2. SYNOPSIS

NAME OF SPONSOR/COMPANY: PCI Biotech AS, Ullernchausséen 64, 0379 Oslo, Norway.
NAME OF FINISHED PRODUCT: Amphinex®
NAME OF ACTIVE INGREDIENT: Fimaporfin
TITLE OF STUDY: 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 (RELEASE Study). Protocol number PCIA 203/18; EudraCT number 2018-002647-29; IND number 128897.
PRINCIPAL INVESTIGATOR NAME, NUMBER OF STUDY SITES AND COUNTRIES: Prof. Dr. Jörg Trojan, Universitätsklinikum Frankfurt, Frankfurt, Germany. Study sites that randomised participants: Denmark (1 site), France (1 site), Germany (5 sites), Norway (1 site), Poland (1 site), South Korea (6 sites), Spain (2 sites), Taiwan (2 sites), US (1 site).
PUBLICATION (REFERENCES): None at the time of this report.
STUDY PERIOD: 03 May 2019 (date of informed consent of the first participant) to 06 May 2022 (date last participant discontinued)**.**
REPORTING PERIOD: Same as the study period.
PHASE OF DEVELOPMENT: 2
BACKGROUND FOR THE STUDY: Cholangiocarcinoma (CCA) is an uncommon adenocarcinoma arising from the neoplastic transformation of cholangiocytes, the epithelial cells lining the intrahepatic and extrahepatic bile ducts. CCA may arise anywhere in the biliary tree and the term CCA includes all bile duct cancers (intrahepatic, perihilar, and distal extrahepatic). CCA is the second most frequent type of primary liver cancer and accounts for approximately 3% of all digestive tumours. CCAs are generally asymptomatic in the early stages and are usually diagnosed when the disease has already metastasised. Late diagnosis compromises effective therapeutic options, which are based on surgical resection and/or liver transplantation, with many chemotherapies being virtually palliative given the marked chemoresistance of this cancer. For patients who are unsuitable for curative resection, the current systemic combination chemotherapy is with cisplatin plus gemcitabine, but response rates are variable and generally poor. 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. The purpose of this study was to evaluate the safety and efficacy of fimaporfin-induced 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), and disease control rate (DCR) at 6 and 12 months, and change in tumour size using 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.

METHODOLOGY:

This study was a multi-centre, randomised, open-label, Phase 2 study 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 PCI treatment. Participants were randomised in a 1:1 ratio to receive the following study treatments:

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

Randomisation was stratified by 2 factors: any measurable disease at baseline (yes versus no) and presence or absence of metastases. Tumour response was assessed according to RECIST 1.1 every 12 weeks (±1 week) from randomisation until disease progression. The primary PFS analysis was based on the local radiological assessment, which was used to guide clinical management decisions. A blinded independent central radiological review (BICR), blinded to treatment and to the local efficacy assessments, also assessed the tumour response data. Participants were to be followed for radiological progression, regardless of whether they discontinued therapy or had symptomatic progression. After radiological progression, participants were to enter a survival follow-up phase, with data collection for OS continuing beyond the PFS assessment.

To evaluate the PK of fimaporfin in plasma, blood samples were obtained from all participants in Arm A at the timepoints specified in the PK sampling schedule. Quality of life (QoL) was measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and the EORTC QLQ-BIL21 questionnaire. The standard tumour markers carbohydrate antigen 19-9 (CA 19-9), cancer antigen 125 (CA 125), and carcinoembryonic antigen (CEA) were to be analysed from blood samples collected for safety laboratory assessments throughout the study.

Safety was assessed by AEs, serious AEs (SAEs), deaths, loco-regional tumour-related events and biliary complications, clinical laboratory assessments, physical examinations, vital signs, and electrocardiograms (ECGs). An Independent Data Monitoring Committee (IDMC) performed periodic reviews of accumulating safety data, with particular focus on biliary tract events, which were defined as AEs of special interest (AESIs). The study included an initial safety review by the IDMC after the initial 8 participants in Arm A had been administered 2 PCI treatments and followed up for 21 days. The IDMC also assessed whether the second PCI treatment during the chemotherapy period should continue to be administered for future participants randomised to Arm A. In addition, based on the periodic or *ad hoc* safety data reviews, the IDMC could make recommendations to continue, amend, or stop the study at any point for safety reasons.

