be interpreted as an average HR over the observed extent of follow-up.

Sensitivity analyses for PFS will be defined in the SAP.

7.7.2 Analysis of Secondary Endpoints

7.7.2.1 Overall Survival

Any patient not known to have died at the time of analysis will be censored on the basis of the last recorded date on which the patient was known to be alive. Overall survival will be descriptively summarised (n, deaths, median, quartiles), and KM plots will be provided as appropriate. The length of OS will be calculated as:

OS time (months) = death date (censor date) - randomisation date + 1

Overall survival data will be analysed using the same methodology, analysis set and model as for the analysis of PFS provided there are sufficient events available for a meaningful analysis (>20 deaths [if not, descriptive summaries will be provided]).

Data collection for OS will continue beyond the PFS analysis and an updated OS analysis will be performed.

7.7.2.2 Best Overall Response

The patient's BOR assignment will depend on findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Table 8 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable disease at baseline, Table 9 should be used.

Table 8 Time Point Response: Patients With Measurable Disease

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

Abbreviations: CR, complete response; NE, non-evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Table 9 Time Point Response: Patients With Non-Measurable Disease

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR / Non-PD	No	Non-CR / Non-PD*
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR, complete response; NE, non-evaluable; PD, progressive disease.
*Non-CR/Non-PD is preferred over stable disease for non-target disease.

The BOR will be summarised for the ITT analysis set and may be further grouped by measurable/non-measurable disease at entry. Summaries and waterfall plots indicating best percentage change from baseline in the sum of the diameters of target lesions will be produced. Bars will be differentially shaded by RECIST 1.1 response.

7.7.2.3 Objective Response Rate

For randomised studies, a confirmatory scan to confirm the response is not required per RECIST-1.1. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the analysis of ORR. Any patient who discontinues treatment without progression, receives subsequent therapy and then responds will not be included as responders in the ORR.

The ORR will be summarised using the ITT analysis set (ie, all randomised patients). ORR will be compared between treatment arms using a Cochran-Mantel-Haenszel (CMH) test stratified by presence of any measurable disease at baseline (yes versus no), and presence/absence of metastases at baseline (1 or 0).

In addition to presenting the ORR and associated exact 95% CI for each treatment arm, the treatment effect will be described using the CMH estimate of the common odds ratio together with its associated 95% CI (Emerson 1994).

As sensitivity analyses, the ORR will be further summarised by measurable/non-measurable disease at entry (as integrated directly from the IVRS to the eCRF) and compared between the arms using the CMH test stratified by presence/absence of metastases at baseline (1 or 0). The ORR analyses will also be repeated using the mITT analysis set.

7.7.2.4 Duration of Response

The DoR is calculated only for those with a documented response of CR or PR and is defined as the time from the date of first documented tumour response until the first date of radiological disease progression or death, whichever is earlier. If a patient does not progress following a response, then their DoR will be censored at the PFS censoring time. The DoR will not be defined for those patients who do not have documented responses. The DoR will be summarised for the ITT analysis set.

7.7.2.5 Disease Control Rate

Data obtained up until progression or last evaluable assessment in the absence of progression, will be included in the analysis of DCR. Any patient who discontinues treatment without progression, receives subsequent therapy, and then responds will not be included as responders in the DCR.

The DCR will be summarised for the ITT analysis set at 6 months and 12 months (ie, best response of CR, PR or SD at 6 or 12 months) and may be further summarised by measurable/non-measurable disease at entry. Summaries and waterfall plots indicating best percentage change from baseline in the sum of the diameters of target lesions will be produced. Bars will be differentially shaded by RECIST 1.1 response.

7.7.2.6 Change in Tumour Size

Percentage change in tumour size will be determined for patients with measurable disease at baseline and is derived at each visit by the percentage change in the sum of the diameters of target (ie, measurable) lesions compared to baseline. The change in tumour size endpoint will be defined as the best overall percentage change in tumour size from baseline.

The change in tumour size will be summarised for patients with measurable disease at study entry. Summaries and waterfall plots indicating best percentage change from baseline in the sum of the diameters of target lesions will be produced. Bars will be differentially shaded by RECIST 1.1 response.

7.7.2.7 Blinded Independent Central Review

For each patient, the BICR will define the overall visit response (ie, the response obtained overall at each visit by independently assessing target lesions, non-target lesions and new

lesion data). If a patient has had a tumour assessment that cannot be evaluated then the patient will be assigned a visit response of NE (unless there is evidence of progression in which case the response will be assigned as PD; for example, if the target lesions are NE but there is evidence of a new lesion).

A BICR will be performed for the interim analysis of ORR (primary data), which will cover all scans up to the data cut-off for the interim analysis, and for the final database lock for PFS, which will cover all of the scans up to the data cut-off (supportive data).

Endpoints (ORR, BOR, PFS, and DoR) will be derived programmatically using the visit responses provided by the BICR. Results of this independent review will not be communicated to Investigators and the management of patients will be based solely upon the results of the RECIST 1.1 assessment conducted by the Investigator.

Cross-tabulations will be produced to describe the consistency between the BICR and local Investigator assessment for the following:

- Best overall response
- Timing of PD
    - Early discrepancy rate (EDR): the frequency at which the local review declares progression early relative to the BICR in each arm as a proportion of the total number of locally assessed progressions; and
    - Late discrepancy rate (LDR): the frequency at which the local review declares progression later than the BICR in each arm as a proportion of the total discrepancies in each arm.

The EDR and LDR will be calculated for each treatment arm and the differential discordance will be summarised as the rate on the experimental arm minus the rate on the control arm. If the discrepancies are similar between the arms, this suggests an absence of evaluation bias that favours one arm. A negative differential discordance for the EDR and/or positive differential discordance for the LDR may be indicative of bias in the local evaluation favouring the experimental arm (Amit et al 2011).

Analyses of PFS by BICR will be described in the SAP.

7.7.2.8 Quality of Life Measurements

Quality of life will be measured by use of the EORTC QLQ-C30 and the EORTC QLQ-B21 questionnaires. Absolute values and changes from baseline will be calculated and summarised descriptively. Further analyses to assess the proportion of patients who show a change in symptoms, time to deterioration of symptoms, and modelling of symptom data will be described in the SAP.

7.7.3 Analyses of Exploratory Endpoints

The exploratory objectives/endpoints of this study are located in Section 2.3. A description of the analysis of the exploratory endpoints in this study will be included in the SAP.

7.7.4 Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic and pharmacodynamic data will be summarised descriptively.

7.7.5 Safety Analyses

Safety and tolerability will be assessed descriptively in terms of AEs, SAEs, deaths, laboratory data, physical findings, vital signs and ECGs. AEs will be listed individually by patient.

Any AEs occurring before treatment will be included in the data listings but will not be included in the summary tables of AEs.

Any AE occurring within 30 days of discontinuation of investigational product will be included in the AE summaries. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of study treatment) will be flagged in the data listings.

7.7.6 Other Analyses

Descriptive summary statistics will be provided for demographics, medical history, physical examination and other variables collected at baseline.

7.7.7 Interim Analyses

A formal interim analysis of ORR will be performed after approximately 120 patients (65%) have been randomised and followed to their first 12-week follow-up scan (estimated to be at approximately 39 months from first patient dosed). There will be >80% power to detect an improvement in ORR from 15% to 45% with 2-sided p<0.0105 (O'Brien and Fleming boundary based on 65% information). A minimum improvement from 15% to 38% will be statistically significant, if observed. If the comparison of the interim ORR data between the arms based on a CMH test is statistically significant, OS data will be formally compared between the arms and summarised to support a conditional marketing authorisation application. PFS and DoR will be summarised descriptively with no formal comparison of PFS.

Three analyses of OS will be performed: at the time of the interim ORR analysis, at the time of the PFS assessment and at an updated (final) analysis.

7.7.7.1 Multiplicity and Control of Type 1 Error

The multiple testing procedure will strongly control the Type I error probability (alpha) at 5% (2-sided) amongst the key efficacy endpoints (PFS, ORR, OS). Strong control of alpha ensures that the probability of rejecting any (ie, one or more) true null hypothesis, in either direction, is at most 5%, irrespective of how many and which null hypotheses are true or false

At the interim and final analysis points, the key endpoints will be tested in a hierarchical order as shown in Figure 4. If any previous analysis in the sequence is not statistically significant, the alpha cannot be transferred to subsequent endpoints. Note: A non-statistically significant ORR result at the interim analysis will not preclude testing of PFS at the final analysis.

An interim analysis of ORR will be conducted after 120 out of 186 patients have been randomised (65% information) and 1.05% of alpha will be spent on the comparison of ORR, based on an O'Brien and Fleming spending function.

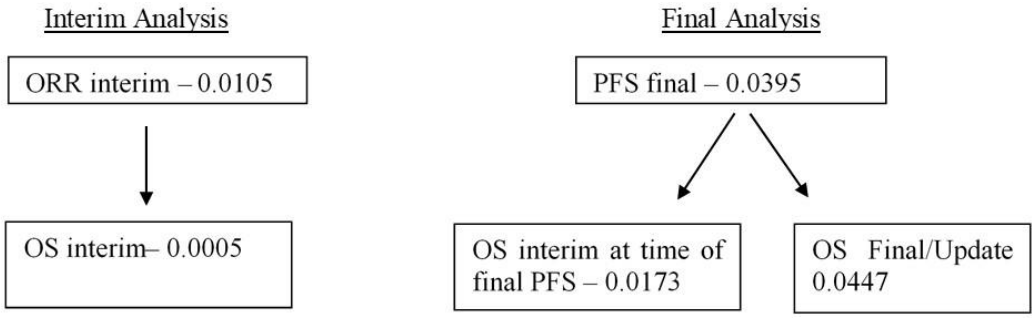
In the case both null hypotheses are true (ie, there is no true difference between the arms, neither for ORR nor for PFS) and assuming independence between these 2 endpoints, the final significance level for PFS can be set at 3.95%.

In the event that the null hypotheses for both ORR and PFS are false, alpha needs to be controlled at 5% over the 3 planned OS analyses; for example, assuming 55 death events (37% information) at the first analysis, 108 death events (73% information) at the second analysis and 147 death events (100% information) at the final OS analysis, the significance levels according to a Lan and De Mets O'Brien and Fleming spending function (Lan and de Mets 1983) will be 0.05%, 1.73% and 4.47%, respectively.

The exact significance levels will be adjusted for the actual information fractions.

Figure 4 Multiple Testing Procedure

The numbers are 2-sided significance levels



Abbreviations: ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

7.7.8 Independent Data Monitoring Committee

An IDMC will be enlisted to perform periodic review of accumulating safety data, with particular focus on biliary tract events (Note: and possibly others, as to be defined in charter) which are defined as AESI. The IDMC will review the incidence, causality, and severity of AESIs in Arm A compared with Arm B as further defined in the IDMC charter.

The first planned periodic IDMC assessment will be performed after the initial 8 patients in Arm A have been followed up for 21 days following a second PCI treatment. In addition to the review of AESIs and other safety parameters, the IDMC will recommend whether or not the second PCI treatment during the chemotherapy period is to continue to be administered for future patients randomised to Arm A.

In addition to the planned meetings, ad hoc IDMC meetings will be required if an Investigator reports an AE/SAE that meets any of the safety stopping criteria as defined in the IDMC charter or induced as a result of aggregate safety or AESIs data, as per definitions in the charter.

Based on these periodic or ad hoc data reviews the IDMC may recommend modifying or stopping the study early due to safety concerns.

The IDMC will comprise at least 2 independent medical professionals relevant to the treatment indication and who are qualified to review the data and 1 independent statistician.

The mandate, composition and operating mode of the IDMC will be described in the IDMC charter.

The IDMC will be advisory to the Trial Steering Committee. The Trial Steering Committee will be responsible for promptly reviewing the IDMC recommendations, to decide whether to continue or terminate the study, and to determine whether amendments to the protocol or changes in the study conduct are required.

Although there are no formal futility stopping rules in the study, the IDMC will review the ongoing safety data and the results of the interim ORR analysis, and provide a recommendation as to whether the study demonstrates a positive risk benefit that is clinically meaningful and meets the pre-defined statistical boundary for efficacy. Further details on the interim efficacy analysis and boundaries for stopping are provided in Section 7.7.7.

Stopping Rules

Further recruitment into the study will be suspended if:

- an AESI (cholangitis and related biliary events) of severity Grade 4 or Grade 5 is reported in Arm A (the PCI treatment arm). An ad hoc IDMC meeting will be held.
- otherwise recommended by the IDMC.

Based on the safety findings, the IDMC may recommend continuing the study, modifying the study or stopping the study early due to safety concerns.

8 Data Quality Assurance

This study will be conducted according to the International Council for Harmonisation (ICH) E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management (ICH Q9).

8.1 Data Management

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports and questionnaires.

[redacted] will supply the eCRF.

Investigative site personnel will enter patient data into Medidata RAVE. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with applicable [redacted] standards and data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data. Adverse event terms will be coded using the MedDRA, an internal validated medical dictionary, and concomitant medications will be coded using the World Health Organisation Drug Dictionary (WHODRUG).

After database lock, each study site will receive a CD-ROM containing all of their site-specific eCRF data as entered into Medidata RAVE for the study, including full discrepancy and audit history. Additionally, a CD-ROM copy of all of the study site's data from the study will be created and sent to the Sponsor for storage. [redacted] will maintain a duplicate CD-ROM copy for their records. In all cases, patient initials will not be collected nor transmitted to the Sponsor. Access to data on these CD-ROMs will be password-protected.

9 Ethics

9.1 Independent Ethics Committee or Institutional Review Board

Federal regulations and the ICH guidelines require that approval be obtained from an IEC/IRB before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients and any other written information regarding this study to be provided to the patient must be approved by the IEC/IRB. Documentation of all IEC/IRB approvals and of the IEC/IRB compliance with ICH harmonised tripartite guideline E6(R2): GCP will be maintained by the site and will be available for review by the Sponsor or its designee.

All IEC/IRB approvals should be signed by the IEC/IRB chairman or designee and must identify the IEC/IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favourable opinion was granted.

Investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IEC/IRB. The Investigator must promptly supply the Sponsor or its designee, the IEC/IRB, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to the study patients.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, the protocol, and all applicable regulations.

9.3 Patient Information and Consent

A written informed consent, in compliance with regulatory authority regulations (21 CFR Part 50, European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC), ICH GCP Guideline, Section 4.8, and the terms of the Declaration of Helsinki (current), shall be obtained from each patient before entering the study or performing any unusual or nonroutine procedure that involves risk to the patient. An informed consent template may be provided by the Sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the Sponsor or its designee or both

before IRB/IEC submission. Once reviewed, the consent will be submitted by the Investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form.

Before recruitment and enrolment, each prospective patient will be given a full explanation of the study and be allowed to read the approved ICF. Once the Investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing the ICF.

The Investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient.

10 Investigator's Obligations

The following administrative items are meant to guide the Investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

10.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient, except as necessary for monitoring and auditing by the Sponsor, its designee, the regulatory agencies/authorities, or the IRB/IEC.

The Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required per applicable regulatory requirements. In addition, the Investigator must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the Sponsor nor [redacted] is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor nor [redacted] is financially responsible for further treatment of the patient's disease.

Prior to beginning the study, the Investigator will be asked to comply with ICH E6(R2) 8.2 and/or 21 CFR by providing the following essential documents, including but not limited to:

- IEC/IRB approval
- Original Investigator-signed Investigator agreement page of the protocol
- Form Food and Drug Administration (FDA) 1572, fully executed, and all updates on a new fully executed Form FDA 1572 (if compatible with local legislations)
- Curriculum vitae for the Investigator and each Sub-Investigator listed on Form FDA 1572
- Financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements required under regional regulations. In addition, the Investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IEC/IRB-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient, and
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with regional regulatory requirements.

10.3 Study Conduct

The Investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted by the Sponsor on publicly available clinical trial registers before enrolment of patients begins.

10.4 Adherence to Protocol

The Investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

10.5 Adverse Events and Study Report Requirements

By participating in this study, the Investigator agrees to submit reports of SAEs and AIs/UADEs to the Sponsor or designee and/or IEC/IRB according to the time line and method outlined in the protocol and Study Plans. In addition, the Investigator agrees to submit annual reports to the study site IEC/IRB as appropriate.

10.6 Investigator's Final Report

Upon completion of the study, the Investigator, where applicable, should inform the institution; the Investigator/institution should provide the IEC/IRB with a summary of the study's outcome and the Sponsor and regulatory authority(ies) with any reports required.

10.7 Records Retention

The Investigator will maintain all study records according to ICH GCP and applicable regulatory requirement(s). 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 clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

10.8 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the Investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over all such issues.

11 Study Management

The administrative structure will include an IDMC.

11.1 Monitoring

11.1.1 Independent Data Monitoring Committee

All information related to the IDMC for this study is located in Section 7.7.8.

11.1.2 Monitoring of the Study

The Clinical Monitor, as a representative of the Sponsor, has the obligation to follow the study closely. In doing so, the Monitor will visit the Investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The Monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and personnel.

All aspects of the study will be carefully monitored, by the Sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

11.1.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, or a regulatory agency, access to all study records.

The Investigator should promptly notify the Sponsor and [redacted] of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the Sponsor or its designee. Amendments to the protocol must be submitted in writing to the Investigator's IRB/IEC and regulatory authorities for approval before patients can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

The Investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study patients without prior IEC/IRB approval. As soon as possible, after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IEC/IRB for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the IEC/IRB and agreed to by the Investigator. A significant deviation occurs when there is non-adherence to the protocol by the patient or Investigator that results in a significant, additional risk to the patient. Significant deviations can include non-adherence to inclusion or exclusion criteria, or non-adherence to FDA regulations or ICH GCP guidelines, and will lead to the patient being withdrawn from the study (Section 4.2).

Significant protocol deviations for this study may include 1) use of prohibited concomitant medications during the study treatment period, 2) tumour assessments (RECIST) for screening not performed within 28 days prior to randomisation, 3) patients who received the wrong treatment, etc.

Protocol deviations will be documented by the Clinical Monitor throughout the course of monitoring visits. Principal Investigators will be notified in writing by the Monitor of deviations. IEC/IRB should be notified of all protocol deviations in a timely manner.

Important protocol deviations will be listed and summarised in the Clinical Study Report.

11.3 Study Termination

Although PCI Biotech has every intention of completing the study, PCI Biotech reserves the right to discontinue the study at any time for clinical or administrative reasons, including but not limited to:

- Occurrence of AEs not seen previously which by virtue of their nature, severity and duration are considered to necessitate study termination; OR the unexpected incidence or severity of known AEs
- Sponsor decision
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients
- Cancellation of the drug development as such or for the given indication.

The end of the study is defined as the date of the final database lock.

If the study is terminated (ie, ended prematurely) for any reason other than for safety, all randomised patients will be allowed to complete their planned treatment and will be followed up for safety for 30 days after the last dose of study treatment. In this case, end of study will be the end of treatment follow-up visit which will take place 30 days after discontinuation or completion of study treatment.

11.4 Final Report

Whether the study is completed or prematurely terminated, the Sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirements. The Sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the Clinical Study Report. The Investigator will be provided

reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the Clinical Study Report, the Sponsor will provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study patients, as appropriate. The study results will be posted on publicly available clinical trial registers.

