2 SYNOPSIS

Name of Sponsor/Company: PCI Biotech AS	**Individual Study Table Referring to Part of the Dossier Volume:** **Page:**	*For National Authority Use Only*
Name of Finished Product: Amphinex® and Gemcitabine		
Name of Active Ingredient: $TPCS_{2a}$, (Di [monoethanolammonium] *meso*-tetraphenyl chlorin disulphonate) for injection and Gemcitabine (gemcitabine hydrochloride) for injection		

Title of Study: A Phase I/II Dose Escalation Study to Assess the Safety, Tolerability and Efficacy of Amphinex®-induced Photochemical Internalisation (PCI) of Gemcitabine Followed by Gemcitabine/Cisplatin Chemotherapy in Patients with Advanced Inoperable Cholangiocarcinomas

Investigators: The Chief Investigator was Dr Richard Sturgess, University Hospital Aintree, Liverpool, United Kingdom (UK)

Study centres: Eight centres (six in Germany, one in the UK and one in Norway)

Publications: None

Studied period (First patient enrolled – last patient last visit):
16 January 2014 – 21 February 2019

Phase of development: Phase I/II

Objectives: The primary and secondary objectives for the Phase I part of the study are presented below. Exploratory objectives are not presented in the Clinical Study Report (CSR) synopsis but are included in the CSR. Objectives and endpoints for the Phase II part of the study, which was not conducted, are not presented here but are included in the protocol.

Primary Objectives

Dose Escalation Part: To determine a tolerable dose and safety profile of Amphinex-induced PCI of gemcitabine followed by systemic gemcitabine/cisplatin chemotherapy in patients with advanced inoperable cholangiocarcinoma (CCA)

Extended Part of Phase I: To determine the tolerability and safety profile of a two-administration schedule of Amphinex-induced PCI of gemcitabine followed by systemic gemcitabine/cisplatin chemotherapy in patients with advanced inoperable CCA

Secondary Objectives

Dose Escalation Part: To characterise the pharmacokinetic (PK) profiles of fimaporfin (the active substance in Amphinex) and gemcitabine, and to make a preliminary assessment of the efficacy of Amphinex-induced PCI of gemcitabine followed by systemic gemcitabine/cisplatin chemotherapy in patients with advanced inoperable CCA

Extended Part of Phase I: To characterise the PK profiles of fimaporfin and gemcitabine, and to make a preliminary assessment of the efficacy of a two-administration schedule of Amphinex-induced PCI of gemcitabine followed by systemic gemcitabine/cisplatin chemotherapy in patients with advanced inoperable CCA

Methodology: This study was planned as an open-label Phase I/II study but only the Phase I part of the study was conducted. The Sponsor decided to modify the Phase II part of the study and conduct this separately. Therefore, this report covers only the Phase I parts of the study; Dose Escalation Part and Extended Part of Phase I.

All patients were screened during a 14 day period before study entry. Patients were monitored for safety at baseline as well as during treatment and follow-up visits. Blood samples for PK analysis of fimaporfin and gemcitabine were collected from all patients at selected timepoints during the study.

Patients in the Dose Escalation Part of the study received a single PCI treatment and patients in the Extended Part of Phase I could receive up to two separate PCI treatments. Patients in the Extended Part of Phase I had to have a tumour evaluation performed (by computed tomography [CT]/magnetic resonance imaging [MRI]) prior to the second PCI treatment. Patients also had to meet predefined safety criteria before receiving a second PCI treatment.

All patients were hospitalised for up to 6 days following treatment; inpatient stay was at the discretion of the Investigator. For all patients, light avoidance measures (described in the protocol) were to be initiated immediately after each Amphinex injection and were to be adhered to by the patient after hospital discharge. Patients were to return to the hospital for administration of combination chemotherapy. The hospitalisation period for the second PCI treatment (Extended Part of Phase I only) was the same as for the first PCI treatment. All patients were to attend a follow-up visit at 30 days (±3 days) after the last study treatment (administration of systemic chemotherapy, intraluminal laser light, or Amphinex injection) and were to be included in the extended follow-up for survival (with assessments every 12 weeks [±4 weeks]). In addition, for patients in the Extended Part of Phase I, post-study treatment and progression/non-progression information were to be collected during the extended follow-up period.

Adverse events (AEs), adverse incidents (AIs) and serious adverse events (SAEs), regardless of suspected relationship to study treatment were recorded from the time the patient provided informed consent until up to 30 days after the last study treatment

(administration of systemic chemotherapy, intraluminal laser light application or Amphinex injection). After 30 days, only AEs and SAEs considered related to study treatment/study procedures or events considered significant for any other reason were to be reported and followed up until resolution. Response and progression were evaluated throughout the study using the international criteria (Version 1.1) proposed by the Response Evaluation Criteria in Solid Tumours (RECIST) Committee. Radiographic tumour assessments were to be performed within 1 month prior to registration, Week 12 and Week 24 of C1D1 of gemcitabine/cisplatin chemotherapy, and then every subsequent 12 weeks (±2 weeks) until confirmed progressive disease (PD) or death. The CT scans were assessed locally by a radiologist and/or an oncologist.