PCI Biotech decided to stop this study early. This decision was based on recent Phase 3 clinical trial results that demonstrated that a combination of immune checkpoint inhibition with gemcitabine and cisplatin provides a significant survival benefit to patients with perihilar or distal CCA. These results are expected to improve the standard of care (SoC) for the intended patient population of this RELEASE study. This change in SoC was expected to render the RELEASE study challenging to complete and potentially inadequate for approval.

NUMBER OF PARTICIPANTS:

Planned: Approximately 186 participants were planned.

Actual: A total of 41 participants were enrolled before the early termination of this study: 21 in Arm A and 20 in Arm B.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION AND EXCLUSION:

Male or female participants ≥18 years of age with CCA verified as adenocarcinoma by histopathology or cytology with a perihilar or distal stenosis that has been stented or would require stenting, and that was accessible for PCI light treatment were eligible for the study. The CCA had to be considered inoperable with respect to radical resection (including partial liver resection or liver transplantation) and at least 1 radiologically evaluable lesion (measurable and/or non-measurable) that could be assessed at baseline and

was suitable for repeated radiological evaluation was required. If metastatic disease was present, the metastasis had to be limited to tissues other than bone or the central nervous system. The participant was also required to have adequate biliary drainage (at least 50% of the liver volume or at least 2 sectors), with no evidence of active uncontrolled infection (participants on antibiotics were eligible), an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and an estimated life expectancy of at least 12 weeks.
Key exclusion criteria were previous anti-tumour treatment (either local or systemic) for CCA, except for up to 2 cycles of gemcitabine/cisplatin as part of SoC; severe visceral disease other than CCA; a history of frequently recurring septic biliary events; porphyria or hypersensitivity to porphyrins; a second primary cancer with a disease-free interval of <5 years; unable to undergo contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI); or current participation in any other interventional clinical study.

INVESTIGATIONAL PRODUCT, DOSE, MODE OF ADMINISTRATION, BATCH NUMBERS:
Arm A PCI treatment consisted of i.v. administration of Amphinex solution for injection 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 was a medical laser system (CE marked), emitting red light at 652 nm. All participants received the established SoC for this indication in addition to the PCI treatment, which comprised systemic chemotherapy of 8 cycles of cisplatin 25 mg/m^2 plus gemcitabine 1000 mg/m^2. Cisplatin was omitted on days when PCI treatment was given (on Day 1 of Cycle 1 and on Day 1 of Cycle 5). Biliary stenting (plastic stents) was to be performed on all participants.
Batch numbers of Amphinex: FAMP1501 and 104047.
Gemcitabine and cisplatin were purchased from commercial stock.

DURATION OF TREATMENT:
Duration of treatment was up to a maximum of 8 gemcitabine/cisplatin cycles, or until a treatment discontinuation criterion was met. Thus, the maximum study duration for a participant was approximately 6 months during the active treatment period, with an additional number of assessments occurring every 3 months until progression, as individually applicable. Treatment discontinuation criteria included severe non-compliance with the study protocol, incorrect enrolment and randomisation, progressive disease, development of toxicity, participant refusal to receive further study treatment, lost to follow-up, intercurrent illness that precluded further study treatment, pregnancy, or any other reasons not listed above as per the investigator's discretion.

CONTROL PRODUCT, DOSE, MODE OF ADMINISTRATION, BATCH NUMBERS:
The control arm (Arm B) received the same SoC as Arm A: systemic chemotherapy of 8 cycles of cisplatin 25 mg/m^2 plus gemcitabine 1000 mg/m^2. Biliary stenting (plastic stents) was to be performed on all participants.
Gemcitabine and cisplatin were purchased from commercial stock.

ENDPOINTS:
Primary Endpoint
PFS, defined as the time from randomisation to radiological disease progression (per RECIST v1.1) or death from any cause.
Secondary Endpoints
- OS, calculated as the time from randomisation to the date of death from any cause.
- BOR, defined as 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).
- ORR, calculated as the proportion of participants who had at least 1 visit response with a complete response (CR) or partial response (PR) noted.
- DoR, defined as time from first documented tumour response until the first documented disease progression, or death in the absence of disease progression.
- DCR, defined as the proportion of participants with stable disease (SD) or better (i.e., CR, PR or SD), 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.
- PK profile of fimaporfin.

- HRQoL/PRO assessments.