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13 Appendices

13.1 Appendix A: Schedule of Events for the Active Treatment Period

Table 10 Schedule of Events for the Active Treatment Period – Arm A Patients

Visit[a]	Screening[b]	Randomisation[c]	Treatment period																		
			PCI treatment No 1										PCI treatment No 2[d]								
Cycle (C)/Day (D)				C1, D1	C1, D8	C1, D15	C2, D1	C2, D8	C3, D1	C3, D8	C4, D1	C4, D8	C4, D18	C5, D1	C5, D8	C6, D1	C6, D8	C7, D1	C7, D8	C8, D1	C8, D8
Day			-4	1									-4	1							
Informed consent	X																				
Stenting[e]	X																				
Inclusion/Exclusion criteria	X																				
Study Assessments																					
Histology/Cytology[f]	X																				
Demographics	X																				
Medical history[g]	X																				
Physical examination and ECOG[h]	X			X			X		X		X			X		X		X		X	
Vital signs[i]	X		XX	X	X	X	X	X	X	X	X	X	XX	X	X	X	X	X	X	X	X
ECG[j]	X		XXX	X			X		X		X		XXX	X		X		X		X	
Adverse events[k]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit[a]	Screening[b]	Randomisation[c]	Treatment period																		
			PCI treatment No 1										PCI treatment No 2[d]								
Cycle (C)/Day (D)				C1, D1	C1, D8	C1, D15	C2, D1	C2, D8	C3, D1	C3, D8	C4, D1	C4, D8	C4, D18	C5, D1	C5, D8	C6, D1	C6, D8	C7, D1	C7, D8	C8, D1	C8, D8
Day			-4	1									-4	1							
Unanticipated adverse device effects/Adverse incidents				X										X[l]							
Photosensitivity evaluation and skin reactions[m]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of life assessment[n]	X			X					X					X				X			
Tumour assessment (CT or MRI RECIST 1.1)[o]	X		Every 12 weeks (± 1 week) from randomisation until progressive disease observed																		
Laboratory Assessments																					
Clinical chemistry and haematology[p]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tumour biomarkers (CA 19-9, CA-125, CEA)[q]			X								X									X	
Urinalysis[r]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Creatinine clearance[s]	X																				
Coagulation[t]	X		X	X			X		X		X			X		X		X		X	
Pregnancy test[u]	X		X	X			X		X		X		X	X		X		X		X	
Fimaporfin pharmacokinetics (Group 1)[v]			XXX	X	X			X		X		X	XXX	X	X		X		X		X

Visit[a]	Screening[b]	Randomisation[c]	Treatment period																		
			PCI treatment No 1										PCI treatment No 2[d]								
Cycle (C)/Day (D)				C1, D1	C1, D8	C1, D15	C2, D1	C2, D8	C3, D1	C3, D8	C4, D1	C4, D8	C4, D18	C5, D1	C5, D8	C6, D1	C6, D8	C7, D1	C7, D8	C8, D1	C8, D8
Day			-4	1									-4	1							
Fimaporfin pharmacokinetics (Group 2)[v]			X	X				X				X	X		X				X		
IMP Administration																					
Fimaporfin (Amphinex)			X										X								
Gemcitabine for PCI				X										X							
Study Procedure																					
Laser light application procedure[w]				X										X							
SoC Treatment																					
Systemic cisplatin and gemcitabine chemotherapy[x]					X		X	X	X	X	X	X			X	X	X	X	X	X	X

Abbreviations: APTT, activated partial thromboplastin time; CA-125, cancer antigen-125; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; ERCP, endoscopic retrograde cholangio-pancreatography; IMP, investigational medicinal product; INR, international normalised ratio; MRI, magnetic resonance imaging; No., number; PCI, photochemical internalisation; RECIST, Response Evaluation Criteria in Solid Tumours; SAE, serious adverse event; SoC, standard of care.

a. Patients who have started gemcitabine/cisplatin treatment before the screening period should continue their treatment as scheduled, including during the screening period. Study visits should be synchronised with ongoing SoC chemotherapy. Study cycles will be counted for all patients from first treatment after enrolment (PCI treatment No. 1). Chemotherapy cycles will be counted from first chemotherapy treatment and cannot exceed 8 cycles.

b. Screening evaluations are to be performed after the patient has signed and dated the informed consent form and within 21 days prior to randomisation. Tumour assessment may be performed within 28 days prior to randomisation. Histology/cytology is to be performed/confirmed before randomisation.

c. Upon completion of all screening evaluations, eligible patients will be randomised via the Interactive Web Response System.
d. A second PCI treatment procedure aimed at the initiation of Cycle 5 or, if patient-related factors demand postponement, at initiation of a later cycle (Section 3.3.2). The PCI treatments must be separated by at least 3 months.
e. Biliary stenting is to be performed on all patients according to local practice; however, the chosen stent must be of an exchangeable plastic type until radiological progression is declared. Stenting may be performed at any time from confirmation of histological/cytological diagnosis until immediately after the first laser light application. Patients who have already undergone stenting before screening should be reviewed to ensure the stent is of plastic type, correctly positioned and adequate liver drainage confirmed. Stents must be removed for the laser light application, and a new stent must be placed immediately after light application. Stent removal, laser light application, and stent replacement will take place during the same one procedure.
f. Histology/cytology to be performed if patient does not already have confirmed disease.
g. Medical history includes evaluation of the history of cholangiocarcinoma and method of confirmation, its previous therapy, pre-existing diseases, and current medication.
h. Physical examination includes height (screening only), weight, ECOG performance status, and body surface area.
i. Vital signs including pulse rate, systolic and diastolic blood pressure (sitting), and temperature. Vital signs will be performed before and after Amphinex administration on Day -4 and Cycle 4, Day 18.
j. Standard 12-lead ECG. Tracings must be interpreted, dated, and signed by the Investigator or his/her designee and filed with the patient's source documents. On Day -4 and Cycle 4, Day 18, ECG will be performed before, approximately 30 minutes after, and approximately 4 hours after Amphinex administration.
k. Adverse events/SAEs are to be recorded from the time of informed consent up to 30 days following the last administration of study treatment. Thereafter, only SAEs considered related to the study treatments/procedures are to be reported.
l. If the second PCI treatment is postponed, unanticipated adverse device effects/adverse incidents recording will be done on the day of administration of postponed second PCI treatment (laser light application).
m. Patients will be asked about possible skin and photosensitivity reactions and their exposure to light during study visits for 3 months following the last Amphinex administration.
n. Quality of life assessments will be performed at selected time points during treatment and thereafter every 12 weeks, preferably before any other study assessments are performed.
o. Radiographic tumour assessment with diagnostic contrast-enhanced CT or MRI scan and clinical assessment performed every 12 weeks (±1 week) from randomisation until disease progression. Baseline (screening) measurement may be performed within 28 days prior to randomisation. CT/MRI scan of abdomen/pelvis only unless clinically indicated or disease progression is suspected. The same imaging modality and contrast protocol used at screening must be used throughout the study.
p. Clinical chemistry includes sodium, potassium, calcium, magnesium, phosphate, chloride, glucose (fasting), creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, C-reactive protein, urea/blood urea nitrogen, total protein, serum amylase, serum lipase, and lactate dehydrogenase. Haematology includes haemoglobin, haematocrit, white blood cell count, differentials (absolute), and platelet count. Safety blood samples do not need to be repeated on Day -4 prior to Amphinex administration if the screening evaluation was done 1 day before. Samples taken within 3 days of Day 1 for any chemotherapy cycle do not need to be repeated on Day 1.
q. Standard tumour markers will be analysed from serum samples collected for clinical chemistry.

r. Urinalysis dipstick for albumin or total protein, glucose, bilirubin and blood (microscopy is to be done if there is more than one positive test).
s. A creatinine clearance at baseline is required. Creatinine clearance prior to treatment should be ≥60 mL/min. Serum creatinine should be checked before each cycle of treatment. If there is a >25% increase in serum creatinine compared to the baseline, then the ethylenediamine tetraacetic acid (EDTA) clearance or equivalent, including estimation of GFR, according to local practice, must be performed and cisplatin dosing modified accordingly.
t. Coagulation tests including INR and APTT should be performed on Day 1 of each 21-day chemotherapy cycle except if patient is receiving warfarin, in which case, assessments should also be done on Day 8 of each cycle and Day 15 of Cycle 1. Tests do not need to be repeated on Day -4 prior to Amphinex administration if done 1 day before.
u. For women of childbearing potential only. A highly sensitive urine or serum pregnancy test is acceptable.
v. PK samples will be collected from all patients in Arm A. Group 1: the 20 first patients randomised to Arm A; Group 2: all other patients randomised to Arm A. On Day -4 and Cycle 4, Day 18, the PK samples will be time matched with ECG: For PK Group 1, PK sampling and ECG will be performed before, approximately 30 minutes after, and approximately 4 hours after Amphinex administration; for PK Group 2, PK sampling and ECG will be performed before Amphinex administration, only ECG will be performed 30 minutes after and approximately 4 hours after Amphinex administration.
w. Laser light application procedure is to be performed 3 hours (±1 hour) after end of the gemcitabine administration. Patients may be admitted for overnight follow-up after the laser light application and related procedures on Day 1 of Cycle 1 and Day 1 of Cycle 5.
x. Day 15 visit (±3 days) required in Cycle 1 of chemotherapy only for standard safety evaluation; no cyclic chemotherapy will be administered on Day 15 visit.

Table 11 Schedule of Events for the Active Treatment Period – Arm B Patients

Visit[a]	Screening[b]	Randomisation[c]	Treatment period																
Cycle (C)/Day (D)			C1, D1	C1, D8	C1, D15	C2, D1	C2, D8	C3, D1	C3, D8	C4, D1	C4, D8	C5, D1	C5, D8	C6, D1	C6, D8	C7, D1	C7, D8	C8, D1	C8, D8
Informed consent	X																		
Stenting[d]	X																		
Inclusion/Exclusion criteria	X																		
Study Assessments																			
Histology/Cytology[e]	X																		
Demographics	X																		
Medical history[f]	X																		
Physical examination and ECOG[g]	X		X			X		X		X		X		X		X		X	
Vital signs[h]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG[i]	X		X			X		X		X		X		X		X		X	
Adverse events[j]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit[a]	Screening[b]	Randomisation[c]	Treatment period															
Cycle (C)/Day (D)			C1, D1	C1, D8	C1, D15	C2, D1	C2, D8	C3, D1	C3, D8	C4, D1	C4, D8	C5, D1	C5, D8	C6, D1	C6, D8	C7, D1	C7, D8	C8, D1	C8, D8
Photosensitivity evaluation and skin reactions			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of life assessment[k]	X		X					X				X				X			
Tumour assessment (CT or MRI RECIST 1.1)[l]	X		Every 12 weeks (±1 week) from randomisation until progressive disease observed																
Laboratory Assessments																			
Clinical chemistry and haematology[m]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tumour biomarkers (CA 19-9, CA-125, CEA)[n]			X							X								X	
Urinalysis[o]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Creatinine clearance[p]	X																		
Coagulation[q]	X		X			X		X		X		X		X		X		X	
Pregnancy test[r]	X		X			X		X		X		X		X		X		X	

Visit[a]	Screening[b]	Randomisation[c]	Treatment period															
Cycle (C)/Day (D)			C1, D1	C1, D8	C1, D15	C2, D1	C2, D8	C3, D1	C3, D8	C4, D1	C4, D8	C5, D1	C5, D8	C6, D1	C6, D8	C7, D1	C7, D8	C8, D1	C8, D8
SoC Treatment																			
Systemic cisplatin and gemcitabine chemotherapy[s]			X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: APTT, activated partial thromboplastin time; CA-125, cancer antigen 125; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; INR, international normalised ratio; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria in Solid Tumours; SAE, serious adverse event; SoC, standard of care.

a. Patients who have started gemcitabine/cisplatin treatment before the screening period should continue their treatment as scheduled, including during the screening period. Study visits should be synchronised with ongoing SoC chemotherapy. Chemotherapy cycles will be counted from first chemotherapy treatment and cannot exceed 8 cycles.
b. Screening evaluations are to be performed after the patient has signed and dated the informed consent form and within 21 days prior to randomisation. Tumour assessments may be performed within 28 days prior to randomisation. Stenting and histology/cytology are to be performed/confirmed before randomisation.
c. Upon completion of all screening evaluation, eligible patients will be randomised via the Interactive Web Response System.
d. Biliary stenting is to be performed on all patients according to local practice, however, the chosen stent must be of an exchangeable plastic type until radiological progression is declared. Stenting may be performed at any time from confirmation of histological/cytological diagnosis until Cycle 1 Day 1. Patients who have already undergone stenting before screening should be reviewed to ensure the stent is of plastic type, correctly positioned and adequate liver drainage confirmed.
e. Histology/cytology to be performed if patient does not already have confirmed disease.

f. Medical history includes evaluation of the history of cholangiocarcinoma and method of confirmation, its previous therapy, pre-existing diseases, and current medication.
g. Physical examination includes height (screening only), weight, ECOG performance status, and body surface area.
h. Vital signs including pulse rate, systolic and diastolic blood pressure (sitting), and temperature.
i. Standard 12-lead ECG. Tracings must be interpreted, dated, and signed by the Investigator or his/her designee and filed with the patient's source documents.
j. Adverse events/SAEs are to be recorded from the time of informed consent up to 30 days following the last administration of study treatment. Thereafter, only SAEs considered related to the study treatments/procedures are to be reported.
k. Quality of life assessments will be performed at selected time points during treatment and thereafter every 12 weeks, preferably before any other study assessments are performed.
l. Radiographic tumour assessment with diagnostic contrast-enhanced CT or MRI scan and clinical assessment performed every 12 weeks (±1 week) from randomisation until disease progression. Baseline (screening) measurement may be performed within 28 days prior to randomisation. CT/MRI scan of abdomen/pelvis only unless clinically indicated or disease progression is suspected. The same imaging modality and contrast protocol used at screening must be used throughout the study.
m. Clinical chemistry includes sodium, potassium, calcium, magnesium, phosphate, chloride, glucose (fasting), creatinine, total bilirubin, gamma glutamyltransferase, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, C-reactive protein, urea/blood urea nitrogen, total protein, serum amylase, serum lipase and lactate dehydrogenase. Haematology includes haemoglobin, haematocrit, white blood cell count, differentials (absolute), and platelet count. Samples taken within 3 days of Day 1 for any chemotherapy cycle do not need to be repeated on Day 1 prior to dosing.
n. Standard tumour markers will be analysed from serum samples collected for clinical chemistry.
o. Urinalysis dipstick for albumin or total protein, glucose, bilirubin and blood (microscopy is to be done if there is more than one positive test).
p. A creatinine clearance at baseline is required. Creatinine clearance prior to treatment should be ≥60 mL/min. Serum creatinine should be checked before each cycle of treatment. If there is a >25% increase in serum creatinine compared to the baseline then the ethylenediamine tetraacetic acid (EDTA) clearance or equivalent, including estimation of GFR, according to local practice, must be performed and cisplatin dosing modified accordingly.
q. Coagulation tests including INR and APTT should be performed on Day 1 of each 21-day chemotherapy cycle except if patient is receiving warfarin, in which case, assessments should also be done on Day 8 of each cycle and Day 15 of Cycle 1.
r. For women of childbearing potential only. A highly sensitive urine or serum pregnancy test is acceptable.
s. Day 15 visit (±3 days) required in Cycle 1 of chemotherapy only for standard safety evaluation; no cyclic chemotherapy will be administered on Day 15 visit.

13.2 Appendix B: Schedule of Events for the Follow-Up Period

Table 12 Schedule of Events for the Follow-Up Period – Arm A and Arm B Patients

Visit	**End of Treatment**		**Follow-up Period**	
			Tumour response follow-up[a]	Survival follow-up[b]
Day	**7[c]**	**30[d]**	**Every 12 Weeks**	
		±3 days	**±1 week**	**±4 weeks**
Study Assessments				
Physical examination and ECOG performance status	X	X	X	
ECG		X		
Adverse events	X	X	X	
Photosensitivity evaluation (Arm A only)	X	X	X[e]	
Concomitant medications	X	X		
Quality of life assessments[f]		X	X	
Tumour assessments	Every 12 weeks (±1 week) from randomisation until progressive disease observed		X	
Laboratory Assessments/Biomarker Assessments				
Clinical chemistry and haematology	X	X		
Standard tumour markers (CA 19-9, CA-125, CEA)			X	
Urinalysis	X	X		
Pregnancy test[g]		X	X	
Follow-up Assessments				
Record details of subsequent anti-cancer therapy			X	X
Serious adverse events[h]				X
Survival[i]	X	X	X	X

Visit	**End of Treatment**		**Follow-up Period**	
			Tumour response follow-up[a]	Survival follow-up[b]
Day	**7**[c]	**30**[d]	**Every 12 Weeks**	
		±3 days	**±1 week**	**±4 weeks**
Pharmacokinetic and ECG Assessment (Arm A patients only)				
Fimaporfin pharmacokinetics		X	X[j]	
ECG		X	X[j]	

Abbreviations: CA-125, cancer antigen-125; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group.

a. For patients who have not progressed, follow-up should be performed every 12 weeks, (±1 week) relative to randomisation until radiological disease progression.
b. For patients who have progressed, follow-up should be performed every 12 weeks (±4 weeks) until death. Additional survival contacts (ie, outside of the 12-weekly calls) may be conducted around the time of the interim and final (data cut-off) analyses to ensure that the survival information is as up to date as possible for the analysis of overall survival.
c. Patients discontinuing treatment because of disease progression or discontinuation for any reason other than planned completion of treatment will have a discontinuation follow-up visit up to 7 days after treatment discontinuation.
d. All patients will have an end of treatment follow-up visit 30 days (±3 days) after the last dose of study treatment.
e. Patients in Arm A will be asked about possible skin photosensitivity reactions and their exposure to light for 3 months following the last Amphinex administration.
f. Quality of life assessments will be performed at selected time points during treatment and thereafter every 12 weeks, preferably before any other study assessments are performed.
g. For women of childbearing potential only. A highly sensitive urine or serum pregnancy test is acceptable.
h. Serious adverse events that occur more than 30 days after the last dose of study treatment do not need to be reported unless the Investigator considers them related to study treatment and/or procedures.

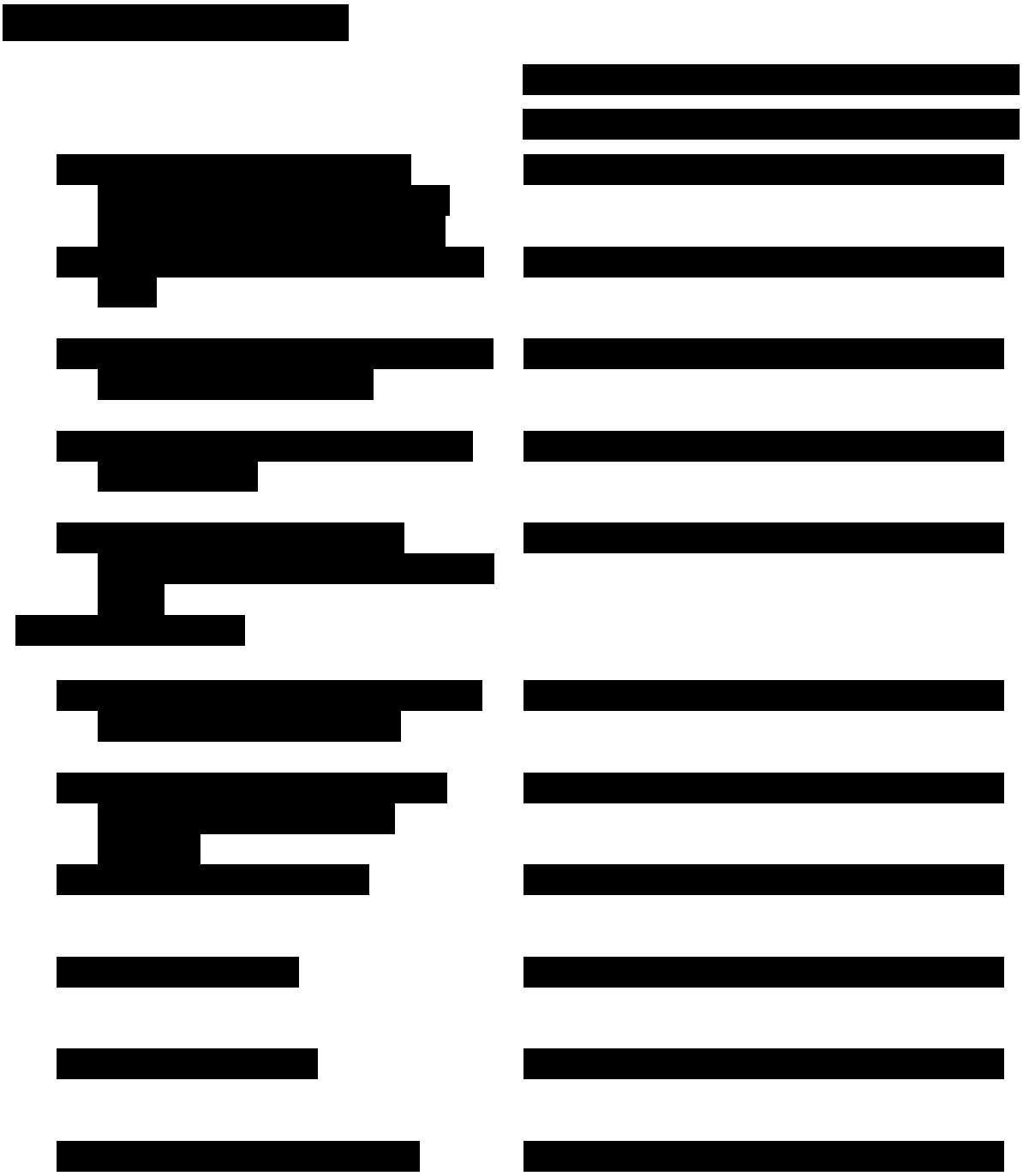
i. Survival status will be assessed for all patients (eg, in a telephone call) every 12 weeks, with a window of ±4 weeks after confirmation of disease progression, discontinuation for any other reason, or study withdrawal if patient has consented to be followed up, until death from any cause.
j. A pharmacokinetic blood sample and corresponding ECG should be taken at the time of the 2 tumour assessments after end of treatment.

13.3 Appendix C: RECIST 1.1

For RECIST 1.1 criteria, please refer to the website located at:

https://project.eortc.org/recist/wp-content/uploads/sites/4/2015/03/RECISTGuidelines.pdf

13.4 Appendix D: Health-Related Quality of Life Questionnaires



[redacted]

[redacted]

13.5 Appendix E: Protocol Amendments

The changes made in the amended protocol have been detailed below. The newly added text has been presented in bold whereas the text that has been removed has been marked as strikethrough.

Version	Date	Changes
Version 1.0	30 Aug 2018	Original Protocol
Version 2.0 Global Amendment 1	04 Dec 2019	**Principal/Coordinating Investigator** Deleted 'Europe' from [redacted] signature page ie, "Principal/Coordinating Investigator ~~(Europe)~~" Removed principal/coordinating investigator signature page for North America:
		Investigator's declaration page Added information that protocol changes may also require approval by regulatory authorities (not only CEC/IRB) as per request from Swedish Medical Products Agency. Removed the country name 'Europe' from the 'Declaration of Investigator' ie, Signature of Principal Investigator ~~(Europe)~~ and Printed Name of Principal Investigator ~~(Europe).~~ Removed 'Declaration of Investigator' page for Principal Investigator in North America.
		Summary of Changes **Protocol Amendment History and Reasons for Amendment** Table added to present an overview of rationale for the changes made in the amended protocol.

Version	Date	Changes
		List of Abbreviations
		ALP **alkaline phosphatase**
		ALT **alanine aminotransferase**
		AST **aspartate aminotransferase**
		CA-125 **cancer antigen 125**
		CI **confidence interval**
		CRC **Cohort Review Committee**
		EDC **electronic data capture**
		EDTA **ethylenediamine tetraacetic acid**
		FSH **follicle-stimulating hormone**
		HNSCC **head and neck squamous cell carcinoma**
		HUS **haemolytic uraemic syndrome**
		KM **Kaplan-Meier**
		NCI **National Cancer Institute**
		PD **progressive disease**
		PRES **posterior reversible encephalopathy syndrome**
		PSC **primary sclerosing cholangitis**
		~~PTC~~ ~~percutaneous transhepatic cholangiography~~
		RP2D **recommended Phase 2 dose**
		SLT **schedule-limiting toxicity**
		SmPC **summary of product characteristics**
		TEAE **treatment-emergent AE**
		WOCBP **women of childbearing potential**
		Section 2.3, Exploratory Objectives
		2. To explore changes in **standard tumour markers and** exploratory ~~tumour~~ biomarkers for the assessment of their **diagnostic and** prognostic relevance in the disease, and for the treatment itself.
		Section 3.1, Study Design

Version	Date	Changes
		Updated Figure 1 (Overall Study Design) to revise the stratification factors at randomisation from: i) presence or absence of measurable/non-measurable disease at baseline and ii) ECOG performance status (0 vs 1) to i) presence or absence of measurable/non-measurable disease at baseline and ii) presence or absence of hepatic metastases
		Section 3.2, Treatment Assignment Patients will be stratified at randomisation according to whether they have **any** measurable disease at baseline (as assessed by the Investigator) versus no measurable disease, and according to ~~Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1)~~ **presence or absence of hepatic metastases**. **Patients with any measurable disease must have at least 1 measurable lesion (bile duct or liver).** It is expected that approximately two-thirds of patients will have measurable disease at baseline.
		Section 3.2.1, Arm A "**Cycles 2 to 4:** Gemcitabine/cisplatin will be administered on Days 1 and 8. In Cycle 4, a second dose of Amphinex will be administered on Day 18 (4 days prior to Day 1 of Cycle 5)." Was split into: "**Cycles 2 to 3: Gemcitabline/cisplatin will be administered on Days 1 and 8**. **Cycle** 4**:** Gemcitabine/cisplatin will be administered on Days 1 and 8. ~~In Cycle 4,~~ A second dose of Amphinex will be administered on Day 18 (4 days prior to Day 1 of Cycle 5)."

Version	Date	Changes
		Section 3.2.1, Arm A Added the following text under Cycles 6 to 8: **Patient-related factors may demand postponement of the second PCI treatment to Cycle 6, 7 or 8. Please see Section 3.3.2 for more detailed information.** **It is expected that all patients in Arm A will be hospitalised for one night after the endoscopic retrograde cholangio-pancreatography (ERCP)/laser light applications on Day 1 of Cycle 1 and on Day 1 of Cycle 5.** **For some patients, 1 to 3 days of hospitalisation after Amphinex administration may be required to ensure adequate initial protection from light. This will be at the Investigator's discretion, as it could depend on factors such as time of year and weather conditions (risk of inadvertent exposure to sunshine or bright daylight) or the patient's disposition and ability to comply with light protection guidance, travel distance, etc.**
		Section 3.3.1, Stent Placement Biliary stenting is to be performed on all patients according to local practice; however, the chosen stent must be of an exchangeable (plastic) type ~~throughout the active treatment period of the study~~ **until radiological progression**. Stenting ~~is to~~ **may** be performed at any time from confirmation of histological/cytological diagnosis until ~~the day of~~ **Cycle 1 Day 1 (immediately after the** first laser light application**, for patients in Arm A)**. Patients who have already undergone stenting before screening should be reviewed to ensure the stent is of an acceptable type, correctly positioned and adequate liver drainage confirmed. Stents ~~will~~ **must** be removed ~~before~~ **for** the laser light application ~~procedure~~**,** and **a** new ~~plastic stents will be inserted after~~ **stent must be placed immediately after light application. Stent removal, laser light application, and stent replacement will take place during the same ERCP procedure.** ~~Refer to the Procedure Manual for a description of the stenting procedure and potential variations.~~ At least 50% of liver volume should be drained. Allowing for pathological changes with atrophy of chronically obstructed segments, this effectively means 2 of 3 sectors (ie, either all of the right or left liver lobe and either anterior or posterior sector of right liver lobe). This may require a combination of percutaneous transhepatic ~~cholangiography (PTC)~~ **biliary drainage** and endoscopic ~~retrograde cholangio-pancreatography (ERCP)~~ **drainage** but is optimally achieved by ~~ERCP~~ **endoscopic drainage**.
		Section 3.3.2, Arm A, Second PCI Treatment Added the following text: **The second PCI treatment may be postponed if:** • **In the opinion of the Investigator, the single dose of gemcitabine cannot be given at the full 1000 mg/m^2 dose due to residual toxicity** • **In the view of the Investigator there is evidence of ongoing inflammation within the PCI illumination area** • **In the opinion of the Investigator, the patient shows significant signs of photosensitivity**

Version	Date	Changes
		• **If one of the following criteria is present:** ○ **Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) or alkaline phosphatase (ALP) >5 × the upper limit of normal (ULN)** ○ **ALT or AST or ALP >3 × ULN with the appearance of symptoms associated with a clinical diagnosis of hepatitis including right upper quadrant pain or tenderness, fever, rash or eosinophilia (>5%)** ○ **ALT or AST >3 × ULN and total bilirubin >2.5 × ULN or international normalised ratio >1.5[1] or other evidence of impairment to the synthesis function of the liver** **In contrast to postponing the second PCI, this treatment will not be given at all if any of the following criteria are fulfilled:** • **The patient experienced a PCI treatment-related schedule-limiting toxicity (SLT) defined as:** ○ **A clinically significant toxicity or abnormal laboratory value occurring after PCI treatment and during the first chemotherapy cycle, assessed as unrelated to the underlying disease, or concomitant medications, that is related to either PCI treatment or related to the combination of PCI treatment with the cisplatin/gemcitabine systemic chemotherapy and meets any of the following criteria, based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0:** ▪ **Photosensitivity Grade 3 outside the treatment area, except for areas exposed for skin sensitivity tests and areas exposed for re-introduction to normal light (patient compliance with light protection guidelines MUST be followed; non-compliance will be taken into account when determining SLT)** ▪ **Phototoxicity Grade 4 inside the treatment area (eg, duodenal ulceration)** ▪ **Non-haematological toxicity (excluding nausea and vomiting) ≥Grade 3** ▪ **Neutropenia or thrombocytopenia Grade 4** ▪ **All other Grade 3 toxicities that are clinically unexpected and considered related to the PCI treatment**

Version	Date	Changes
		▪ **The patient is expected not to be able to receive the single dose of gemcitabine at a dose of 1000 mg/m^2 at any time** Furthermore, if the patient ~~clearly displays poor tolerability of the first~~ **is unwilling to undergo a second** PCI treatment, the second PCI ~~should~~ **can** be omitted~~.~~**, however, the patient can continue to receive the gemcitabine/cisplatin standard combination chemotherapy.** If treatment is delayed, computed tomography (CT)/magnetic resonance imaging (MRI) scans should still be conducted at the scheduled time point relative to randomisation. This is to avoid the risk of a difference between arms in the primary endpoint of PFS that can be attributed to changes in scanning frequency rather than treatment. The second PCI treatment will **continue to** be included in the Arm A treatment schedule only if the first PCI treatment is found to be tolerable and recommended to be continued by an Independent Data Monitoring Committee (IDMC) based on an initial safety review of the first 8 patients treated with 2 PCI treatments; otherwise, only a single PCI administration schedule integrated in Cycle 1 will be employed. In patients still in the study (ie, not formally discontinued or withdrawn), the reason(s) for delays, postponement, or omitting of the second PCI must be documented **and recorded in the electronic case report form (eCRF)**. **Patients should continue their randomised chemotherapy treatment until a maximum of 8 systemic gemcitabine/cisplatin cycles or RECIST 1.1-defined progression or until a treatment discontinuation criterion is met.** **[1] Unless on anti-coagulants**
		Section 3.3.3, Arm B Patients ~~in both arms~~ should continue their randomised chemotherapy treatment until a maximum of 8 systemic gemcitabine/cisplatin cycles or RECIST 1.1-defined progression or until a treatment discontinuation criterion is met.
		Section 3.4.1, Rationale for Patient Population Thus, it is proposed that PCI of gemcitabine complemented by gemcitabine/cisplatin chemotherapy in patients with ~~advanced~~ inoperable **extrahepatic** CCA should demonstrate and advantage in this subset of patients.

Version	Date	Changes
		[redacted]
		Section 3.4.4, Rationale for Dose **In terms of safety, Amphinex has been well-tolerated in doses up to the maximum tolerated dose of 0.87 mg/kg as established in the Phase 1 study PCI 101/06 and as shown by the absence of dose-limiting toxicities in the Phase 1 dose escalation of the ongoing study PCIA 202/12 in CCA. Overall, Amphinex shows a suitable safety and tolerability profile for the treatment of advanced CCA.** [redacted]

Version	Date	Changes
		[redacted]
		Section 3.4.5, Rationale for Treatment Regimen **A single treatment schedule of Amphinex-induced PCI of gemcitabine has been found to be both well-tolerated and clinically active in Cohorts 3 and 4 of the Phase**

Version	Date	Changes
		1 dose escalation part of study PCIA 202/12. This has raised the question as to whether a 2-administration schedule would increase the clinical effectiveness of Amphinex-induced PCI of gemcitabine by further treating any residual tumour while maintaining the tolerability profile. **During the extended part of Phase 1 in study PCIA 202/12, the 2-administration schedule will be considered non-tolerated if 2 or more of the first 6 evaluable patients experience an SLT. If none or 1 of the first 6 evaluable patients experience an SLT (see definition in Section 3.3.2), the 2-administration schedule will be considered tolerated.** **A total of 5 patients underwent the 2 PCI treatment procedures and completed the required 21-day safety window following the second procedure as per protocol. All SLT criteria were assessed and it was concluded that no SLTs were reported in these 5 eligible patients who completed both PCI procedures. The CRC concluded that the procedure was tolerable based on the fact that no SLTs were observed in the 5 eligible patients. Therefore, the 2-administration schedule can be considered tolerated.** [redacted] **In this study PCIA 203/18, an IDMC will be convened to perform periodic reviews of accumulating safety data, with focus on biliary tract events which are defined as AEs of special interest (AESIs). The study will include an initial safety review by the IDMC after the initial 8 patients in Arm A have been administered 2 PCI treatments and followed up for 21 days. The IDMC will assess whether the second PCI treatment during the chemotherapy period should continue to be administered for future patients randomised to Arm A.**
		[redacted]

Version	Date	Changes
		Section 4.1, Selection of Study Population Approximately 186 patients with inoperable CCA will be enrolled at approximately ~~40~~**50** sites in **Asia, Europe** and North America ~~and Europe~~.
		Section 4.1.1, Inclusion Criteria 3. ~~Histopathologically/cytologically (C5) verified adenocarcinoma consistent with CCA;~~ **Cholangiocarcinoma verified as adenocarcinoma by histopathology or cytology (C5) with a perihilar or distal stenosis that has been stented or will require stenting, and that is accessible for PCI light treatment**; 4. Cholangiocarcinoma must be considered inoperable with respect to radical resection **(including partial liver resection or liver transplantation)**; 5. At least 1 **radiologically evaluable** lesion (measurable and/or non-measurable ~~but evaluable~~) that can be ~~accurately~~ assessed at baseline and is suitable for repeated **radiological** evaluation 6. If metastatic~~, metastases~~ **disease, metastasis** must be limited to the liver parenchyma ~~only~~ and/or ~~restricted only to the~~ local lymph nodes ~~with peritoneal engagement locally (~~within close proximity to the hepatoduodenal ligament~~,~~); ~~7. Biliary lesion causing bile obstruction that requires stenting and is accessible for PCI light treatment;~~
		Section 4.1.2, Exclusion Criteria 1. Previously received any ~~prior~~ anti-tumour (either local or systemic) treatment for CCA; 3. **A history of frequently recurring septic biliary events caused by non-malignant strictures (**primary sclerosing cholangitis **[PSC], autoimmune hepatitis or advanced chronic liver dysfunction)**; 7. Currently participating in ~~in~~ any other interventional clinical ~~trial~~**study**; 11. Known allergy or sensitivity to photosensitisers, (the active substance and/or any of the excipients); or chronic use of other photosensitising therapies (Section 5.5.3); **treatment with amiodarone during the last 12 months**; 19. Male patients unwilling to use highly effective contraception or ~~female patients~~ **women** of childbearing potential **(WOCBP) (see definition in Section 5.6)** unwilling to use a highly effective form of contraception such as the following: o ~~Hormonal contraceptives~~**Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[2] (oral, intravaginal and transdermal)** o **Progestogen-only hormonal contraception associated with inhibition of ovulation[2]** (oral, injectable, or ~~patches~~**implantable**) o Intrauterine device~~s (hormonal-eluting or not)~~ o **Intrauterine hormone-releasing system** o Bilateral tubal ligation o **Vasectomised partner[3] (Section 5.6)**

Version	Date	Changes
		~~o Male sterilisation~~ ~~o Double-barrier (condoms with spermicide)~~ o **Sexual abstinence[4]** Patients must continue the use of contraception during PCI treatment and subsequent chemotherapy, and for at least ~~6~~**9** months ~~thereafter~~ **after last dose of Amphinex or 6 months after last dose of chemotherapy, whichever is the latest**. **Footnotes:** **[2] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.** **[3] Vasectomised partner is a highly effective birth control method only if the partner is the sole sexual partner of the WOCBP study participant and if the vasectomised partner has received medical assessment of the surgical success.** **[4] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.** **23.** Inadequate renal function, ~~defined as creatinine clearance <60 mL/min or <45 mL/min~~ as determined by local practice for patients on fractionated platinum-based chemotherapy. **Patients with creatinine clearance <60 mL/min must not be included.**
		Section 4.2.1, Discontinuation From Study Treatment In addition, a patient may be discontinued from study treatment in any of the following situations: • Severe non-compliance to study protocol • Incorrect enrolment and randomisation • **Progressive disease** • **Development of toxicity** o **Arm A patients after first PCI treatment: the development of toxicity, which precludes further treatment with both:** ▪ **PCI treatment, see SLT definition in Section 3.3.2 and** ▪ **standard gemcitabine/cisplatin combination chemotherapy, as per local practice**

Version	Date	Changes
		Note: If a patient no longer can receive PCI treatment due to toxicity but can continue on the standard gemcitabine/cisplatin combination chemotherapy, or vice versa, then the patient will not be considered as discontinued from treatment. ○ **Arm A patients after second PCI treatment and Arm B patients: the development of toxicity, which precludes further treatment with standard gemcitabine/cisplatin combination chemotherapy, as per local practice** • **Patient refusal to receive further study treatment** **Note: If a patient no longer wishes to receive PCI treatment but can continue on the standard gemcitabine/cisplatin combination chemotherapy, or vice versa, then the patient will not be considered as discontinued from treatment.** • **Lost to follow-up** • **Intercurrent illness precluding further study treatment** • **Pregnancy** • Any other reasons not listed above as per Investigator discretion The reason for treatment discontinuation must be adequately documented **and recorded in the eCRF**.
		Section 4.2.2, Withdrawal From Study Further, a patient will be withdrawn from the study in any of the following situations: • Patient is lost to follow-up • Patient decides to withdraw consent from participating in the study • **Screen failure** • **Study terminated by Sponsor** • **Other** The reason for withdrawal from the study must be **adequately documented and** recorded in~~on~~ the eCRF.
		Section 4.2.3, Handling of Discontinuations/Withdrawals Added the text: **All randomised patients will be included in the primary Intent-to-Treat (ITT) analysis set regardless of treatment received.**

Version	Date	Changes
		Section 4.2.4, Replacements **Randomised** patients who **discontinue treatment or** withdraw from the study will not be replaced. **If a randomised patient is withdrawn, the patient identifier number will not be reused.** **All randomised patients must be included in the primary analysis under the principles of ITT and therefore collection of follow-up data for patients who discontinue is important.**
		Section 5.1, Method of Assigning Patients to Treatment Arms The randomisation will be stratified by 2 factors: **any** measurable disease at baseline (yes versus no) and ~~ECOG performance status (0 or 1)~~ **presence or absence of hepatic metastases**. Approximately 186 patients will be enrolled at approximately ~~40~~**50** sites and randomised in a 1:1 ratio (fimaporfin-induced PCI of gemcitabine complemented by gemcitabine/cisplatin chemotherapy versus gemcitabine/cisplatin chemotherapy alone). If a **randomised** patient is withdrawn ~~and replaced~~, the patient identifier number will not be reused.
		Section 5.2, Identity of Investigational Products/Background Treatment A single PCI treatment consists of IV administration of Amphinex solution for injection (dose 0.25 mg/kg fimaporfin-di-olamine, equivalent to 0.22 mg/kg fimaporfin), followed 4 days later by gemicitabine IV infusion (1000 mg/m^2) and intraluminal laser light application (light dose 30 J/cm). ~~As gemcitabine~~ **Gemcitabine** is currently not licensed for the treatment of patients with advanced inoperable CCA~~, gemcitabine used in combination with Amphinex for PCI treatment will be treated as an investigational product~~.
		Section 5.2.1.1, Fimaporfin-Associated Photosensitivity All patients who receive Amphinex (fimaporfin) are expected to become temporarily photosensitive **and must take precautions to protect skin and eyes in order to prevent photosensitivity reactions. A gradual return to normal light conditions is required. Luxmeters will be provided to the patients to enable them to measure light in their surroundings and to guide the gradual increase in exposure**. The duration and degree of photosensitivity varies between patients, **and patients must be encouraged to follow guidance and test for skin sensitivity.** • As some pulse oximeters produce red light of a wavelength close to 652 nm, oximeters must be repositioned at least every 10 to 15 minutes to avoid the risk of local skin burns. Any non-compliance with regard to light protection should be **adequately** documented **and recorded** in the eCRF.