Exploratory Endpoints

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

STATISTICAL METHODS:

As this study was terminated early, a reduced statistical analysis was conducted, as detailed in the addendum to the SAP provided in Appendix 2. The following efficacy endpoints were reported: PFS, OS, BOR, ORR, DCR, DoR, and change in tumour size. The investigator-reported responses captured at each scan assessment were used in the assessment of RECIST-based efficacy endpoints and not the BICR assessments. PFS was analysed using the modified intent-to-treat (mITT) analysis set, which included all randomised participants who received at least 1 dose of study treatment and had a RECIST assessment at baseline. The hazard ratio (HR) was estimated using an unstratified Cox-proportional hazards model using the Efron approach for handling ties, together with the associated 95% confidence intervals (CI) for the HR based on the Wald method. In addition, PFS Kaplan-Meier (KM) estimates at 3, 6, 9, 12 months and the median with corresponding 95% CIs based on Brookmeyer and Crowley were presented. A KM plot of PFS based on PROC Lifetest was presented by treatment group for the primary PFS analysis. As a sensitivity analysis, the KM plot of PFS was repeated with PFS calculated from first dose of study treatment to take into account participants who received up to 2 cycles of gemcitabine/cisplatin as part of SoC before randomisation. OS was analysed in the same way as PFS. BOR, DCR, and ORR were summarised by randomised treatment group using the mITT analysis set. For ORR, an exact 95% CI was presented for each arm. DoR was listed only. Percentage change in tumour size was also determined for participants with measurable disease at baseline and was derived at each visit by the percentage change in the sum of the longest diameters (SoD) of target (i.e., measurable) lesions compared to baseline. The best overall percentage change in SoD from baseline was calculated and displayed as a Waterfall plot.
Safety and tolerability were assessed descriptively in terms of AEs, SAEs, deaths, laboratory data, physical findings, vital signs, and ECGs.

SUMMARY OF RESULTS AND CONCLUSIONS:

Analysis Sets: A total of 41 participants were randomised and included in the intent-to-treat (ITT) analysis set, with 34 participants being included in the safety analysis set (18 in Arm A and 16 in Arm B) and 34 participants being included in the mITT analysis set (19 in Arm A and 15 in Arm B) (Table 1). The difference in the number of participants in each arm between the safety analysis set and the mITT is due to 1 participant who was randomised to Arm A but received Arm B treatment.

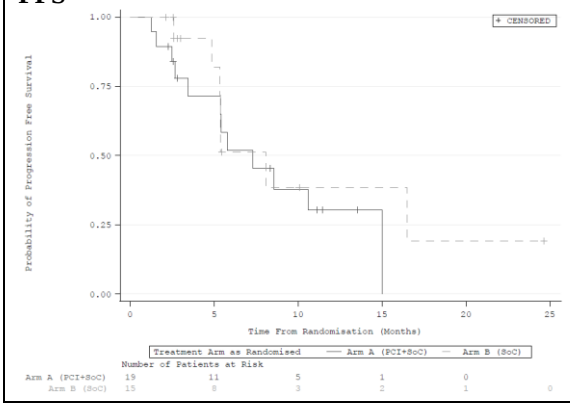
Participant Disposition: Out of the 41 participants in the ITT population, 34 received treatment, and 11 participants completed the full 8 cycles of treatment. A total of 23 participants discontinued study treatment, with the most common reasons for treatment discontinuation being AEs (7 participants), disease progression (6 participants), and refusal of the participant to receive further treatment (4 participants). All 41 participants in the ITT population ultimately discontinued from the study: 20 due to the study termination by the sponsor, 11 due to withdrawal of consent, 7 due to death, 2 lost to follow-up, and 1 due to other reasons (Table 1). Disposition was generally similar in the 2 treatment arms, although more deaths occurred in Arm A (7 out of a total of 9 deaths) (Listing 9) and more discontinuations of study treatment due to AEs occurred in Arm A (5 out of the 7 cases). A listing of disposition for each participant is provided in Listing 1.

Demography and Baseline Characteristics: The overall mean age of participants in the ITT population was 66.3 years (range 32 to 86 years). A similar number of male and female participants were randomised (56.1% male and 43.9% female), and 53.7% of the ITT population were White and 46.3% were Asian. The majority of participants (90.2%) had measurable disease at baseline and 56.1% had metastases at baseline (Table 2). A listing of demographic details for each participant is provided in Listing 2 and a listing of disease history is provided in Listing 3.