Version	Date	Changes

For at least 4 weeks following Amphinex injection, precautions must be taken to avoid exposure of skin and eyes to direct sunlight or bright indoor light. Procedures for gradual re-introduction to light are provided in Table 1. Investigator must inform the patient of these procedures and document this counselling in the eCRF. **In addition, all patients who receive Amphinex will receive a patient leaflet with information on how to protect from light, how to test for light sensitivity, and how to gradually increase exposure to light.**

Table 1, Precautions for the Prevention of Skin and Eye Photosensitivity Reactions

Time after Amphinex (fimaporfin) injection	Precautions to prevent skin and eye photosensitivity reactions
Patients should be made aware that there can be marked variation in sensitivity and duration of sensitivity between people.	
Day 1 (0–24 hours)	Patients should avoid direct exposure of eyes to any light sources and avoid ~~exposure to~~ direct **and indirect** daylight **exposure**. • The patient should stay indoors with low intensity (dim) indoor light **(max 100 lux)**. • Patients should avoid watching television or using computers, tablets, or smart phones. • **To avoid exposure to daylight from the window, curtains and blinds should be closed.** **Lighting choice: warm white light bulbs (not more than 800 lumen: max 60W tungsten filament warm light bulb, 13W energy saver, or 6W LED)**
~~First 2 Weeks~~ **Day 2-7:**	Indoors: Patients should avoid direct daylight coming through the window or direct light from household appliances such as reading lamps. Beginning at 100 lux on Day 1, patients may gradually return to normal indoor lighting by a stepwise increase in the light ~~(by~~ **of** 100 lux per day~~)~~, **to reach 700 lux by Day 7**. Outdoors: Patients may go outdoors after dusk. If ~~it is absolutely necessary~~ **need** to ~~go outdoors~~ **travel** during the ~~hours of daylight~~ **day, such as to hospital appointments**, the patient must **sit away from windows** and cover all skin including face and hands, and wear **the** dark glasses **provided by Sponsor**. The type of clothes the patient must wear are: • Wide-brimmed hat: for head, neck, **face**, nose and ears

Version	Date	Changes	
			• Scarf: for head and neck • Dark glasses with side panels ~~provided by Sponsor~~: for eyes and skin around eyes • Long sleeved top: for upper body/arms • Long trousers: for lower body/legs • Gloves: for hands, wrist and fingers • Socks: for feet and ankles • Closed shoes: for feet Skin photosensitivity reactions are caused by visible light. Sunscreens that protect from ultraviolet light will not protect from visible light. **Dark, tightly woven clothing should be worn.** Very thin clothing will not protect from strong light ~~and dark, closely woven clothing should be worn~~. If exposed to excessive bright light, the patient may feel a burning sensation on the skin. The patient must ~~then~~ move away from the light source immediately~~, and~~**. If a photosensitivity reaction develops,** contact the Clinical Investigator for advice **(see below).**
		Day 8-15:	**Indoors: Patients should avoid direct daylight coming through the window or direct light from household appliances such as reading lamps.** **Continue to gradually return to normal indoor lighting by a stepwise increase in the light (by 100 lux per day, ie, from 800 lux on Day 8 to 1500 lux on Day 15).** **Outdoors: Patients may go outdoors but only if it is cloudy, shaded and not sunny.** **If need to travel during the day, such as to hospital appointments, the patient must sit away from windows and cover all skin including face and hands, and wear the dark glasses provided by Sponsor.** **Skin test: Patient should try cautious exposure only to back of hands over 5-15 minutes on non-sunny days. If any prickling or discomfort occurs then patient should stop exposure immediately, cover up and go indoors.** **If there is no reaction 24 hours later, patient can continue to extend and gradually build up exposure time.** **If exposed to excessive bright light, the patient may**

Version	Date	Changes	
			feel a burning sensation on the skin. The patient must move away from the light source immediately. If a photosensitivity reaction develops, contact the Clinical Investigator for advice (see below).
		After 2 Weeks:	A gradual increase in exposure to light should be encouraged, and the patient should **continue to** test for skin ~~sensitivity~~ **photosensitivity** as described **above. If there are no reactions 24 hours after the exposure, the duration of light exposure can be increased by 15 minutes per day**. Indoors: **gradually build up to normal levels of exposure**. Patients should still take precautions to avoid exposure of skin to direct sunlight or bright indoor light for at least 4 weeks following administration of Amphinex. Eyes can remain sensitive to bright light for ~~2~~**3** months. Outdoors: During the first days of outdoor exposure the patient should stay in shaded areas or go out only when cloudy. The patient should continue to wear dark glasses and dark, ~~closely woven clothing~~ **tightly woven clothing. Two weeks after Amphinex injection, the patient should start to gradually return to normal levels of direct sunlight exposure.** The patient's eyes may ~~also~~ be very sensitive to bright light during the first ~~2~~**3** months; therefore, ~~patients~~ **when outdoors the patient** should **continue to** wear **the** dark glasses ~~(~~provided by the Sponsor~~)~~. If at any time the patient experiences ~~a burning sensation~~ **symptoms – prickling, discomfort** or ~~skin reddening after exposure to sun, (s)~~ **redness** – **then** he/**she** ~~should wait for at least 2 days or until the reaction disappears, whichever is the later, before re-exposing the skin to light.~~**cover up and go indoors and let the symptom settle fully before repeating exposure**.

Version	Date	Changes	
			~~Testing for skin sensitivity~~ ~~After 2 weeks patients are advised to test their skin sensitivity by exposing the back of a hand to sunlight for a maximum of 5 minutes. Exposure should be stopped immediately if tingling, burning or stinging sensations occur in the exposed area.~~ ~~The patient should wait for 24 hours after the exposure to see any erythema, oedema, or blistering appears. If such reactions occur, the patient should contact the investigator immediately who will advise the patient. The patient should wait 2 days before repeating the test. If there is no reaction, the patient can go outdoors, but only for 15 minutes on the first day. If there are no reactions 24 hours after the first outdoor exposure, the duration of light exposure can be increased by 15 minutes per day.~~
		Surgery:	Surgery or dental treatment involving the use of light for visualisation or treatment should be avoided during the first 4 weeks following Amphinex administration, unless it is absolutely necessary and only if the potential benefits for the patient outweigh the risks. Direct illumination of the patient with the operating room lights, including the surgeon's headlamp, should be avoided. If an acute surgical intervention is needed, yellow or green light should be used. Ideally this could come from a sodium lamp but it may be more practical to use green filters that absorb wavelengths that activate fimaporfin (**around 415 nm and 652 nm,** contact Sponsor for advice). All incisions should be shielded from light. **Some pulse oximeters may produce red light of a wavelength close to that used for the photoactivation of fimaporfin. To avoid the risk of local skin burns, pulse oximeters must be repositioned every 10 minutes and must not be used for longer than**

Version	Date	Changes

	needed.
Up to 3 Months:	For at least 3 months following PCI treatment: Eye tests that use bright lights should be avoided. Patients should contact their Investigator if eye tests using bright light are planned. Patients should avoid ultraviolet tanning beds and should not sunbathe.
After 3 Months	Some patients may experience photosensitivity reactions beyond 3 months. Hence, the precautionary measures may be required for longer. Liver or renal impairment may prolong the elimination of fimaporfin, requiring longer periods of **light** protection. Patients should continue to test for photosensitivity periodically as described above until such time that no reactions are observed.
Treatment of photosensitivity reactions	**If patients experience skin photosensitivity reactions, they can be treated in the same way as sunburn: Use of cooling emollients, skin moisturiser, topical corticosteroids. Analgesics can be considered for symptomatic relief. Extra care must be taken to protect skin while it heals.**

Section 5.2.5, Light Source

[redacted]

Section 5.2.6, Dose Modification

5.2.6.1 Dose Modifications for Amphinex and PCI treatment

Version	Date	Changes

No dose modifications are allowed for Amphinex or gemcitabine given as part of the PCI treatment. See Section 3.3.2 regarding postponements or omissions of PCI treatment.

5.2.6.2 Dose Modifications for Systemic Chemotherapy Cycles

The investigator site is expected to follow local practice for dose modifications of the standard gemcitabine/cisplatin combination chemotherapy; however, the following information is provided for guidance.

Haematological Toxicity

The absolute neutrophil count must be ≥1,500 × 10^6/L and the platelet count must be ≥100,000 × 10^6/L in order to administer full doses of gemcitabine and cisplatin in combination. Patients should be monitored prior to each dose for platelet, leucocyte and granulocyte counts, and, if necessary, the dose of gemcitabine and cisplatin may be either reduced or withheld in the presence of haematological toxicity according to the following scale (Table 2).

Table 2 Dose Modifications for Haematological Toxicities

Day 1				
Absolute neutrophil count (× 10^6 /L)		**Platelet count (× 10^6 /L)**	**Percent (%) of full dose gemcitabine**	**Percent (%) of full dose cisplatin**
≥1,500	**and/or**	**≥100,000**	**100**	**100**
≥500 - <1,000	**and/or**	**≥50,000 - <100,000**	**delay dose until recovery, then 75**	**100**
<500	**and/or**	**<50,000**	**omit dose until recovery, then 75**	**omit dose until recovery, then 75**
Day 8				
Absolute neutrophil count (× 10^6 /L)		**Platelet count (× 10^6 /L)**	**Percent (%) of full dose gemcitabine**	**Percent (%) of full dose cisplatin**
≥1,000	**and/or**	**≥100,000**	**100**	**100**
≥500 - <1,000	**and/or**	**≥50,000 - <100,000**	**omit dose until recovery, then 75**	**100**
<500	**and/or**	**<50,000**	**omit dose until recovery, then 75**	**omit dose until recovery, then 75**

Version	Date	Changes

Non-Haematological Toxicity

Renal toxicity: The creatinine clearance must be ≥ 60 mL/min in order to administer the full dose of cisplatin. Serum creatinine should be checked before each cycle of treatment. If there is a >25% increase of serum creatinine compared to the baseline, then the ethylenediamine tetraacetic acid (EDTA) clearance (or equivalent) must be performed.

Pulmonary toxicity: Transient dyspnoea occurs in <10% of patients after gemcitabine, secondary to mild bronchospasm. Rarely, more severe pulmonary toxicity characterised by tachypnoea, hypoxia diffuse interstitial infiltrates, acute respiratory distress syndrome and respiratory failure may also occur. The patient should be withdrawn from treatment.

Table 3 Dose Modifications for Non-Haematological Toxicities

	Percent (%) of Full Dose Gemcitabine	Percent (%) Full Dose Cisplatin
Renal Function		
≥60 mL/min	**100**	**100**
40–59 mL/min	**100**	**50**
<40 mL/min	**Omit**	**Omit**
Biliary Tract Obstruction		
Bilirubin >2.5 × ULN	**Omit**	**Omit**
AST/ALT/ALP >5.0 × ULN	**Omit**	**Omit**
Peripheral Neuropathy		
Grade 1–2	**100**	**Delay until recovery, then 100**
Grade 3–4	**100**	**Discontinue**
Tinnitus		
If full recovery between cycles	**100**	**100**
If no full recovery between cycles	**100**	**Omit**
Lethargy		
Grade 3–4	**75 (if no response, stop treatment)**	**100**
Oedema		
Grade 3–4	**75 (if no response, stop treatment)**	**100**

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST; aspartate aminotransferase; ULN, upper limit of normal.

Version	Date	Changes
		Gemcitabine-Specific Non-Haematological Toxicity **Posterior Reversible Encephalopathy Syndrome: Reports of posterior reversible encephalopathy syndrome (PRES) with potentially severe consequences have been reported in patients receiving gemcitabine as a single agent or in combination with other chemotherapeutic agents. Acute hypertension and seizure activity were reported in most gemcitabine patients experiencing PRES, but other symptoms such as headache, lethargy, confusion and blindness could also be present. Diagnosis is optimally confirmed by MRI. Posterior reversible encephalopathy syndrome was typically reversible with appropriate supportive measures. Gemcitabine should be permanently discontinued and supportive measures implemented, including blood pressure control and anti-seizure therapy, if PRES develops during therapy.** **Haemolytic Uraemic Syndrome: Clinical findings consistent with the haemolytic uraemic syndrome (HUS) were rarely reported (post-marketing data) in patients receiving gemcitabine. Haemolytic uraemic syndrome is a potentially life-threatening disorder. Gemcitabine should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, and/or elevation of serum bilirubin, serum creatinine, blood urea nitrogen or lactate dehydrogenase. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.**
		Section 5.3.1, Study Drug Packaging and Storage [redacted]
		Section 5.3.3, Other Supplies Added the text: **Only the supplies provided by the Sponsor should be used. Additional items supplied by the Sponsor are described in the Procedure Manual and Laboratory Manual.**
		Section 5.4, Treatment Compliance The details of the study treatment will be **adequately** documented **and recorded** in the eCRF and drug accountability forms as applicable. All study treatment-related procedures will be performed at the investigational site by qualified health care personnel. All instances of ~~noncompliance~~non-compliance and all resulting protocol deviations will be **adequately documented and** recorded in the eCRF.
		Section 5.4.1, Light Protection Compliance Investigators must counsel patients to observe light protection precautions described in Table 1 to prevent photosensitivity reactions. It should be **adequately** documented **and recorded** in the eCRF that the patient was thoroughly informed on the light protection precautions. Any non-compliance with regard to light protection should be **adequately** documented **and recorded** in the eCRF.
		Section 5.6, Contraception **A woman is considered of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and**

Version	Date	Changes
		bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. A WOCBP must continue the use of contraception during treatment and until the end of relevant systemic exposure (at least 9 months after last dose of Amphinex or 6 months after last dose of chemotherapy, whichever is the latest). **Only men with pregnant or non-pregnant partners considered of childbearing potential will need to follow contraception requirements. A condom is also required to be used by vasectomised men to prevent delivery of the drug via seminal fluid. As the treatment includes genotoxic investigational medicinal products, the male patient should use condoms during treatment and until the end of relevant systemic exposure in the male patient (at least 9 months after last dose of Amphinex or 6 months after last dose of chemotherapy, whichever is the latest), plus a further 90 days.** **Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence will need to be evaluated by site personnel in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient.** **Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together.**
		Section 6.1.1, Tumour Assessment The study will evaluate tumour responses as determined by Investigator according to ~~radiological (~~RECIST 1.1~~) and/or clinical assessment~~. Efficacy assessments of PFS, ORR, DoR, and DCR will be derived using Investigator RECIST 1.1 assessments~~ and/or clinical assessment~~. **Note: in cases of symptomatic progression, patients will continue to be followed for-radiological RECIST progression.** From the Investigator's review of the imaging scans, the RECIST tumour response data will be used to determine each patient's visit response according to RECIST v1.1. At each visit, patients will be programmatically assigned a RECIST v1.1 visit response of CR, PR, ~~stable disease (~~SD~~)~~, or progressive disease **(for measurable/target lesions) or CR, progressive disease, or non-CR/non-PD (for non-measurable/non-target lesions)** depending on the status of their disease compared with baseline and previous assessments. If a patient has had a tumour assessment which cannot be evaluated, the patient will be assigned a visit response of not evaluable ~~unless there is any evidence of progression in which case the response will be assigned as progressive disease~~. Radiological assessments use images from contrast-enhanced CT or MRI scans, collected during screening/baseline and at regular follow-up intervals following study treatment. The RECIST 1.1 guidelines (link in Appendix C) provide a method of assessment of change in tumour burden in response to treatment. Screening/baseline imaging should be performed no more than 28 days before the ~~start of study treatment~~**randomisation**. The RECIST 1.1 assessments of baseline images identify

Version	Date	Changes

target, (measurable), and non-target **(non-measurable)** lesions, and each lesion is evaluated in subsequent follow-up images (the same imaging modality and contrast protocol used at baseline must be used for all subsequent follow up imaging). This allows determination of follow-up target lesion response, non-target lesion response, and overall time point tumour responses (CR, PR, SD, **non-CR/non-PD,** progressive disease, or not evaluable).

Table 5, Tumor Response Criteria for Target Lesions

Stable Disease: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum of diameters ~~since the treatment started~~**while on study**.

Table 6 Tumour Response Criteria for ~~Nontarget~~Non-target Lesions ~~Outside of the Bone~~

Response	**Evaluation of ~~Nontarget~~Non-target Lesions ~~Outside of the Bone~~**
Complete Response	Disappearance of all ~~nontarget~~**non-target** lesions. All lymph nodes should be non-pathological **in size** (<10 mm in the short axis)
Non-CR/Non-PD	Persistence of 1 or more ~~nontarget~~**non-target** lesion(s)
Progressive Disease	Appearance of 1 or more new ~~lesions~~**lesion(s)** and/or unequivocal progression of existing ~~nontarget~~**non-target** lesions

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 progressive disease for measurable disease, ie, 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) or an increase that is sufficient to require a change in therapy.

If a patient has a response of SD or PR for target lesions, a modest 'increase' in size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

Tumour response will be assessed according to RECIST 1.1 every 12 weeks (±1 week), from randomisation until disease progression and should NOT follow delays incurred in the treatment period. Patients will be followed for ~~objective~~**radiological** progression, regardless of whether they discontinue therapy or have symptomatic progression.

The local radiological assessment will be used to guide clinical management decisions. The primary analysis of PFS and the secondary RECIST **1.1**-based endpoints will also be based on the local radiological assessment. In addition, an independent central radiological review, blinded to the assessment of the local radiologist and/or oncologist, will be performed for the tumour response data. The data from the independent central reviewer(s) will provide data for the supportive~~/sensitivity~~ analysis.

Version	Date	Changes
		Survival follow-up phase Following discontinuation of randomised treatment, patients will be followed up for survival and information on **any** subsequent anti-cancer treatments as detailed in the study plan, unless they have withdrawn their consent. Additional survival contacts (ie, outside of the 12-weekly calls) may be conducted around the time of interim **ORR** analysis and final PFS analysis at data cut-off to ensure that the survival information is as up to date as possible for the analysis of OS. **Determination of survival may be collected through publicly available death registry information, where permitted locally.**
		Section 6.1.2, Biomarkers Section 6.1.2, Biomarkers was moved to Section 6.3, Biomarkers (and the existing Section 6.3, Exploratory Biomarkers became Section 6.3.2) and was amended as follows: Section 6.3 **Standard Tumour Markers and Exploratory** Biomarkers Section 6.3.1 ~~CA-125, CA-19-9, and CEA~~**Standard** Tumour Markers **The standard tumour markers cancer antigen 125 (CA-125), carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) will be analysed from blood samples collected for safety laboratory assessments throughout the study.** Section 6.3**.2** Exploratory Biomarkers ~~Plasma and serum~~**Blood** samples (~~each 5ml~~**20 mL**) **for exploratory biomarkers in plasma** will be collected at baseline and at approximately 3-month intervals throughout the study. Samples will be banked for a collective post hoc analysis, enabling an evaluation of the relative importance and covariance of various biochemical changes to treatment outcome in the 2 study arms. **As described in Section 6.3.1, traditional tumour diagnostic markers may exhibit low sensitivity and there is an urgent need for novel, more sensitive, and easy to detect biomarkers which can be used in cancer diagnosis and prognosis. For example, cell free nucleic acids such as microRNA (a type of small non-coding RNA molecule) may have a potential application as specific and sensitive biomarkers for clinical diagnosis or prognosis.** As the study is well-sized in consideration of this rare cancer population, an exploratory assessment of changes ~~over time and with treatment by multiplex analyses of genetic cancer pathways and immunological characteristics is highly motivated. In addition, in a subset of study sites with facilities and resources for the purpose, sampling for the characterisation of circulating cells (tumour and leukocyte subsets) will be collected and analysed~~ **in known and novel biomarkers over time, and with treatment, is highly motivated**.
		Section 6.1.2, Quality of Life Measurements In this study, HRQoL will be measured by use of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and the EORTC ~~QLQ-B21~~**QLQ-BIL21** questionnaire (Appendix D). Patients will complete the questionnaires at the time points specified in Table 10, Table 11 **and** Table 12**, preferably before any other study assessments are performed**.
		Section 6.2, Pharmacokinetic Assessments [redacted]

Version	Date	Changes
		Section 6.4.1.4, Reporting Adverse Events **Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST 1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through the use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.**
		Section 6.4.1.5, Reporting Serious Adverse Events **The investigator must report any** ~~Any~~ AE that meets SAE criteria (Section 6.4.1.2) ~~must be reported~~ to [redacted] using the electronic data capture (EDC) system, immediately (ie, within 24 hours) after the time the site personnel first learn about the event.
		Section 6.4.1.6, Suspected Unexpected Serious Adverse Reactions and Adverse Events of Special Interest **The Sponsor will ensure that all relevant information about SUSARs that are fatal or life threatening is recorded and reported as soon as possible to the competent authorities in all the Member States concerned, and to the IECs/IRBs, and in any case no later than 7 calendar days after knowledge by the Sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional 8 calendar days.** **All other SUSARs will be reported to the competent authorities concerned in accordance with their specific requirement and to the IECs/IRBs concerned as soon as possible but within a maximum of 15 calendar days of first knowledge by the Sponsor. The Sponsor will also inform all Investigators.**
		Section 6.4.1.7, Assessment of Severity The severity, or intensity, of an AE refers to the extent to which an AE affects the patient's daily activities. The intensity of all AEs will be graded in accordance with the **current version of** NCI CTCAE ~~version 4.03 or later~~.
		Section 6.4.3.1, Safety Laboratory Analysis Blood and urine samples will be collected at times specified in the schedule of events (~~Table 8 and Table 10~~**, Table 10, Table 11 and Table 12**) and sent to ~~central~~ **a local** laboratory for analysis. Added **standard tumour markers (S – CA - 125, CA 19-9, CEA)** to the list of laboratory variables that should be measured in the study. Updated footnote 'a': **Serum creatinine should be checked before each cycle of treatment. If there is a >25% increase compared to the baseline then the ethylenediamine tetraacetic acid (EDTA) clearance or equivalent method must be performed and cisplatin dosing modified accordingly**~~Creatinine clearance will be calculated and checked before each cyclic chemotherapy treatment~~. **Standard tumour markers will be analysed from serum samples collected for clinical chemistry.** Additionally, a urine **or blood serum** sample will be collected from all ~~females of childbearing potential~~ **WOCBP** at screening**,** ~~and~~ on the first day of each cycle of

Version	Date	Changes

chemotherapy **and at the end of treatment (Day 30)**, for a **highly sensitive** pregnancy test.