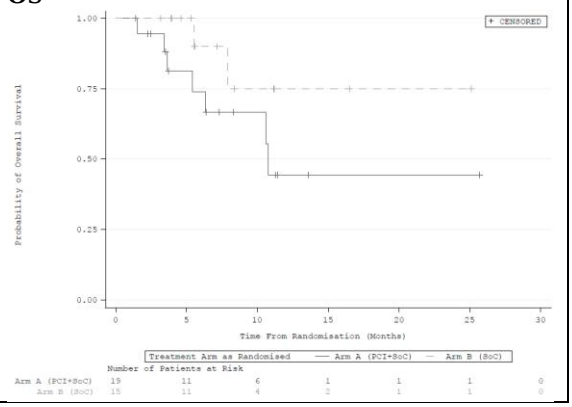
Exposure: The mean duration of chemotherapy for all participants in the safety analysis set was 128.3 days (range 28 to 203 days) (Table 3). Eleven participants (61.1%) received 2 fimaporfin injections, 6 participants (33.3%) received 1 fimaporfin injection, and 1 participant (5.6%) received 3 fimaporfin injections (note: this participant did not receive the PCI treatment, including the laser, after 1 of the injections and so was given a third injection) (Table 3). The number of red light illuminations is shown in Table 4. A listing of all study treatments and drug exposure for each participant is provided in Listing 4.

Efficacy Results: The primary endpoint in this study was PFS. KM analysis of PFS is shown in Table 19 for the mITT population, with the median PFS being similar in the 2 arms: 7.29 months in Arm A and 8.08 months in Arm B (HR [95% CIs] = 1.39 [0.51, 3.75]). KM analysis of OS is shown in Table 20 for the mITT population, but the number of events was too small to draw any conclusions. The KM plots for PFS and OS are shown below. A sensitivity KM plot for PFS from first dose rather than from randomisation showed similar results (Figure 3). A listing of all time-to-event endpoints for each participant is provided in Listing 11.

PFS



OS



OS=overall survival; PCI=photochemical internalisation; PFS=progression-free survival; SoC=standard of care.
Data Source: Figure 2 and Figure 4

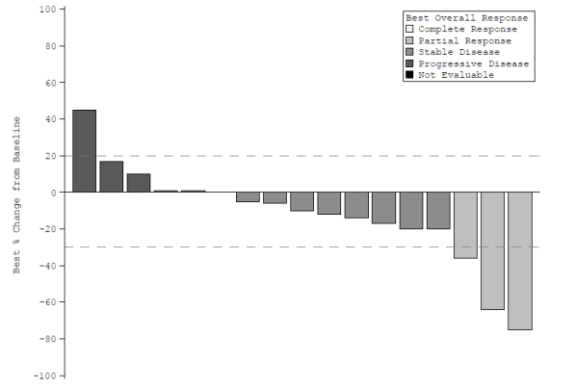
A summary of the efficacy results in the mITT analysis set is provided below, with a listing of disease response for each participant provided in Listing 10.

Response	**Arm A (PCI + SoC) N=19**	**Arm B (SoC) N=15**
Best overall response, n (%)		
Complete response	0	0
Partial response	3 (15.8)	3 (20.0)
Stable disease	12 (63.2)	11 (73.3)
Progressive disease	4 (21.1)	1 (6.7)
Objective response rate, n (%) [95% CI]	3 (15.8) [0.03, 0.40]	3 (20.0) [0.04, 0.48]
Overall disease control rate, n (%) [95% CI]	15 (78.9) [0.54, 0.94]	14 (93.3) [0.68, 1.00]
Disease control rate at 6 months, n (%) [95% CI]	11 (57.9) [0.33, 0.80]	10 (66.7) [0.38, 0.88]
Sum of diameters at baseline and percentage change in tumour size from baseline: median (min, max)		
Baseline	27.00 (10.0, 111.0) [N=18]	40.00 (23.3, 145.4) [N=11]
To 12 weeks	-11.00 (-75.0, 45.0) [N=16]	-7.50 (-39.0, 10.0) [N=10]
To 24 weeks	-11.50 (-75.0, 162.0) [N=8]	-12.0 (-33.0, 9.0) [N=5]
To 36 weeks	-28.00 (-75.0, 0.0) [N=6]	-9.00 (-9.0, -9.0) [N=2]
To 48 weeks	-23.50 (-50.0, -10.0) [N=4]	-16.50 (-27.0, -6.0) [N=2]
Best percentage change from baseline	-10.00 (-75.0, 45.0) [N=17]	-15.00 (-39.0, 10.0) [N=11]