Table 7 Blood Sampling Volume:

Tests Patients	Blood volume each patient and each sampling point	Sampling points Number of samples	Total blood volume Arm A	Total blood volume Arm B
Analysis of Exploratory Biomarkers in plasma ~~and serum~~ All patients (Arm A and B)	**20 mL (**Total**)** ~~10 mL;~~ ~~5 mL for plasma~~ ~~5 mL for serum)~~	~~• Screening~~ • **Baseline** • In cycle 4 • In cycle 8 • Every third month 6 sampling points estimated	~~60~~**120** mL	~~60~~**120** mL
~~Analysis of Exploratory Biomarkers in blood (PBMCs)~~ ~~Subset of patients at dedicated site~~ ~~Arm A and B~~	~~20 mL~~	~~• Screening~~ ~~• In cycle 4~~ ~~• In cycle 8~~ ~~• Every third month~~ ~~6 sampling points estimated~~	~~120 mL~~	~~120 mL~~
Amphinex Pharmacokinetics Arm A **patients**	5 mL	~~10~~ **Up to 19** sampling points	~~50~~**95** mL	NA
Clinical chemistry **(including standard tumour markers in serum)**	20 mL for serum	22 sampling points **in Arm A** **20 sampling points in Arm B**	440 mL	~~440~~ **400** mL
Haematology	3.5 mL (EDTA plasma)	22 sampling points	77 mL	77 mL
Coagulation	3.5 mL (citrate plasma)	10 sampling points **in Arm A** **9 sampling points in Arm B**	35 mL	~~35~~ **31.5** mL
Total[a]			~~782~~**767** mL	~~732~~**628.5** mL

Section 6.4.3.2, Hepatotoxicity

In the event that a patient shows AST or ALT ≥3 × ULN indicative of hepatotoxicity related to chemotherapy (ie, with an ensured proper biliary drainage in place and a clinical picture indicative of a correlation to chemotherapy treatments), the **delay,** postponement or omission of the following chemotherapy administration is to be decided at the discretion of the treating physician as per local standard procedures applicable to gemcitabine/cisplatin treatment.

Section 6.4.4, Loco-Regional Tumour-Related Events and Biliary Complications

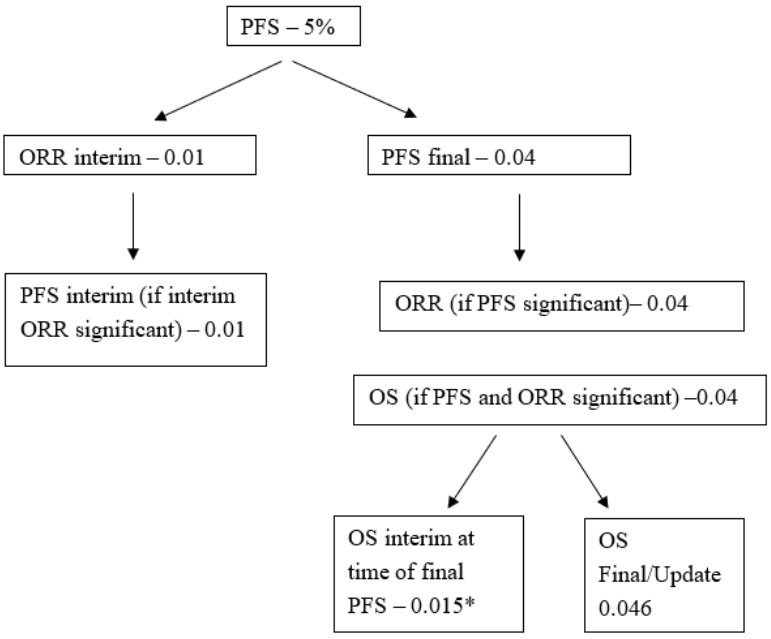
Unless caused by a terminal, intractable overgrowth of the loco-regional tumour in patients with established progressive disease, unplanned or emergency hospital visits caused by clinical signs of sudden bile duct obstruction, including but not limited to malaise, pain, jaundice, septicaemia, or several symptoms combined, and with clinical,

Version	Date	Changes
		laboratory and radiological findings confirmatory of unexpected, biliary obstruction leading to unplanned hospitalisation will be recorded **and reported as SAEs (see Section 6.4.1.5)**.
		Section 6.4.5, Vital Signs ~~The~~ **Vital signs on** Day -4 **and Cycle 4, Day 18**~~vital signs~~ must be collected both before and after Amphinex administration.
		Section 6.4.6, Electrocardiograms For all ECGs, details of rhythm, PR, R-R, QRS and QT intervals and an overall evaluation will be recorded. **Corrected QT intervals will be calculated using Bazett's formula (QTcB) and Fridericia's formula (QTcF).** The **ECG on** Day -4 **and on Cycle 4, Day 18**~~ECG~~ must be performed **before and 30 minutes and 4 hours** after Amphinex administration.
		Section 6.4.7, Photosensitivity Measurements and Skin Reactions The title of this section was amended to include **and Skin Reactions**. The following text was added: **For patients in both treatment arms, skin reactions will be documented and recorded in the eCRF.**
		Section 7.1.1, Progression-Free Survival Progression-free survival is defined as the time from randomisation until the date of ~~objective~~**radiological** disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anti-cancer therapy prior to progression.
		Section 7.2.5, Disease Control Rate The DCR is defined as the proportion of patients with ~~BOR of~~ **stable disease or better (ie,** CR, PR or SD**)**; it will be assessed at 6 and 12 months.
		Section 7.3, Exploratory Endpoints • To ~~serially collect~~**analyse** blood samples for ~~the subsequent analysis of treatment effects on~~**standard tumour markers and** exploratory ~~tumour~~ biomarkers ~~(multiplex analysis of cancer pathways and cancer immune profiling), as well as (in as subset of patients) changes in circulating leukocyte subtypes, cancer cells and DNA~~.
		Section 7.4, Sample Size Calculations The primary (final) analysis of PFS, as assessed by local radiological review, will be conducted when approximately ~~120~~**129** progression events (~~65~~**69**% maturity) have been observed. If the PFS result is statistically significant at the ~~4.9~~% (2-sided) alpha level, ORR will be compared between the arms and an interim analysis of OS will then be assessed, **as detailed in Section 7.7.7**. If the true HR for the comparison of fimaporfin-induced PCI of gemcitabine complemented by gemcitabine/cisplatin chemotherapy versus gemcitabine/cisplatin chemotherapy alone is 0.6, ~~120~~ **129** progression events will provide approximately 80% power to demonstrate a statistically significant difference in PFS at a ~~4.9~~% 2-sided significance level (this may translate to an improvement in median PFS from 7.4 to 12.3

Version	Date	Changes
		months, if PFS is exponentially distributed). A minimum or critical HR of 0.7 (eg, 7.4 to 10.6 months), if observed, would give a 2-sided p<0.~~049~~**04**, but there is only 50% power associated with the critical HR. Assuming linear recruitment of 186 patients over 48 months with a site set-up period of approximately 6 months, ~~120~~**129** PFS events are expected to occur between approximately 48 and 51 months (4 to 4.3 years) from the date on which the first patient was randomised. In addition to the ~~potential~~ interim analysis of OS at the time of the final PFS analysis (approximately ~~50~~**58**% of patients are predicted to have died at this point), data collection for OS will continue beyond the final PFS analysis and an updated OS analysis will be performed. ~~The level of maturity will be determined based on the final PFS and interim OS results, in discussion with the regulatory authorities. For example, if the final~~ **The final OS** analysis ~~of OS~~ will occur after approximately ~~155~~ **147** death events ~~(>80%)~~ **have been observed in 186 patients (>75%** maturity~~,~~**)**. Assuming a true OS HR of 0.~~7~~63, there will be ~~60~~**80**% power to detect an improvement in ~~median~~ OS from 11.7 **to 18.7** months **with 2-sided p<0.046 (O'Brien and Fleming boundary based on interim OS at approximately 103 events). A minimum or critical HR of 0.72 (eg, 11.7 to** ~~16.7 months~~**16.3 months**), **if observed, would be statistically significant. The exact level of maturity will be determined based on the final PFS and interim OS results, in discussion with the regulatory authorities.** The ~~155~~**147** death events are expected to occur at approximately ~~72~~**65 to 68** months from first patient randomised. **Further details on the interim analyses are provided in Section 7.7.7.**
		<u>Section 7.6, Description of Subgroups to be Analysed</u> Subgroup analyses will be performed for the stratification factors used at the point of randomisation (measurable disease – yes versus no and ~~ECOG performance status – 0 or 1~~**presence or absence of hepatic metastases**). Exploratory subgroup analyses will also be performed to assess key endpoints by loco regional tumour control, metastatic lesions within the liver parenchyma, and other metastatic lesions. **Four distinct groups will be explored: primary; primary with liver metastases; primary with local lymph nodes; and primary with liver metastases and local lymph nodes. An additional subgroup analysis will be performed to compare patients with and without PSC at study entry.** If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 20 events per level in a subgroup), the relationship between that subgroup and PFS/OS will not be assessed. In this case, only descriptive summaries will be provided. Further details **and any other exploratory subgroups of interest** will be provided in the SAP
		<u>Section 7.7.1, Analysis of Primary Endpoint</u> The primary endpoint for this study is PFS. Progression-free survival will be analysed using the ITT ~~population~~**analysis set** and ~~a~~ supportive ~~analysis~~ **analyses** will be performed using **the BICR data and also** the mITT ~~population~~**analysis set**. Progression-free survival, as assessed by local radiological review, will be analysed using a log rank test stratified by **any** measurable disease at baseline (yes versus no), and ~~ECOG performance status (0 and 1)~~ **presence or absence of hepatic metastases**. If these 2 stratification factors lead to low numbers (eg, <10 progression events) within a single stratum, one or more stratification factors may be removed from the statistical analysis. The criteria for removal will be pre-defined in the SAP. ~~The HR and CI will be~~

Version	Date	Changes
		~~obtained directly from the U and V statistics (Selke and Siegmund 1983; Berry et al 1991).~~ ~~A sensitivity/supportive analysis of PFS will be performed based on data assessed by BICR.~~ **The HR will be estimated using a stratified Cox-proportional hazards model using the Efron approach for handling ties (Efron 1977), together with the associated profile likelihood 95% CI for the HR.** **The effect of treatment will be estimated by the HR together with its corresponding 95% CI and p-value for the ITT analysis set.** **The primary analysis of PFS based on the local evaluation will be repeated using the BICR data as a supportive analysis.** A Kaplan-Meier (KM) plot of PFS will be presented by treatment group. **Median PFS with 95% CIs will be presented. In addition, KM landmark PFS estimates at 6 months and 12 months with corresponding CIs will also be presented using KM methodology. KM estimates may be presented for other timepoints of interest.** The assumption of proportionality will be assessed.
		Section 7.7.2.2, Best Overall Response The BOR will be summarised for the ITT ~~population~~**analysis set** and may be further grouped by measurable/non-measurable disease at entry. **Summaries of BOR will also be repeated using the BICR data. Furthermore, two-by-two tables will be produced to describe the consistency between the BICR and local evaluation assessment for BOR (and also the timing of PD to show how often the investigator declares PD at the same time, before or after the BICR).**
		Section 7.7.2.3, Objective Response Rate For randomised studies, a confirmatory scan to confirm the response is not required per RECIST ~~v1~~ **1.1**. The ORR will be summarised using the Evaluable for Response analysis set (ie, all randomised patients who have measurable disease at study entry). **ORR will be compared between treatment arms using a logistic regression model with the covariate (stratification factor) of hepatic metastases. However, if there are <10 patients within a stratum, this stratification factor will be removed from the statistical analysis.** **The results of the analysis will be presented in terms of an odds ratio together with its associated 95% profile likelihood CI. The p-value will be based on a test statistic that is calculated as twice the change in log-likelihood resulting from the addition of a treatment factor to a model that contains the covariates defined above. The test statistics is chi-squared distributed with 1 degree of freedom.**
		Section 7.7.2.5, Disease Control Rate The DCR will be summarised for the ITT ~~population~~**analysis set** at 6 months and 12 months (ie, best response of CR, PR or SD at 6 or 12 months) and may be further summarised by measurable/non-measurable disease at entry.
		Section 7.7.2.6, Change in Tumour Size The change in tumour size will be summarised for the Evaluable for Response ~~population~~**analysis set**.
		Section 7.7.7, Interim Analysis A formal interim analysis of ~~PFS~~**ORR** will be performed after approximately ~~60~~

Version	Date	Changes
		~~progression events (defined in RECIST 1.1 [])~~**120 patients (65%)** have been ~~observed (across both arms of the study). It is predicted that 60 PFS events will occur at approximately 36 months (3 years) from the date upon which the first patient was~~ randomised; ~~and at the point of data cut-off, approximately 120~~ **and followed to their first 12-week follow-up scan. Based on an assumption that ~80** patients will have ~~been recruited (ie, the PFS data will be approximately 50% mature).~~ ~~Assuming that the interim PFS analysis occurs after 60 events out of a planned 120 events, a PFS HR of <0.46 would need to be observed~~ **measurable disease, there will be >80% power** to ~~conclude a~~ **detect an improvement in ORR from 20% to 57% with 2-sided p<0.01 (approximates an O'Brien and Fleming boundary based on 65% information). An improvement from 20% to 47% will be** statistically significant ~~result at the 2-sided p<0.003 level, according to an O'Brien & Fleming boundary.~~ **, if observed**. If the comparison of **the** interim ~~PFS~~**ORR data** between the arms is statistically significant ~~(based on an O'Brien and Fleming boundary), the secondary endpoint of ORR will be assessed in a hierarchical manner at the same time as the interim PFS assessment and DoR~~ , **it** will be summarised **together with PFS and DoR** to support a conditional marketing authorisation application. ~~Assuming 80 of the 120 patients recruited (ie, two-thirds) have measurable disease, an improvement in ORR from 20% on the SoC arm to 54% on the PCI arm would need to be observed to give p<0.003. The survival data available at the time of the interim PFS assessment will be~~ **survival data will be** limited ~~(<20 death events)~~ **at this point** and will be summarised descriptively ~~only~~. An interim analysis of OS will be performed at the time of the final PFS assessment (**when** approximately ~~50% of~~ **103** patients are predicted to have died ~~at this point) and an updated OS analysis will be performed at a later time point.~~ **A 2-sided p<0.015 will be required to demonstrate statistical significance**.
		Section 7.7.7.1, Multiplicity and Control of Type 1 Error Updated section heading to '**Multiplicity and** Control of Type 1 Error'. Added a figure for multiple testing procedure and updated the text as follows: In order to provide strong control of the type I error rate **at the 2-sided 5% level,** the primary endpoint of PFS and key secondary endpoints of ORR and OS will be tested in this sequential (hierarchical) order~~.~~ **at the time of the primary analysis**. If any previous analysis in the sequence is not statistically significant, the alpha cannot be transferred to subsequent ~~analyses~~ **endpoints (ie, the multiple testing procedure will recycle the test mass to the endpoint not yet rejected in the hierarchy outlined in Figure 4)**. ~~The Lan-DeMets approach that approximates the O'Brien and Fleming spending function will be used to maintain an overall 2-sided 5% type I error across the interim (60 events) and final PFS analysis (120 events).~~ **The interim analysis of ORR will be conducted after approximately 120 out of 186 patients have been randomised.** ~~The significance level for the PFS analyses will be calculated by specifying the information fraction for each analysis. The information fraction is calculated as the number of PFS events at the analysis time-point divided by the total number of events at the final analysis time-point (for example, the information fraction would be entered as 0.5 [60/120 events] for the main interim analysis resulting in a 2-sided p-value of 0.003).~~ **Assuming 65% information at the interim, statistical significance will be declared for ORR if 2-sided p<0.01, which approximates an O'Brien and Fleming spending**

Version	Date	Changes
		function. The remaining **2-sided** alpha (**of** ~~4.9%~~**4%**) will be spent at the final PFS analysis**, which will be triggered after approximately 129 progression events**. Note, a non-statistically significant ~~PFS~~ **ORR** result at the interim analysis will not preclude ~~further~~ testing of PFS at the final analysis. **If the final PFS is statistically significant at 2-sided p<0.04, the alpha will be recycled to ORR. If both are significant, an interim analysis of OS at the full 5% alpha will be performed.** Statistical alpha will ~~also~~ be shared across the interim and final assessments of OS using the Lan DeMets approach. ~~A detailed multiple testing strategy incorporating PFS, ORR and OS will be described in the SAP.~~ **Assuming 70% information (number of events at interim / number of events at final analysis) at the interim, statistical significance will be declared for interim OS if 2-sided p<0.015, based on an O'Brien and Fleming spending function. The exact significance levels will be adjusted for the actual information fractions.** **Figure 4, Multiple Testing Procedure** The numbers are 2-sided significance levels  *O'Brien and Fleming boundary based on 5% alpha and approximately 70% information at interim (assumes 103/147 deaths at interim)
		Section 7.7.8, Independent Data Monitoring Committee Although there are no formal futility stopping rules in the study, the IDMC will review the ongoing safety data and the results of the interim ~~PFS~~**ORR** analysis and provide a recommendation as to whether the study demonstrates a positive risk benefit that is clinically meaningful and meets the pre-defined statistical boundary for efficacy.
		Section 9.1, Independent Ethics Committee or Institutional Review Board Before study onset, the protocol, informed consent, advertisements to be used for the

Version	Date	Changes
		recruitment of study patients and any other written information regarding this study to be provided to the patient ~~or the patient's legal guardian~~ must be approved by the IEC/IRB.
		Section 9.3, Patient Information and Consent Before recruitment and enrolment, each prospective patient ~~or his or her legal guardian~~ will be given a full explanation of the study and be allowed to read the approved ICF. Once the Investigator is assured that the patient~~/legal guardian~~ understands the implications of participating in the study, the patient~~/legal guardian~~ will be asked to give consent to participate in the study by signing the ICF. The Investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient ~~or legal guardian~~.
		Section 10.1, Confidentiality Clinical information will not be released without the written permission of the patient ~~(or the patient's legal guardian)~~, except as necessary for monitoring and auditing by the Sponsor, its designee, the regulatory agencies/authorities, or the IRB/IEC.
		Section 10.2, Financial Disclosure and Obligations • IEC/IRB-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient ~~or legal guardian~~, and
		Section 11.2.1, Modification of the Protocol Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the Sponsor or its designee. Amendments to the protocol must be submitted in writing to the Investigator's IRB/IEC **and regulatory authorities** for approval before patients can be enrolled into an amended protocol.
		Section 11.2.2, Protocol Deviations Significant protocol deviations for this study may include 1) use of prohibited concomitant medications during the study, 2) tumour assessments (RECIST) for screening not performed with 28 days ~~of start of treatment~~**prior to randomisation**, 3) patients who received the wrong treatment, etc.
		Section 11.3, Study Termination Although PCI Biotech has every intention of completing the study, PCI Biotech reserves the right to discontinue the study at any time for clinical or administrative reasons, **including but not limited to**: • **Occurrence of AEs not seen previously which by virtue of their nature, severity and duration are considered to necessitate study termination; OR the unexpected incidence or severity of known AEs** • **Sponsor decision** • **Medical or ethical reasons affecting the continued performance of the study** • **Difficulties in the recruitment of patients** • **Cancellation of the drug development as such or for the given indication.** The end of the study is defined as the date **of the final database lock**~~on which the last patient completes the last visit (includes follow-up visit)~~.