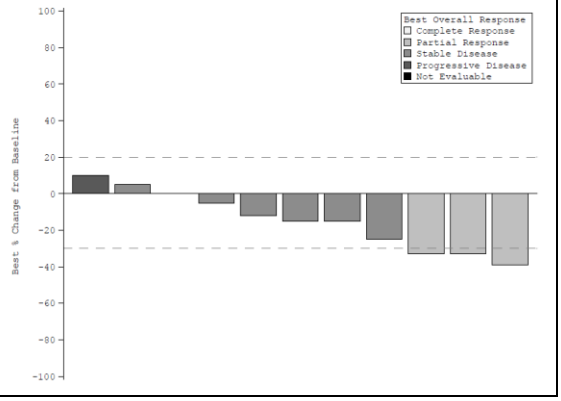
CI=confidence interval; max=maximum; min=minimum; PCI=photochemical internalisation; SoC=standard of care.
Data Source: Tables 16, 17, and 18.

Three PRs were seen in each arm, with the number of participants with SD also being similar in the 2 arms (12 participants [63.2%] in Arm A and 11 participants [73.3%] in Arm B). Waterfall plots of the changes in tumour sizes for participants with measurable disease at baseline are shown below:

Treatment Arm A: PCI + SoC



Treatment Arm B: SoC



PCI=photochemical internalisation; SoC=standard of care.
Data Source: Figure 1

The ORR was similar in both arms (15.8% in Arm A and 20.0% in Arm B) (Table 16). The DCR was slightly lower in Arm A compared to Arm B: overall DCR was 78.9% in Arm A and 93.3% in Arm B, and DCR at 6 months was 57.9% in Arm A and 66.7% in Arm B (Table 17).
DoR is shown for the 3 PRs in each arm in Listing 12. In Arm A, the duration of response was 169 days in 1 participant before radiological progression was seen. In the other 2 participants in Arm A, the events were censored at 260 and 264 days, respectively. In Arm B, the duration of response was 85 days in 1 participant before radiological progression was seen. In the other 2 participants in Arm B, the events were censored at 1 day due to the early termination of the study.
The exploratory endpoint analyses were not conducted due to the early termination of the study.
PK results: Due to the early termination of the study, the PK analyses were not conducted.
QoL results: Due to the early termination of the study, the HRQoL results were not analysed.
Safety Results: An overview of treatment-emergent adverse events (TEAEs) in the safety analysis set is provided below, with further details provided in Table 5. A listing of all AEs for each participant is provided in Listing 5.

TEAE Parameter	Arm A (PCI + SoC) N=18 n (%) [events]	Arm B (SoC) N=16 n (%) [events]	Total N=34 n (%) [events]
Any TEAE	18 (100) [216]	16 (100) [143]	34 (100) [359]
Related to any study treatment	18 (100) [107]	16 (100) [91]	34 (100) [198]
Related to IMP	13 (72.2) [63]	0	13 (38.2) [63]
Any CTCAE Grade 3 or 4	13 (72.2) [45]	11 (68.8) [30]	24 (70.6) [75]
Related to any study treatment	11 (61.1) [21]	9 (56.3) [20]	20 (58.8) [41]
Related to IMP	8 (44.4) [10]	0	8 (23.5) [10]
Any TEAE leading to death	2 (11.1) [2]	0	2 (5.9) [2]
Related to any study treatment	1 (5.6) [1]	0	1 (2.9) [1]
Related to IMP	1 (5.6) [1]	0	1 (2.9) [1]
Any serious TEAE	12 (66.7) [31]	8 (50.0) [14]	20 (58.8) [45]
Related to any study treatment	9 (50.0) [15]	5 (31.3) [6]	14 (41.2) [21]
Related to IMP	3 (16.7) [6]	0	3 (8.8) [6]
Any TEAE leading to discontinuation	3 (16.7) [3]	1 (6.3) [1]	4 (11.8) [4]
Related to any study treatment	1 (5.6) [1]	1 (6.3) [1]	2 (5.9) [2]
Related to IMP	0	0	0

IMP includes fimaporfin, gemcitabine, and red light illumination/laser light application.
CTCAE=Common Terminology Criteria for Adverse Events; IMP=investigational medicinal product; PCI=photochemical internalisation; SoC=standard of care; TEAE=treatment-emergent adverse event
Data Source: Table 5

All participants had at least 1 TEAE during the study, with the most common TEAEs in Arm A being pyrexia and cholangitis (both 38.9%), vomiting and anaemia (both 33.3%), and nausea and abdominal pain (both 22.2%). The most common TEAEs in Arm B were anaemia (56.3%), pyrexia, nausea, diarrhoea, and platelet count decreased (all 31.3%), and cholangitis and constipation (both 25.0%) (Table 6). A summary of all TEAEs of special interest is provided in Table 11 and listed by participant in Listing 6. The only notable difference in AESIs between the 2 arms was for skin and subcutaneous tissue disorders (including

erythema, photosensitivity reaction, dermatitis, pruritus, and rash), which were reported in 6 participants (33.3%) in Arm A and no participants in Arm B.
The occurrence of all TEAEs by injection timepoint (within 21 days after first PCI treatment and within 21 days after the second PCI treatment) is summarised in Table 13.
All participants had at least 1 TEAE that was considered related to any of the study treatments, with the most common TEAEs related to any study treatment in Arm A being pyrexia and vomiting (both 27.8%) and cholangitis, nausea, and abdominal pain (all 22.2%). The most common TEAEs related to any study treatment in Arm B were anaemia (56.3%), nausea and platelet count decreased (both 31.3%), and diarrhoea (25.0%) (Table 7). A summary of all TEAEs of special interest that were considered related to any study treatment is provided in Table 12. In Arm A, 72.2% of participants had at least 1 TEAE related to the IMP (combines fimaporfin, gemcitabine, and red light illumination/laser light application), with the most common TEAEs related to the IMP being abdominal pain (22.2%), and nausea, vomiting, erythema, neutropenia, and cholangitis (all 16.7%) (Table 8).
A total of 20 participants (58.8%) had at least 1 SAE. SAEs that occurred in more than 1 participant were cholangitis (9 participants, 26.5%), stent malfunction (3 participants, 8.8%), and biliary tract infection, acute cholangitis, and pyrexia (all in 2 participants, 5.9% of participants). The limited available data suggests that the incidents of SAEs was numerically higher in Arm A compared to Arm B (12 participants [66.7%] reporting 31 events in Arm A compared to 8 participants [50.0%] reporting 14 events in Arm B), with more SAEs associated with the biliary tract being seen in Arm A (Table 9). The only SAEs considered related to the study treatment that occurred in more than 1 participant were cholangitis (5 participants, 14.7% [4 participants in Arm A and 1 participant in Arm B]), and stent malfunction and pyrexia (both in 2 participants, 5.9% [1 participant in each Arm]) (Table 10).
TEAEs leading to permanent discontinuation of all study treatments were reported for 4 participants: 3 in Arm A and 1 in Arm B. These comprised blood bilirubin increased, cholangitis, and aortic thrombosis in Arm A and leukopenia in Arm B (Listing 8).
No adverse incidents related to the laser device were seen in this study (Listing 7).
Two TEAEs led to death (Listing 9). Both events occurred in Arm A and comprised aortic thrombosis, which was not related to the study treatment, and sepsis, which was classified by the investigator as probably related to the red light illumination (Listing 5). The TEAE of sepsis developed following the second PCI treatment (the first PCI treatment for this participant was uneventful). Sepsis developed one day after another TEAE of cholangitis, which started a few hours after endoscopic retrograde cholangiopancreatography (ERCP), removal of the old stent, illumination, and placement of a new stent. The participant died 13 days after the start of the sepsis.
Shifts from baseline in selected safety laboratory parameters of interest are shown in Table 14. Greater increases from baseline (2 grades or more) in Arm A compared to Arm B were seen for alanine aminotransferase (ALT) increased (61.1% in Arm A compared to 18.8% in Arm B), aspartate aminotransferase (AST) increased (33.3% in Arm A compared to 12.5% in Arm B), alkaline phosphatase increased (33.3% in Arm A compared to 6.3% in Arm B), and neutrophil count decreased (44.4% in Arm A compared to 25.0% in Arm B).
Shifts from baseline in QTcF are shown in Table 15. Some changes were seen in a small number of participants, but the changes were similar in both arms of the study.

Conclusions:

- Due to the early termination of this study, no definitive conclusions can be drawn since an insufficient number of participants was recruited.
- The efficacy results obtained from the limited study population did not seem to indicate a notable difference between the 2 treatment arms in any of the efficacy parameters evaluated, however, there was insufficient statistical power to draw any definitive conclusions with respect to the efficacy data.
- Similar incidences of TEAEs of Grade 3 or 4 were observed in the 2 treatment groups. A numerically higher incidence of SAEs was observed in Arm A compared to Arm B, with more SAEs associated with the biliary tract being seen in Arm A.

DATE AND VERSION OF THIS REPORT: Synoptic Clinical Study Report – 17 August 2022