Version	Date	Changes
		Section 12, Reference List ~~Berry G, Kitchin RM, Mock PA. A comparison of 2 simple hazard ratio estimators based on the logrank test. Stat Med. 1991;10(5):749-55.~~ **Efron B. The Efficiency of Cox's Likelihood Function for Censored Data. J Am Stat Assoc 1977;72(359):557-65.** National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers. ~~Version 4.2017 – October 9, 2017~~ **Version 3.2019 – August 1, 2019**. ~~Selke T, Siegmund D. Sequential analysis of the proportional hazards model. Biometrika. 1983;70(2):315-26.~~
		Appendix A: Schedule of Events for the Active Treatment Period Schedule of events was split for Arm A and Arm B patients. Updates were made to Table 10 to include only the event schedule for Arm A patients and a separate table (**Table 11**) was created for Arm B patients with additional details.
		Appendix A, Table 10 The following changes were made to the schedule of events: • Removed footnote "b" from column heading 'PCI treatment No 1'. • Orientation of the 'Day' row was made vertical to improve table formatting. • Day removed from the Screening column heading; clarification of time window for Screening evaluations is provided in footnote "a". • Randomisation row removed and Randomisation added as a column heading after Screening to visually clarify that all Screening procedures must be performed prior to randomisation. • Removed empty columns for 'Day -3' 'Day -2' and 'Day -1' under 'PCI treatment No. 1' and 'C4, D19', 'C4, D20' and 'C4, D21' under 'PCI treatment No. 2', to improve table formatting. • An additional assessment point for vital signs was added on Day -4 and C4, D18 to clarify that vital will be checked twice ie, before and after Amphinex administration on these dates. • Additional assessment points for ECG were added on Day -4 and C4, D18 to clarify that ECG will be monitored thrice ie, before and approximately 30 minutes and 4 hours after Amphinex administration (time matched with PK samples) on these dates. • Pregnancy test was added on 'Day -4' and 'Cycle 4, Day 18'. • Added detailed sampling for assessment of fimaporfin pharmacokinetics which was previously provided in a separate table (Table 9 in original protocol). The PK sampling schedule was revised to include 2 groups; Group 1 - rich sampling and Group 2 - sparse sampling. Groups 3 and 4 were deleted. All patients in Arm A will now undergo the PK sampling schedule as follows: o Group 1: Day -4; Cycle 1, Day 1; Cycle 1, Day 8; Cycle 2, Day 8; Cycle 3, Day 8; Cycle 4, Day 8; Cycle 4, Day 18; Cycle 5, Day 1; Cycle 5, Day 8; Cycle 6, Day 8; Cycle 7, Day 8; Cycle 8, Day 8.

Version	Date	Changes
		○ Group 2: Day -4; Cycle 1, Day 1; Cycle 2, Day 8; Cycle 4, Day 8; Cycle 4, Day 18; Cycle 5, Day 8; Cycle 7, Day 8. • Removed footnote "c" from row heading 'Informed consent'; information within footnote "c" merged into footnote "a". • Biomarker assessments for standard tumour markers (CA-19-9/ CA-125/CEA) moved to 'Laboratory Assessments'. Both rows for 'Biomarker Assessments' (exploratory biomarkers and standard tumour biomarkers) were updated as follows: an 'X' was added to Day -4 (baseline assessment) for consistency with text in the protocol body, and the 'X' included under the 'C7, D8' column in error was deleted and correctly added under the 'C8, D1' column. The footnote 'p' was added to standard tumour markers to clarify that they will be analysed from serum samples collected for clinical chemistry. The footnote 'v' only applied to the optional sampling for exploratory biomarkers analysis, and not to the sampling for the standard tumour markers. • Removed row containing background treatment information for Arm B patients. • Revised footnote 'a' to merge the former footnote 'a' and 'c': Screening evaluations to be performed **after the patient has signed and dated the informed consent form and within**~~up to~~ 14 days prior to **randomisation**~~Day -4~~**.** ~~except tumour evaluation, stenting, and histology/cytology, which may be performed up to 28 days before Day 1~~ **Tumour assessment may be performed within 28 days prior to randomisation. Histology/cytology is to be performed/confirmed before randomisation.** • Footnote 'b' (former footnote 'e' moved): ~~Patients in Arm A only~~ **Upon completion of all screening evaluations, eligible patients will be randomised via the Interactive Web Response System.** • Footnote 'c': **A second PCI treatment procedure aimed at the initiation of Cycle 5 or, if patient-related factors demand postponement, at initiation of Cycle 6, 7, or 8 (Section 3.3.2)**. • Footnote 'd': Biliary stenting is to be performed on all patients according to local practice, however, the chosen stent must be of an exchangeable (plastic) type ~~throughout the active treatment period of the study~~ **until radiological progression is declared**. Stenting ~~is to~~ **may** be performed at any time from confirmation of histological/cytological diagnosis until ~~the day of~~ **immediately after the** first laser light application. Patients who have already undergone stenting before screening should be reviewed to ensure the stent is of an acceptable type, correctly positioned and adequate liver drainage confirmed. Stents ~~will~~ **must** be removed ~~before~~ **for the laser light application,** and **a** new ~~plastic stents will be inserted~~ **stent must be placed immediately** after ~~the procedure for Arm A patients.~~ **light application. Stent removal, laser light application, and stent replacement will take place during the same ERCP procedure**. • Footnote 'h' (former footnote 'i'): Vital signs including pulse rate, systolic and diastolic blood pressure (sitting), and temperature. Vital signs will be performed before and after Amphinex administration on Day -4 **and Cycle 4, Day 18**.

Version	Date	Changes
		• Footnote 'i' (former footnote 'j'): Standard 12-lead ECG. Tracings must be interpreted, dated, and signed by the Investigator or his/her designee and filed with the patient's source documents. ~~The ECG will be performed after Amphinex administration on Day -4.~~ **On Day -4 and Cycle 4, Day 18, the ECG will be time matched with PK samples: For PK Group 1, ECG will be performed before, approximately 30 minutes after, and 4 hours after Amphinex administration, and for PK Group 2, ECG will be performed before Amphinex administration.** • Footnote 'k' (former footnote 'l'): If the second PCI treatment is ~~delayed~~**postponed**, unanticipated adverse device effects/adverse incidents recording will be done on the day of administration of ~~delayed~~**postponed** second PCI treatment (laser light application). • Footnote 'l' (former footnote 'm'): Patients ~~in Arm A~~ will be asked about possible skin **and** photosensitivity reactions and their exposure to light during study visits for 3 months following the last Amphinex administration. • Footnote 'm' (former footnote 'n'): Quality of life assessments will be performed at selected time points during treatment and thereafter every 12 weeks**, preferably before any other study assessments are performed**. • Footnote 'n' (former footnote 'o'): Radiographic tumour assessment with diagnostic contrast-enhanced CT or MRI scan and clinical assessment performed every 12 weeks (±1 week) from randomisation until disease progression. Baseline (screening) measurement may be performed within 28 days prior to ~~Day -4~~ **randomisation**. • Footnote 'o' (former footnote 'p'): Clinical chemistry includes sodium, potassium, calcium, magnesium, **phosphate,** chloride, glucose **(fasting)**, creatinine, total bilirubin, gamma-glutamyltransferase, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, C-reactive protein, urea/blood urea nitrogen, total protein, serum amylase, serum lipase and lactate dehydrogenase. Haematology includes haemoglobin, haematocrit, white blood cell count, differentials (absolute), ~~international normalised ratio,~~ and platelet count. Safety blood samples do not need to be repeated on Day -4 prior to Amphinex administration, if the screening evaluation was done 1 day before. Samples taken within 3 days of Day 1 for any chemotherapy cycle do not need to be repeated on Day 1 ~~prior to dosing~~. • Added footnote 'p'**: Standard tumour markers will be analysed from serum samples collected for clinical chemistry.** • Footnote 'q': Urinalysis dipstick for albumin or **total** protein, glucose, bilirubin and blood (microscopy is to be done if there is more than one positive test). • Footnote 'r': A ~~serum~~ creatinine clearance at baseline is required. Creatinine clearance prior to treatment should be ~~>45 mL/min~~ **≥60 mL/min**. Serum creatinine should be checked before each cycle of treatment ~~based on calculation~~. If there is a >25% increase **in serum creatinine** compared to the baseline then the ethylenediamine tetraacetic acid (EDTA) clearance **or equivalent method** must be performed and cisplatin dosing modified accordingly.

Version	Date	Changes
		• Footnote 's': Coagulation tests including INR and APTT should be performed on Day 1 of each 21-day chemotherapy cycle except if patient is receiving warfarin, in which case, assessments should also be done on Day 8 **of each cycle** and Day 15 of ~~each cycle~~**Cycle 1**. Tests do not need to be repeated on Day -4 prior to Amphinex administration, if ~~the pre-treatment evaluation was~~ done 1 day before. • Footnote 't': For women of childbearing potential only. A **highly sensitive** urine or serum pregnancy test is acceptable. • Footnote 'u': **PK** samples will be collected from all patients in Arm A ~~only, please see Table 12 for details of sub-groups and sampling time points~~. **Group 1: the 20 first patients randomised to Arm A; Group 2: all other patients randomised to Arm A. On Day -4 and Cycle 4, Day 18, the PK samples will be time matched with ECG: For PK Group 1, PK sampling will be performed before, approximately 30 minutes after, and 4 hours after Amphinex administration; for PK Group 2, PK sampling will be performed before Amphinex administration.** • Footnote 'v': **Blood**~~Plasma and serum~~ samples (~~each 5 ml~~**20 mL**) **for exploratory biomarkers in plasma** will be collected at baseline and at **approximately** 3-month intervals throughout the study. ~~In addition, in a subset of study sites with facilities and resources for the purpose, sampling for the characterisation of circulating cells (tumour and leukocyte subsets) will be collected and analysed.~~ • Footnote 'w': Laser light application procedure is to be performed 3 hours (±1 hour) after end of gemcitabine administration ~~(Arm A patients only)~~. **It is expected that all patients will be hospitalised for one night after the ERCP/laser light applications on Day 1 of Cycle 1 and Day 1 of Cycle 5.** • Footnote 'y' ('To be recorded as long as the patient has not withdrawn the consent.') was removed.
		Appendix A, Pharmacokinetic Sampling Schedule (Arm A) The separate table of pharmacokinetic sampling schedule for Arm A patients (Table 9 in original protocol) was removed and PK sampling details were incorporated into Table 10, Schedule of Events for the Active Treatment Period-Arm A Patients (see list of changes to Table 10 for details of changes above to PK sampling schedule).
		Appendix B, Table 12, Schedule of Events for the Follow-Up Period The following changes were made to the schedule of events: • Added ECG to be performed at 30 days after the end of the active treatment (end of treatment [Day 30]). • Specified that photosensitivity evaluation will be done for Arm A patients only and will be also performed in follow-up period (every 12 weeks ± 1 week); a new footnote 'e' was inserted: **Patients in Arm A will be asked about possible skin photosensitivity reactions and their exposure to light during study visits for 3 months following the last Amphinex administration**. • Specified timing of quality of life assessments relative to other study assessments. New footnote 'f' was inserted: **Quality of life assessments will be performed at**

Version	Date	Changes
		selected time points during treatment and thereafter every 12 weeks, preferably before any other study assessments are performed. • Row heading 'Exploratory assessments' was changed to 'Exploratory biomarkers'. • Pregnancy testing was added at the end of the active treatment (end of treatment period Day 30) and follow-up period (12 weeks ± 1 week). A new footnote 'g' was inserted: **For women of childbearing potential only. A highly sensitive urine or serum pregnancy test is acceptable**. • Serious adverse event reporting was added to the survival follow-up period for consistency with text in the protocol body and a new footnote 'i' was inserted: **Serious adverse events that occur more than 30 days after the last dose of study treatment do not need to be reported unless the Investigator considers them related to study treatment and/or procedures.** • Due to the insertion of footnote 'e', 'f', 'g', and 'i', numbering of subsequent footnotes was updated. • Footnote 'j' wording was clarified: Survival status will be assessed for all patients (eg, in a telephone call) every 12 weeks, with a window of ±4 weeks after ~~study withdrawal (either after~~ confirmation of disease progression ~~or~~**,** discontinuation for any other reason~~)~~**, or study withdrawal if patient has consented to be followed up,** until death from any cause. • Follow-up fimaporfin pharmacokinetic sampling and time-matched ECGs for Arm A patients only were added to this table at 30 days (±3 days) after last dose of study treatment or chemotherapy and every 12 weeks (±1 week), due to the removal of the separate PK sampling schedule table (Table 12). New footnote 'k' was inserted: **A pharmacokinetic blood sample and corresponding ECG should be taken at the time of the 2 tumour assessments after end of treatment.**
		Section 13.3, Appendix C: RECIST 1.1 Updated the website link for RECIST 1.1: ~~http://recist.eortc.org/wp-content/uploads/2015/03/RECISTGuidelines.pdf~~ https://project.eortc.org/recist/wp-content/uploads/sites/4/2015/03/RECISTGuidelines.pdf
		Appendix D: Health-Related Quality of Life Questionnaires • Swapped the order of subheadings 'EORTC QLQ-BIL21' and 'EORTC QLQ-C30', and questionnaires renumbered starting from EORTC QLQ-C30. • Removed EORTC QLQ-BIL21 question: 'Have you had pain in your shoulder?'
		Section 13.5, Appendix E: Protocol Amendments were added.
Version 3.0 Global Amendment 2	13 Jul 2020	**Title Page, Protocol Approval - Sponsor Signatory** The Chief Medical Officer and Sponsor contact details were updated [redacted] The Medical Monitor details were updated.
		Summary of Changes An overview of rationale for the changes made as a result of Protocol Amendment 2

Version	Date	Changes
		were added.
		List of Abbreviations **DLTs** **dose-limiting toxicities** **EDR** **early discrepancy rate** **LDR** **late discrepancy rate** **NE** **not evaluable** ~~RP2D~~ ~~recommended Phase 2 dose~~ **List of Definitions** **PCI treatment** **In the present protocol, a single PCI treatment consists of IV administration of Amphinex solution for injection (dose 0.25 mg/kg fimaporfin-di-olamine, equivalent to 0.22 mg/kg fimaporfin), followed 4 days later by gemcitabine IV infusion (1000 mg/m^2) and bile duct intraluminal laser light application (light dose 30 J/cm).** **Amphinex®** **Amphinex solution for injection is a sterile solution containing active substance fimaporfin di-olamine; 30 mg/mL (equals 26 mg/mL of fimaporfin), [redacted]** **Fimaporfin** **Active substance (salt form: fimaporfin di-olamine)**
		Section 2.3, Exploratory Objectives 2. To explore changes in standard tumour markers ~~and exploratory biomarkers~~ for the assessment of their diagnostic and prognostic relevance in the disease, and for the treatment itself.
		Section 3.1, Study Design Updated Figure 1 (Overall Study Design) to reflect the changes to the study design.
		Section 3.2, Treatment Assignment Patients will be stratified at randomisation according to whether they have any measurable disease at baseline (as assessed by the Investigator) versus no measurable disease, and according to presence or absence of ~~hepatic~~ metastases. ~~Patients with any measurable disease must have at least 1 measurable lesion (bile duct or liver).~~ It is expected that approximately two-thirds of patients will have measurable disease at baseline.
		Section 3.2.1, Arm A Patients randomised to Arm A will be treated with PCI, integrated into 21-day cycles of ~~standard~~ gemcitabine/cisplatin combination chemotherapy (~~background~~ **SoC** treatment). ~~as follows:~~

Version	Date	Changes
		Patients who have started gemcitabine/cisplatin treatment before the screening period should continue their treatment as scheduled. PCI treatment should be synchronised with the schedule of the ongoing gemcitabine/cisplatin treatment. Study cycles will be counted from enrolment – as for all patients in the study; however, the number of chemotherapy cycles with gemcitabine/cisplatin will be counted from first treatment. For clarification, treatment with gemcitabine/cisplatin cannot exceed 8 treatment cycles. **Treatment schedule as follows:** Cycle 1: Amphinex® (fimaporfin) will be administered on Day -4 (4 days before gemcitabine administration), followed by gemcitabine administration and laser light application on Day 1, and gemcitabine/cisplatin on Day 8. **Note: Cisplatin is omitted from Cycle 1 Day 1 treatment.** '...' Cycle 5: Gemcitabine administration and laser light application will be given on Day 1, and gemcitabine/cisplatin on Day 8. **Note: Cisplatin is omitted from Cycle 5 Day 1 treatment.** '...' Patient-related factors may demand postponement of the second PCI treatment to **a later** ~~C~~**c**ycle ~~6, 7 or 8~~. Please see Section 3.3.2 for more detailed information. ~~It is expected that all~~ ~~p~~**P**atients in Arm A ~~will~~**may** be **admitted for overnight follow-up after** ~~hospitalised for one night after the endoscopic retrograde cholangio-pancreatography (ERCP)/~~laser light application~~s~~ **and related procedures** on Day 1 of Cycle 1 and on Day 1 of Cycle 5. ~~For some patients, 1 to 3 days of hospitalisation after Amphinex administration may be required to ensure adequate initial protection from light. This will be at the Investigator's discretion, as it could depend on factors such as time of year and weather conditions (risk of inadvertent exposure to sunshine or bright daylight) or the patient's disposition and ability to comply with light protection guidance, travel distance, etc.~~
		Section 3.2.2, Arm B Patients randomised to Arm B (control arm) will be administered ~~background~~ **SoC** treatment (~~standard~~ gemcitabine/cisplatin chemotherapy) only, on Days 1 and 8 of each 21-day cycle, for up to 8 cycles. **Patients who have started gemcitabine/cisplatin treatment before the screening period should continue their treatment as scheduled. Cycle 1, Day 1 visit should be synchronised with the schedule of the ongoing gemcitabine/cisplatin treatment. Study cycles will be counted from enrolment – as for all patients in the study; however, the number of chemotherapy cycles with gemcitabine/cisplatin will be counted from first treatment. For clarification, treatment with gemcitabine/cisplatin cannot exceed 8 treatment cycles.**

Version	Date	Changes
		Section 3.3.1, Stent Placement Biliary stenting is to be performed on all patients according to local practice; however, the chosen stent must be of an exchangeable ~~(~~plastic~~)~~ type until radiological progression. Stenting **must be performed at the latest before first study treatment (Arm B) or immediately after the first laser light application (Arm A)** ~~may be performed at any time from confirmation of histological/cytological diagnosis until Cycle 1 Day 1 (immediately after the first laser light application, for patients in Arm A)~~. Patients who have already undergone stenting before screening should be reviewed to ensure the stent is of ~~an acceptable~~ **plastic** type, correctly positioned and adequate liver drainage confirmed**; at least 50% of liver volume, or at least 2 sectors, should be drained**. Stents must be removed for the laser light application, and a new stent must be placed immediately after light application. Stent removal, laser light application, and stent replacement will take place during the same ~~ERCP~~ **one** procedure. ~~At least 50% of liver volume should be drained. Allowing for pathological changes with atrophy of chronically obstructed segments, this effectively means 2 of 3 sectors (ie, either all of the right or left liver lobe and either anterior or posterior sector of right liver lobe). This may require a combination of percutaneous transhepatic biliary drainage and endoscopic drainage but is optimally achieved by endoscopic drainage.~~
		Section 3.3.2, Arm A Patients randomised to Arm A will receive up to 2 PCI treatments, **separated by at least 3 months,** together with up to 8 cycles of gemcitabine/cisplatin combination chemotherapy (Figure 2). '...' This regimen replaces the ~~standard~~ gemcitabine/cisplatin administration of Day 1 in the first chemotherapy cycle. Patients will thereafter receive the remaining treatments as per ~~standard~~ **SoC** gemcitabine/cisplatin combination chemotherapy in Cycle 1 (Day 8) to Cycle 4 with cisplatin at 25 mg/m^2 and gemcitabine at 1000 mg/m^2, administered on Day 1 and Day 8 of each 21-day cycle. '...' A second PCI treatment following the same schedule will be performed at the start of Cycle 5 (Amphinex injection on Cycle 4, Day 18) followed by gemcitabine infusion and intraluminal laser light application on Cycle 5, Day 1. **The second PCI treatment should be separated by at least 3 months from the first PCI treatment.** '...' If delays in the chemotherapy schedule have occurred or the schedule has been altered for any reason; or if a second PCI treatment in Cycle 5 is deemed medically inappropriate, temporarily unsafe, presents with an increased risk related to the endoscopy or PCI treatment; or if the patient strongly prefers its postponement for other reasons**, or the patient has had chemotherapy before enrolment**, the second PCI can be conducted in any of **the later c**~~C~~ycles ~~6 to 8~~ at the discretion of the treating physician. However, the general goal should be to schedule the second PCI treatment at the start of Cycle 5 and avoid postponements unless an event or cause as outlined above is present to justify it. The second PCI treatment may be postponed if: • In the opinion of the Investigator, the single dose of gemcitabine cannot be given at the full 1000 mg/m^2 dose due to residual toxicity • **The Investigator determines that the patient will not tolerate a second PCI treatment at the scheduled time based on the patient's poor tolerability of the first PCI treatment**

Version	Date	Changes
		• '...' • **Total bilirubin >2.5 × ULN** In contrast to postponing the second PCI, this treatment will not be given at all if any of the following criteria are fulfilled: • The patient experienced a PCI treatment-related schedule-limiting toxicity (SLT) defined as: o A clinically significant toxicity or abnormal laboratory value occurring after PCI treatment and during the first chemotherapy cycle, assessed as unrelated to the underlying disease, or concomitant medications, **where there is a reasonable possibility** that **it** is related to either PCI treatment or ~~related~~ to the combination of PCI treatment with the cisplatin/gemcitabine systemic chemotherapy and meets any of the following criteria, based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0: '...' In patients ~~still in the~~**on** study **treatment**~~(ie, not formally discontinued or withdrawn)~~, the reason(s) for delays, postponement, or omitting of the second PCI must be adequately documented and recorded in the electronic case report form (eCRF). Patients should continue their randomised chemotherapy treatment until a maximum of 8 ~~systemic~~ gemcitabine/cisplatin cycles ~~or RECIST 1.1 defined progression~~ or until a treatment discontinuation criterion is met.
		Section 3.3.3, Arm B Patients randomised to Arm B (control arm) will receive ~~background~~ **SoC** treatment only, ~~with SoC~~ ~~systemic~~ gemcitabine/cisplatin combination chemotherapy for nonresectable or metastatic CCA as follows: '...' Patients should continue their randomised chemotherapy treatment until a maximum of 8 ~~systemic~~ gemcitabine/cisplatin cycles ~~or RECIST 1.1 defined progression~~ or until a treatment discontinuation criterion is met.
		Section 3.4.2, Rationale for Study Endpoints **The authors discussed that a PFS HR<0.7 observed in a randomised clinical trial of advanced biliary tract cancer treatment with a superiority design could translate to a 20% improvement in OS.**
		[redacted]

Version	Date	Changes
		[redacted]
		Section 3.4.4, Rational for Dose In terms of safety, Amphinex has been well tolerated in doses up to the maximum tolerated dose of 0.87 mg/kg as established in the Phase 1 study PCI 101/06 and as

Version	Date	Changes
		shown by the absence of dose-limiting toxicities in the Phase 1 dose escalation **part** of the ~~ongoing~~ study PCIA 202/12 in CCA. Overall, Amphinex shows a suitable safety and tolerability profile for the treatment of advanced CCA. [redacted]
		Section 3.4.5, Rational for Treatment Regimen ~~During~~ **In** the extended part of Phase 1 in study PCIA 202/12, the 2-administration schedule ~~will~~ **was to** be considered non-tolerated if 2 or more of the first 6 evaluable

Version	Date	Changes
		patients experience**d** an SLT. If none or 1 of the first 6 evaluable patients experience**d** an SLT (see definition in Section 3.3.2), the 2-administration schedule ~~will~~**was to** be considered tolerated. A total of 5 patients underwent the 2 PCI treatment procedures and completed the required 21-day safety window following the second procedure as per protocol. All SLT criteria were assessed and ~~it was concluded that~~ no SLTs were reported in these 5 eligible patients ~~who completed both PCI procedures~~. The CRC concluded that the procedure was tolerable based on the fact that no SLTs were observed in the 5 eligible patients. Therefore, the 2-administration schedule can be considered tolerated. '...' [redacted]
		[redacted]
		Section 4.1.1, Inclusion Criteria 3. Cholangiocarcinoma verified as adenocarcinoma by histopathology or cytology ~~(C5)~~ with a perihilar or distal stenosis that has been stented or will require stenting, and that is accessible for PCI light treatment; 6. If metastatic disease, metastasis must be limited **to tissues other than bone or the central nervous system**~~to the liver parenchyma and/or local lymph nodes (within~~

Version	Date	Changes
		~~close proximity to the hepatoduodenal ligament)~~;
		7. Adequate biliary drainage (~~either~~ at least 50% of the liver volume, or at least 2 sectors), with no evidence of active uncontrolled infection (patients on antibiotics are eligible);
		Section 4.1.2, Exclusion Criteria
		1. Previously received any anti-tumour (either local or systemic) treatment for CCA**, except for previous treatment of up to 2 cycles of gemcitabine/cisplatin**;
		3. A history of frequently recurring septic biliary events ~~caused by non-malignant strictures (primary sclerosing cholangitis [PSC], autoimmune hepatitis or advanced chronic liver dysfunction);~~
		5. A~~n active~~ second primary cancer~~, defined as one~~ with a disease-free interval of <5 years ~~before screening~~. **A second primary cancer that has been treated with intent to cure may be allowed after consultation with the study Medical Monitor.**~~, with the exception of a~~**A**dequately treated basal cell carcinoma, squamous cell carcinoma or other non-melanomatous skin cancer, in situ carcinoma of the uterine cervix, or prostate cancer that is controlled by hormone therapy (patients may continue hormone therapy while on study) **are allowed**;
		10. Clinically significant and uncontrolled cardiac disease including unstable angina, acute myocardial infarction within 6 months prior to baseline, congestive heart failure, and arrhythmia requiring therapy, ~~with the~~ except~~ion~~ **for**~~of~~ extra systoles or minor conduction abnormalities and controlled and well treated chronic atrial fibrillation;
		~~16. Significant hearing impairment;~~
		~~19.~~**18**. Male patients unwilling to use highly effective contraception, or women of childbearing potential (WOCBP) (see definition in Section 5.6) unwilling to use a highly effective form of contraception such as the following:
		o Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[2] (oral, intravaginal and transdermal)
		o Progestogen-only hormonal contraception associated with inhibition of ovulation[2] (oral, injectable, or implantable)
		o Intrauterine devices
		o Intrauterine hormone-releasing system
		o Bilateral tubal ligation
		~~[2] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.~~
		~~22.~~**21**. Inadequate liver function despite satisfactory ~~endoscopic or percutaneous~~ biliary ~~tree stenting~~**drainage**, defined as:
		o Serum (total) bilirubin persisting at >~~2.~~5 × the ULN for the institution
		o AST or ALT >3.0 × ULN (>5 × ULN if liver metastases are present)
		o ALP levels >5.0 × ULN;
		Section 4.2.1, Discontinuation From Study Treatment
		Study treatment will continue until a maximum of 8 gemcitabine/cisplatin chemotherapy cycles or ~~objective disease progression or other~~ criteria for discontinuation **of treatment** are met. A study patient is ~~at any time~~ free to discontinue study treatment prematurely **at any time**~~, without prejudice to further treatment~~. If so, the patient shall always be asked

Version	Date	Changes
		about the reason(s) for **treatment** discontinuation, and the presence of SAEs and AEs. If AEs are ongoing, these will be followed up as detailed in the study plan. ~~In addition, a~~**A** patient may ~~be~~ discontinue~~d from~~ study treatment in any of the following situations: '...'
		Section 4.2.2, Withdrawal From Study In case of death, ~~a~~**the** randomised patient will be considered withdrawn from the study. '...' Patients who choose to withdraw from the study **shall always be asked about the reason(s) for withdrawal from study. Patients** should always be asked specifically whether they ~~would still allow~~**consent to be** contact**ed** for determination of survival follow-up. If patients who withdraw do not consent to survival follow-up, no further study procedures or follow up assessments will be performed following withdrawal, and no further data will be collected through patient interactions. For patients whose reason for withdrawal is not death, **if permitted,** determination of survival may be collected through publicly available death registry information~~, where permitted locally~~.
		Section 4.2.3, Handling of Discontinuations/Withdrawals Patients who discontinue study treatment or active participation in the study will no longer receive study treatment from the Sponsor. When a patient withdraws from the study treatment or active participation in the study, the reason(s) for withdrawal shall be recorded by the Investigator on the relevant page of the eCRF. ~~Whenever possible, all~~ **P**~~p~~atients who discontinue study treatment prematurely will continue to be followed for ~~objective~~ **radiological** progression and survival. Patients who fail to return for final assessments will be contacted by the site (eg, 2 documented phone calls followed by 1 registered letter) in an attempt to have them comply with the protocol. **To achieve the goals of the study and maintain patient safety, i**~~I~~t is vital to obtain follow-up data on any patient withdrawn **from the study** ~~because of an AE or SAE~~. In every case, efforts must be made to undertake protocol-specified, safety, follow-up procedures.
		Section 4.2.3, Replacements Randomised patients who discontinue treatment or withdraw from the study will not be replaced. If a randomised patient is withdrawn, the patient identifier number will not be reused. ~~All randomised patients must be included in the primary analysis under the principles of ITT and therefore collection of follow-up data for patients who discontinue is important.~~
		Section 5.1, Method of Assigning Patients to Treatment Arms Upon completion of all screening evaluations to confirm eligibility to participate in the study, eligible patients will be randomised via the Interactive Web Response System (IWRS). The randomisation will be stratified by 2 factors: any measurable disease at baseline (yes versus no) and presence or absence of ~~hepatic~~ metastases.
		Section 5.2, Identity of Investigational Products/~~Background~~ Standard of Care Treatment A single PCI treatment consists of IV administration of Amphinex solution for injection (dose 0.25 mg/kg fimaporfin-di-olamine, equivalent to 0.22 mg/kg fimaporfin), followed 4 days later by gemcitabine IV infusion (1000 mg/m^2) and **bile duct** intraluminal laser

Version	Date	Changes
		light application (light dose 30 J/cm). Gemcitabine is currently not licensed for the treatment of patients with advanced inoperable CCA**, but it is part of the current recognised SoC therapy**.
		Section 5.2.1.1, Fimaporfin-Associated Photosensitivity All patients who receive Amphinex (fimaporfin) are expected to become temporarily photosensitive and must take precautions to protect **the** skin and **the** eyes in order to prevent photosensitivity reactions. **Data from clinical studies (studies PCI 101-06, PCIA 202-10 and PCIA 202-12) showed that all photosensitivity-related AEs were mild or moderate.** [redacted] **Based on non-clinical data (Gederaas et al 2017) it is expected that fimaporfin photoactivation properties are diminished upon exposure to light ("bleaching" effect) and therefore a~~A~~** gradual return to normal light conditions is ~~required~~**recommended to shorten the time of light sensitivity.** '...' • ~~Operators and persons assisting during the treatment must wear glasses protecting against the laser emission wavelength 652 nm (green glasses).~~ Patients must wear glasses that protect against laser emission wavelength, and all wavelength that activates fimaporfin, ie, ultravisible and visible light (dark glasses). The ~~laser and~~ eyewear will be provided by the Sponsor. '...' ~~For at least 4 weeks~~ **F**~~f~~ollowing Amphinex injection, precautions ~~must~~ **should** be taken **for at least 4 weeks** to avoid exposure of skin and eyes to direct sunlight or bright indoor light. *In Table 1, the following changes were made:* Day 2-7: '...' The type of clothes **and accessories** the patient must wear are: • Wide-brimmed hat: for head, neck, face, nose and ears • Scarf: for head and neck • Dark glasses with side panels: for eyes and skin around eyes • Long sleeved top: for upper body/arms • Long trousers: for lower body/legs • Gloves: for hands, wrist and fingers • Socks: for feet and ankles • Closed shoes: for feet • **An umbrella/parasol can give additional protection** Skin photosensitivity reactions are caused by visible light. Sunscreens that protect from ultraviolet light will not protect from visible light. Dark, tightly woven clothing should be worn. Very thin clothing will not protect from strong light. If exposed to excessive bright light, the patient may feel a burning sensation on the skin. The patient must move away from the light source ~~immediately~~. If a photosensitivity reaction develops, contact the Clinical Investigator for advice (see below). Day 8-15: '...' If exposed to excessive bright light, the patient may feel a burning sensation on the skin. The patient must move away from the light source ~~immediately~~. If a photosensitivity

Version	Date	Changes
		reaction develops, contact the Clinical Investigator for advice (see below).
		Section 5.2.5, Light Source Laser light is used to activate fimaporfin. The light source used in this study will be supplied by ~~PCI Biotech~~**the Sponsor** and is a CE marked medical laser system, emitting red light at 652 nm. [redacted]
		Section 5.2.6.2, Dose Modifications for Systemic Chemotherapy Cycles Renal toxicity: The creatinine clearance must be ≥ 60 mL/min in order to administer the full dose of cisplatin. Serum creatinine should be checked before each cycle of treatment. If there is a >25% increase of serum creatinine compared to the baseline, then the ethylenediamine tetraacetic acid (EDTA) clearance (or equivalent**, including estimation of GFR, according to local practice**) must be performed.
		Section 5.5.1, Permitted Treatments Patients will be allowed to receive supportive care therapies (including cytokine growth factors) concomitantly during the study. Other than the chemotherapy given during the course of the study, the use of any other chemotherapy, immunotherapy, radiation therapy, or experimental medications is prohibited during the study **treatment period**. Patients with prostate cancer that is controlled by hormone therapy may continue that therapy while on study. Disease progression requiring other specific anti-tumour therapy will be cause for discontinuation from the study treatment. '...' Any prior, concurrent, or procedural medications or therapy given to or taken by the patient will be recorded in the eCRF along with the indication for its use. All concomitant medication **taken from the time that the informed consent form (ICF) is signed, until 30 days after end of treatment, will be recorded in the eCRF. The date of first administration and reason for use will be recorded in the eCRF. Major changes in dose, schedule, or reason for use will also be recorded in the eCRF.**~~should be recorded for up to 4 weeks following the last protocol treatment.~~ '...' ~~All concomitant medication taken during the study, from the time that the informed consent form (ICF) is signed, until 30 days following the last dose of chemotherapy, will be recorded in the eCRF. The date of first administration and reason for use will be recorded in the eCRF. Major changes in dose, schedule, or reason for use will also be recorded in the eCRF.~~
		Section 5.5.2, Prohibited Therapies The following therapies are prohibited during the ~~course of the~~ study **treatment period**: • **Phenytoin** • **Anti-cancer treatment other than the study treatments. Hormone therapy**

Version	Date	Changes
		for prostate cancer that started before randomisation is allowed to continue during the study. • **Any experimental treatment other than PCI treatment.**
		Section 5.6, Contraception Only men with pregnant or non-pregnant partners considered of childbearing potential will need to follow contraception requirements. A condom is also required to be used by vasectomised men to prevent delivery of the drug via seminal fluid. As the treatment includes genotoxic investigational medicinal products, the male patient should use condoms during treatment and until the end of relevant systemic exposure in the male patient (at least 9 months after last dose of Amphinex or 6 months after last dose of chemotherapy, whichever is the latest)~~, plus a further 90 days~~.
		Section 6.1.1, Tumour Assessments The study will evaluate tumour responses as determined by Investigator according to RECIST 1.1. ~~Efficacy assessments of PFS, ORR, DoR, and DCR will be derived using Investigator RECIST 1.1 assessments.~~ **The primary PFS analysis will be based on the local radiological assessment, which will be used to guide clinical management decisions.** Note: ~~i~~**I**n cases of symptomatic progression, patients will continue to be followed for radiological RECIST progression. '...' The local radiological assessment will be used to guide clinical management decisions **and will be the basis for**~~. T~~**t**he primary analysis of PFS an~~d the secondary RECIST 1.1 based endpoints will also be based on the local radiological assessment~~. In addition, a~~n~~ **blinded** independent central radiological review **(BICR)**, blinded to the assessment of the local radiologist and/or oncologist, will be performed for the tumour response data. The data from the ~~independent central reviewer(s)~~ **BICR** will provide data for ~~the~~**a** supportive analysis **of PFS**. **For the interim analysis of ORR, the assessment made by the BICR will be considered the primary analysis.** '...' Additional survival contacts (ie, outside of the 12 weekly calls) may be conducted around the time of interim ORR analysis and ~~final~~ PFS analysis at data cut-off to ensure that the survival information is as up to date as possible for the analysis of OS. Determination of survival may be collected through publicly available death registry information, where permitted locally. *<Other minor administrative updates were made.>*
		Section 6.2, Pharmacokinetic Assessments [redacted]
		Section 6.3, Standard Tumour Markers ~~and Exploratory Biomarkers~~ **~~Section 6.3.1 Standard Tumour Markers~~** **~~6.3.2 Exploratory Biomarkers~~** ~~Blood samples (20 mL) for exploratory biomarkers in plasma will be collected at baseline and at approximately 3-month intervals throughout the study. Samples will be banked for a collective post hoc analysis, enabling an evaluation of the relative~~

Version	Date	Changes
		~~importance and covariance of various biochemical changes to treatment outcome in the 2 study arms. As described in Section 6.3.1, traditional tumour diagnostic markers may exhibit low sensitivity and there is an urgent need for novel, more sensitive, and easy to detect biomarkers which can be used in cancer diagnosis and prognosis. For example, cell free nucleic acids such as microRNA (a type of small non-coding RNA molecule) may have a potential application as specific and sensitive biomarkers for clinical diagnosis or prognosis. As the study is well-sized in consideration of this rare cancer population, an exploratory assessment of changes in known and novel biomarkers over time, and with treatment, is highly motivated.~~
		Section 6.4.1.4, Reporting Adverse Events Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST 1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression ~~through the use of objective criteria~~**radiologically**. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.
		Section 6.4.3.1, Safety Laboratory Analyses a Serum creatinine should be checked before each cycle of treatment. If there is a >25% increase compared to the baseline, then the ethylenediamine tetraacetic acid (EDTA) clearance or equivalent method**, including estimation of GFR, according to local practice,** must be performed and cisplatin dosing modified accordingly. *Analysis of exploratory biomarkers in plasma was removed from Table 7 and the total blood volume updated for each arm.*
		Section 6.4.6, Electrocardiograms After paper ECGs have been recorded, the Investigator or designated physician will review each of the ECGs and may refer to a local Cardiologist if appropriate. A signed and dated ~~paper~~ copy, with relevant results noted by the Investigator, should be filed in the patient's medical records. If an abnormal ECG finding at screening is considered to be clinically significant by the Investigator, it should be reported as a concurrent condition. For all ECGs, details of rhythm, PR, R-R, QRS and QT intervals and an overall evaluation will be recorded. Corrected QT intervals will be calculated using Bazett's formula (QTcB) and Fridericia's formula (QTcF). The ECG on Day -4 and on Cycle 4, Day 18 must be performed before and **approximately** 30 minutes and 4 hours after Amphinex administration.
		Section 6.4.7, Photosensitivity ~~Measurements~~ and Skin Reactions **In both study arms, skin reactions and photosensitivity reactions will be documented as AEs in the eCRF and coded using MedDRA and followed to adequate resolution.**~~Patients in Arm A who receive Amphinex will be photosensitive and must observe precautions to avoid exposure of skin and eyes to prevent photosensitivity reactions (Table 1) according to the instructions in the patient guidance document. The written instructions must be reviewed and explained verbally to each patient and allow for questions and answers to ensure proper understanding of the instructions. Photosensitivity reactions will be documented and coded (using MedDRA) as AEs and followed to adequate resolution.~~

Version	Date	Changes
		~~For patients in both treatment arms, skin reactions will be documented and recorded in the eCRF.~~
		Section 6.4.9, Physical Examinations A complete physical examination with weight ~~and body surface area~~, will be performed. Height will be recorded at screening only. **Body surface area will be calculated.**
		Section 7.2.2, Best Overall Response The BOR is the best response recorded from the start of the treatment until disease progression/recurrence ~~(using the smallest measurements recorded since the treatment started as reference for progressive disease)~~.
		Section 7.2.3, Objective Response Rate The ORR is calculated as the proportion of patients ~~with measurable disease at baseline~~ who have at least one visit response with a CR or PR noted.
		Section 7.2.4, Duration of Response The DoR is defined as the time from the first documented tumour response until ~~the first documented~~**radiological** disease progression, or death in the absence of disease progression.
		Section 7.2.9, Quality of Life Assessments An evaluation and comparison of HRQoL/PRO associated with the fimaporfin-induced PCI of gemcitabine complemented by ~~systemic~~ gemcitabine/cisplatin chemotherapy versus gemcitabine/cisplatin alone, will be conducted by use of EORTC QLQ-30 and QLQ-BIL21.
		Section 7.3, Exploratory Endpoints The following exploratory endpoints will be evaluated in this study: • Tumour response (ORR, DCR, and PFS) by location of disease, as pre-defined further in the SAP, including: o Loco-regional tumour control o Metastatic lesions ~~within the liver parenchyma~~ o ~~Other metastatic lesions~~**Local lymph nodes** • To analyse blood samples for standard tumour markers ~~and exploratory biomarkers~~.
		Section 7.4, Sample Size Calculations Approximately 186 patients with inoperable CCA will be randomised in a 1:1 ratio (fimaporfin-induced PCI of gemcitabine complemented by gemcitabine/cisplatin chemotherapy versus gemcitabine/cisplatin chemotherapy alone) to this study. The primary ~~(final)~~ analysis of PFS, as assessed by local radiological review, will be conducted when approximately 129 progression events (69% maturity) have been observed. If the PFS result is statistically significant at the ~~4~~**3.95**% ~~(~~2-sided~~)~~ alpha level **(adjusted for interim analysis of ORR)**, ~~ORR will be compared between the arms and~~ an interim analysis of OS will then be assessed, as detailed in Section 7.7.7. If the true HR for the comparison of fimaporfin-induced PCI of gemcitabine complemented by gemcitabine/cisplatin chemotherapy versus gemcitabine/cisplatin chemotherapy alone is 0.6, 129 progression events will provide approximately 80% power to demonstrate a statistically significant difference in PFS at a ~~4~~**3.95**% 2-sided significance level (this may translate to an improvement in median PFS from 7.4 to 12.3

Version	Date	Changes
		months, if PFS is exponentially distributed). A minimum or critical HR of 0.**69**~~7~~ (eg, 7.4 to 10.**7**~~6~~ months), if observed, would give a 2-sided p<0.0**3954**, but there is only 50% power associated with the critical HR. '...' In addition to the interim analysis of OS at the time of the ~~final~~ PFS analysis (approximately 58% of patients are predicted to have died at this point), data collection for OS will continue beyond the ~~final~~ PFS analysis and an updated OS analysis will be performed. The final OS analysis will occur after approximately 147 death events have been observed in 186 patients (>75% maturity). Assuming a true OS HR of 0.63, there will be 80% power to detect an improvement in median OS from 11.7 to 18.7 months with 2-sided p<0.04**47**~~6~~ (O'Brien and Fleming boundary **adjusted for 2 interim analyses of** ~~based on interim~~ OS ~~at approximately 103 events~~). A minimum or critical HR of 0.72 (eg, 11.7 to 16.3 months), if observed, would be statistically significant. The exact level of maturity will be determined based on the ~~final~~ PFS and interim OS results, in discussion with the regulatory authorities. The 147 death events are expected to occur at approximately ~~65~~**63** to ~~68~~**66** months from first patient randomised.
		Section 7.5, Analysis Sets The following analysis sets will be used in the statistical analyses. '...' • ~~The Evaluable for Response analysis set is a subset of the ITT analysis set that includes all randomised patients who have measurable disease at study entry. The Evaluable for Response analysis set will be used for summaries of ORR, DoR, and change in tumour size.~~
		Section 7.6, Description of Subgroups to be Analysed Subgroup analyses will be performed for the stratification factors used at the point of randomisation (measurable disease – yes versus no and presence or absence of ~~hepatic~~ metastases). Exploratory subgroup analyses will also be performed to assess key endpoints by loco regional tumour control, metastatic lesions **and local lymph nodes**~~within the liver parenchyma, and other metastatic lesions~~. Four distinct groups will be explored: primary; primary with ~~liver~~ metastases; primary with local lymph nodes; and primary with ~~liver~~ metastases and local lymph nodes. An additional subgroup analysis will be performed to compare patients with and without PSC at study entry. If there are too few events available for a meaningful analysis of a particular subgroup ~~(it is not considered appropriate to present analyses where there are less than 20 events per level in a subgroup)~~, the relationship between that subgroup and PFS/OS will not be assessed. In this case, only descriptive summaries will be provided. Further details and any other exploratory subgroups of interest will be provided in the SAP.
		Section 7.7.1, Analysis of Primary Endpoint Progression-free survival, as assessed by local radiological review, will be analysed using a log rank test stratified by any measurable disease at baseline (yes versus no), and presence or absence of ~~hepatic~~ metastases. If these 2 stratification factors lead to low numbers (eg, <**5**~~10~~ progression events) within a single stratum, **data will be pooled across strata in the stratified analyses** ~~one or more stratification factors may be removed from the statistical analysis~~. The criteria for ~~removal~~ **pooling** will be pre-defined in the SAP. The HR will be estimated using a stratified Cox proportional hazards model using the Efron approach for handling ties (Efron 1977), together with the associated ~~profile likelihood~~ 95% CI for the HR **based on the Wald method**. '...'

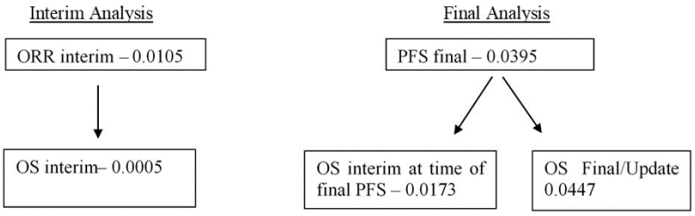
Version	Date	Changes
		A Kaplan-Meier (KM) plot of PFS will be presented by treatment group. Median PFS with 95% CIs will be presented. In addition, KM landmark PFS estimates at 6 months and 12 months with corresponding CIs will also be presented using KM methodology. KM estimates may be presented for other timepoints of interest. The assumption of proportionality will be assessed. In the event of non-proportionality, the HR will be interpreted as an average HR over the observed extent of follow-up. ~~Proportionality will be tested firstly by examining the plots of complementary log-log (event times) versus log (time) and, if necessary, a time dependent covariate will be fitted to assess the extent to which this represents random variation.~~
		Section 7.7.2.1, Overall Survival Data collection for OS will continue beyond the ~~final~~ PFS analysis and an updated OS analysis will be performed.
		Section 7.7.2.2, Best Overall Response ~~Summaries of BOR will also be repeated using the BICR data. Furthermore, two-by-two tables will be produced to describe the consistency between the BICR and local evaluation assessment for BOR (and also the timing of PD to show how often the investigator declares PD at the same time, before or after the BICR).~~
		Section 7.7.2.3, Objective Response Rate The ORR will be summarised using the ~~Evaluable for Response~~**ITT** analysis set (ie, all randomised patients ~~who have measurable disease at study entry~~). ORR will be compared between treatment arms using a **Cochran-Mantel-Haenszel (CMH) test stratified by presence of any measurable disease at baseline (yes versus no), and presence/absence of metastases at baseline (1 or 0)**. ~~logistic regression model with the covariate (stratification factor) of hepatic metastases. However, if there are <10 patients within a stratum, this stratification factor will be removed from the statistical analysis.~~ **In addition to presenting the ORR and associated exact 95% CI for each treatment arm, the treatment effect will be described using the CMH estimate of the common odds ratio together with its associated 95% CI (Emerson 1994).** **As sensitivity analyses, the ORR will be further summarised by measurable/non-measurable disease at entry (as integrated directly from the IVRS to the eCRF) and compared between the arms using the CMH test stratified by presence/absence of metastases at baseline (1 or 0). The ORR analyses will also be repeated using the mITT analysis set.** ~~The results of the analysis will be presented in terms of an odds ratio together with its associated 95% profile likelihood CI. The p-value will be based on a test statistic that is calculated as twice the change in log-likelihood resulting from the addition of a treatment factor to a model that contains the covariates defined above. The test statistics is chi-squared distributed with 1 degree of freedom.~~
		Section 7.7.2.4, Duration of Response **The DoR is calculated only for those with a documented response of CR or PR and is defined as the time from the date of first documented tumour response until the first date of radiological disease progression or death, whichever is earlier.** If a patient does not progress following a response, then their DoR will be censored at the PFS censoring time. The DoR will not be defined for those patients who do not have documented responses. **The DoR will be summarised for the ITT analysis set.** ~~The DoR will be summarised using the Evaluable for Response analysis set (ie, all~~

Version	Date	Changes
		~~randomised patients who have measurable disease at study entry).~~
		Section 7.7.2.6, Change in Tumour Size The change in tumour size will be summarised for **patients with measurable disease at study entry**~~the Evaluable for Response analysis set~~. Summaries and waterfall plots indicating best percentage change from baseline in the sum of the diameters of target lesions will be produced. Bars will be differentially shaded by RECIST 1.1 response.

		Section 7.7.2.7, Blinded Independent Central Review
		For each patient, the BICR will define the overall visit response (ie, the response obtained overall at each visit by independently assessing target lesions, non-target lesions and new lesion data). If a patient has had a tumour assessment that cannot be evaluated then the patient will be assigned a visit response of NE (unless there is evidence of progression in which case the response will be assigned as PD; for example, if the target lesions are NE but there is evidence of a new lesion).
		A BICR will be performed for the interim analysis of ORR (primary data), which will cover all scans up to the data cut-off for the interim analysis, and for the final database lock for PFS, which will cover all of the scans up to the data cut-off (supportive data).
		Endpoints (ORR, BOR, PFS, and DoR) will be derived programmatically using the visit responses provided by the BICR. Results of this independent review will not be communicated to Investigators and the management of patients will be based solely upon the results of the RECIST 1.1 assessment conducted by the Investigator.
		Cross-tabulations will be produced to describe the consistency between the BICR and local Investigator assessment for the following:
		• **Best overall response**
		• **Timing of PD**
		  ○ **Early discrepancy rate (EDR): the frequency at which the local review declares progression early relative to the BICR in each arm as a proportion of the total number of locally assessed progressions; and**
		  ○ **Late discrepancy rate (LDR): the frequency at which the local review declares progression later than the BICR in each arm as a proportion of the total discrepancies in each arm.**
		The EDR and LDR will be calculated for each treatment arm and the differential discordance will be summarised as the rate on the experimental arm minus the rate on the control arm. If the discrepancies are similar between the arms, this suggests an absence of evaluation bias that favours one arm. A negative differential discordance for the EDR and/or positive differential discordance for the LDR may be indicative of bias in the local evaluation favouring the experimental arm (Amit et al 2011).
		Analyses of PFS by BICR will be described in the SAP.

		Section 7.7.7, Interim Analyses A formal interim analysis of ORR will be performed after approximately 120 patients (65%) have been randomised and followed to their first 12-week follow-up scan **(estimated to be at approximately 39 months from first patient dosed)**. ~~Based on an assumption that ~ 80 patients will have measurable disease, t~~There will be >80% power

Version	Date	Changes
		to detect an improvement in ORR from ~~20~~**15**% to ~~57~~**45**% with 2-sided p<0.01**05** (~~approximates an~~ O'Brien and Fleming boundary based on 65% information). A~~n~~ **minimum** improvement from ~~20~~**15**% to ~~47~~**38**% will be statistically significant, if observed. If the comparison of the interim ORR data between the arms b**ased on a CMH test** is statistically significant, **OS data will be formally compared between the arms and** ~~it will be~~ summarised ~~together with PFS and DoR~~ to support a conditional marketing authorisation application. **PFS and DoR will be summarised descriptively with no formal comparison of PFS**~~Survival data will be limited at this point and will be summarised descriptively.~~ **Three analyses of OS will be performed: at the time of the interim ORR analysis, at the time of the PFS assessment and at an updated (final) analysis.**~~An interim analysis of OS will be performed at the time of the final PFS assessment when approximately 103 patients are predicted to have died. A 2-sided p<0.015 will be required to demonstrate statistical significance.~~
		Section 7.7.7.1, Multiplicity and Control of Type 1 Error **The multiple testing procedure will strongly control the Type I error probability (alpha) at 5% (2-sided) amongst the key efficacy endpoints (PFS, ORR, OS). Strong control of alpha ensures that the probability of rejecting any (ie, one or more) true null hypothesis, in either direction, is at most 5%, irrespective of how many and which null hypotheses are true or false** **At the interim and final analysis points, the key endpoints will be tested in a hierarchical order as shown in Figure 4. If any previous analysis in the sequence is not statistically significant, the alpha cannot be transferred to subsequent endpoints. Note: A non-statistically significant ORR result at the interim analysis will not preclude testing of PFS at the final analysis.** **An interim analysis of ORR will be conducted after 120 out of 186 patients have been randomised (65% information) and 1.05% of alpha will be spent on the comparison of ORR, based on an O'Brien and Fleming spending function.** **In the case both null hypotheses are true (ie, there is no true difference between the arms, neither for ORR nor for PFS) and assuming independence between these 2 endpoints, the final significance level for PFS can be set at 3.95%.** **In the event that the null hypotheses for both ORR and PFS are false, alpha needs to be controlled at 5% over the 3 planned OS analyses; for example, assuming 55 death events (37% information) at the first analysis, 108 death events (73% information) at the second analysis and 147 death events (100% information) at the final OS analysis, the significance levels according to a Lan and De Mets O'Brien and Fleming spending function (Lan and de Mets 1983) will be 0.05%, 1.73% and 4.47%, respectively.** **The exact significance levels will be adjusted for the actual information fractions.** ~~In order to provide strong control of the type I error rate at the 2-sided 5% level, the primary endpoint of PFS and key secondary endpoints of ORR and OS will be tested in this sequential (hierarchical) order at the time of the primary analysis. If any previous analysis in the sequence is not statistically significant, the alpha cannot be transferred to subsequent endpoints (ie, the multiple testing procedure will recycle the test mass to the endpoint not yet rejected in the hierarchy outlined in Figure 4).~~ ~~The interim analysis of ORR will be conducted after approximately 120 out of 186 patients have been randomised. Assuming 65% information at the interim, statistical~~

Version	Date	Changes
		~~significance will be declared for ORR if 2-sided p<0.01, which approximates an O'Brien and Fleming spending function.~~ ~~The remaining 2-sided alpha of 4% will be spent at the final PFS analysis, which will be triggered after approximately 129 progression events. Note, a non statistically significant ORR result at the interim analysis will not preclude testing of PFS at the final analysis.~~ ~~If the final PFS is statistically significant at 2-sided p<0.04, the alpha will be recycled to ORR. If both are significant, an interim analysis of OS at the full 5% alpha will be performed. Statistical alpha will be shared across the interim and final assessments of OS using the Lan DeMets approach. Assuming 70% information (number of events at interim / number of events at final analysis) at the interim, statistical significance will be declared for interim OS if 2-sided p<0.015, based on an O'Brien and Fleming spending function. The exact significance levels will be adjusted for the actual information fractions.~~ *Figure 4 was updated:*  Abbreviations: ORR, objective response rate; OS, overall survival; PFS, progression-free survival. ~~*O'Brien and Fleming boundary based on 5% alpha and approximately 70% information at interim (assumes 103/147 deaths at interim)~~
		Section 8.1, Data Management Clinical data management will be performed in accordance with applicable ~~PCI Biotech~~ [redacted] standards and data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data.
		Section 11.2.2, Protocol Deviations Significant protocol deviations for this study may include 1) use of prohibited concomitant medications during the study **treatment period**, 2) tumour assessments (RECIST) for screening not performed within 28 days prior to randomisation, 3) patients who received the wrong treatment, etc.
		Section 12, Reference List The following 4 references were added: **Amit O, Mannino F, Stone AM, et al. Blinded independent central review of progression in cancer clinical trials: results from a meta-analysis. Eur J Cancer. 2011;47(12):1772-8.** **Emerson JD. Combining estimates of the odds ratio: the state of the art. Stat Methods Med Res. 1994;3(2):157-78.** **Gederaas OA, Johnsson A, Berg K, et al. Photochemical internalization in bladder cancer – development of an orthotopic in vivo model. Photochem Photobiol Sci. 2017;16(11):1664 76.** **Lan KKG and DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983;70(3):659–63.** National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology:

Version	Date	Changes
		Hepatobiliary Cancers. Version 4. 2020 – ~~August~~ **June 19 1,** 202**0**~~19~~**.**
		Appendix A, Table 10 The following changes were made to the schedule of events: • Removed the rows for biomarker assessments and exploratory biomarkers. • "Background" was replaced with "SoC". • A new footnote "a" was added: **Patients who have started gemcitabine/cisplatin treatment before the screening period should continue their treatment as scheduled, including during the screening period. Study visits should be synchronised with ongoing SoC chemotherapy. Study cycles will be counted for all patients from first treatment after enrolment (PCI treatment No. 1). Chemotherapy cycles will be counted from first chemotherapy treatment and cannot exceed 8 cycles.** • Footnote "b": Screening evaluations are to be performed after the patient has signed and dated the informed consent form and within **21**~~1~~4 days prior to randomisation. Tumour assessment may be performed within 28 days prior to randomisation. Histology/cytology is to be performed/confirmed before randomisation. • Footnote "d": A second PCI treatment procedure aimed at the initiation of Cycle 5 or, if patient-related factors demand postponement, at initiation of **a later c**~~C~~ycle ~~6, 7 or 8~~ (Section 3.3.2). **The PCI treatments must be separated by at least 3 months.** • Footnote "e": Biliary stenting is to be performed on all patients according to local practice; however, the chosen stent must be of an exchangeable ~~(~~plastic~~)~~ type until radiological progression is declared. Stenting may be performed at any time from confirmation of histological/cytological diagnosis until immediately after the first laser light application. Patients who have already undergone stenting before screening should be reviewed to ensure the stent is of ~~an acceptable~~**plastic** type, correctly positioned and adequate liver drainage confirmed. Stents must be removed for the laser light application, and a new stent must be placed immediately after light application. Stent removal, laser light application, and stent replacement will take place during the same ~~ERCP~~**one** procedure. • Footnote "j": Standard 12 lead ECG. Tracings must be interpreted, dated, and signed by the Investigator or his/her designee and filed with the patient's source documents. On Day -4 and Cycle 4, Day 18, ~~the ECG will be time matched with PK samples: For PK Group 1,~~ ECG will be performed before, approximately 30 minutes after, and **approximately** 4 hours after Amphinex administration~~, and for PK Group 2, ECG will be performed before Amphinex administration~~. • Footnote "s": A creatinine clearance at baseline is required. Creatinine clearance prior to treatment should be ≥60 mL/min. Serum creatinine should be checked before each cycle of treatment. If there is a >25% increase in serum creatinine compared to the baseline, then the ethylenediamine tetraacetic acid (EDTA) clearance or equivalent**, including estimation of GFR**, according to local practice, ~~method~~ must be performed and cisplatin dosing modified accordingly. • Footnote "v": PK samples will be collected from all patients in Arm A. Group 1: the 20 first patients randomised to Arm A; Group 2: all other patients randomised to Arm A. On Day -4 and Cycle 4, Day 18, the PK samples will be time matched with ECG: For PK Group 1, PK sampling **and ECG** will be performed before,

Version	Date	Changes
		approximately 30 minutes after, and **approximately** 4 hours after Amphinex administration; for PK Group 2, PK sampling **and ECG** will be performed before Amphinex administration**, only ECG will be performed 30 minutes after and approximately 4 hours after Amphinex administration**. • Footnote "w": ~~Blood samples (20 mL) for exploratory biomarkers in plasma will be collected at baseline and at approximately 3-month intervals throughout the study.~~ • Footnote "x": Laser light application procedure is to be performed 3 hours (±1 hour) after end of the gemcitabine administration. ~~It is expected that all p~~**P**atients ~~will~~ **may** be **admitted for overnight follow-up** ~~hospitalised for one night~~ after the ~~ERCP/~~laser light application~~s~~ **and related procedures** on Day 1 of Cycle 1 and Day 1 of Cycle 5.
		Appendix A, Table 11 The following changes were made to the schedule of events: • Removed the rows for biomarker assessments and exploratory biomarkers. • "Background" was replaced with "SoC". • A new footnote "a" was added: **Patients who have started gemcitabine/cisplatin treatment before the screening period should continue their treatment as scheduled, including during the screening period. Study visits should be synchronised with ongoing SoC chemotherapy. Chemotherapy cycles will be counted from first chemotherapy treatment and cannot exceed 8 cycles.** • Footnote "b": Screening evaluations are to be performed after the patient has signed and dated the informed consent form and within **21**~~14~~ days prior to randomisation. Tumour assessments may be performed within 28 days prior to randomisation. Stenting and histology/cytology are to be performed/confirmed before randomisation. • Footnote "d": Biliary stenting is to be performed on all patients according to local practice; however, the chosen stent must be of an exchangeable ~~(~~plastic~~)~~ type until radiological progression is declared. Stenting may be performed at any time from confirmation of histological/cytological diagnosis until immediately after the first laser light application. Patients who have already undergone stenting before screening should be reviewed to ensure the stent is of ~~an acceptable~~**plastic** type, correctly positioned and adequate liver drainage confirmed. • Footnote "p": A creatinine clearance at baseline is required. Creatinine clearance prior to treatment should be ≥60 mL/min. Serum creatinine should be checked before each cycle of treatment. If there is a >25% increase in serum creatinine compared to the baseline, then the ethylenediamine tetraacetic acid (EDTA) clearance or equivalent**, including estimation of GFR, according to local practice**, ~~method~~ must be performed and cisplatin dosing modified accordingly. • Footnote "s": ~~Blood samples (20 mL) for exploratory biomarkers in plasma will be collected at baseline and at approximately 3-month intervals throughout the study.~~
		Appendix B, Table 12 The following changes were made to the schedule of events: • Removed the row for exploratory biomarkers • Record details of subsequent anti-cancer therapy was added to the tumour response follow-up of the follow-up period

Version	Date	Changes
		• Footnote “h” was deleted: ~~To be recorded as long as the patient has not withdrawn the consent.~~