Number of patients (planned and analysed): Following Protocol Amendment 7 (addition of the Extended Part of Phase I), it was planned to enrol 16 patients in the single arm, Dose Escalation Part of the study and up to 12 patients in the Extended Part of Phase I at multiple sites in Europe. A total of 23 patients were enrolled and treated (16 patients in the Dose Escalation Part of the study and 7 patients in the Extended Part of Phase I). In addition, one patient was enrolled but not treated; this patient was enrolled in error as inclusion criteria were not met.

Diagnosis and main criteria for inclusion: Patients had to have histopathologically/cytologically (C5) verified adenocarcinoma consistent with CCA; prior to Protocol Amendment 5, the population was patients with *locally* advanced inoperable CCA. In Protocol Amendment 5, patients with metastatic disease were also allowed to enter the study. In Protocol Amendment 6, allowable metastatic disease was confined to the liver only. The CCA had to be considered inoperable, have a primary lesion in the perihilar biliary duct region that required stent placement, and have nodal enlargement ≤N1 per CT/MRI assessment. Patients also had to be ≥18 years of age, have an Eastern Cooperative Oncology Group Performance Status ≤1, and an estimated life expectancy of ≥12 weeks. Patients could not have received any prior anti-cancer (either local or systemic) treatment for CCA, and were not to have any of the following: extrahepatic metastatic CCA; severe visceral disease other than CCA; primary sclerosing cholangitis; porphyria or hypersensitivity to porphyrins; an active (disease free interval of <5 years) second primary cancer, with the exception of adequately treated basal cell carcinoma, squamous cell carcinoma or other non-melanomatous skin cancer, or in situ carcinoma of the uterine cervix.

Test product, dose and mode of administration, batch number: The Investigational Medicinal Product (IMP) was defined as the PCI treatment which consisted of intravenous administration of Amphinex solution for injection on Day 0, followed by a single intravenous gemcitabine infusion and intraluminal laser light application on Day 4. The intraluminal laser light activates the photosensitiser fimaporfin, the active substance in the drug product Amphinex. During the Dose Escalation Part of the study, escalating doses of Amphinex in combination with different intraluminal laser light settings, as defined by the Cohort Review Committee (CRC), were evaluated. The CRC reviewed safety data and made recommendations about dose escalation, the PCI treatment schedule, study conduct, and study continuation. Doses of Amphinex and intraluminal laser light administered were:

Cohort 1: Amphinex 0.06 mg/kg with a light dose 15 J/cm
Cohort 2: Amphinex 0.06 mg/kg with a light dose 30 J/cm
Cohort 3: Amphinex 0.12 mg/kg with a light dose 30 J/cm
Cohort 4: Amphinex 0.25 mg/kg with a light dose 30 J/cm

All patients also received the standard gemcitabine dose (1000 mg/m^2) as part of the PCI treatment.

For the Extended Part of Phase I, a safe and tolerable dose of Amphinex and intraluminal laser light were selected following the Dose Escalation Part of the study. The dose selected was Amphinex 0.25 mg/kg with the standard gemcitabine dose (1000 mg/m^2) and intraluminal laser light of 30 J/cm. In the Extended Part of Phase I, all patients were to receive two separate PCI treatments (administration of Amphinex followed by gemcitabine and intraluminal light application). The first PCI treatment was to be given as an initial treatment before combination chemotherapy treatment (gemcitabine/cisplatin) and the second PCI treatment included administration of Amphinex at C4D18 followed by administration of gemcitabine and intraluminal laser light 4 days later at C5D1.

Two batches of Amphinex were used in this study. Individual batch numbers and further information are included in the CSR.

Duration of treatment:

Dose Escalation Part: One PCI treatment (administered in a 4 day period) plus up to eight 21-day cycles of systemic chemotherapy starting between 7 and 21 days after the intraluminal laser light on Day 4.

Extended Part of Phase I: Two PCI treatments (each administered in a 4 day period) plus up to eight 21-day cycles of systemic chemotherapy starting between 7 and 21 days after the first intraluminal laser light on Day 4.

Criteria for evaluation:

Safety

Dose Escalation Part: Safety was assessed by evaluating the incidence of dose limiting toxicities (DLTs) and review of the safety profile (AEs, laboratory assessments, and physical findings). A DLT was defined as a clinically significant toxicity or abnormal laboratory value assessed as unrelated to the underlying disease or concomitant medications, occurring after PCI and/or during the first chemotherapy cycle that was related to either PCI treatment or related to the combination of PCI treatment with the gemcitabine/cisplatin systemic chemotherapy and met any of the following criteria, based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02: Photosensitivity Grade 3 outside the treatment area; Phototoxicity Grade 4 inside the treatment area; Non-haematological toxicity (excluding nausea and vomiting) ≥Grade 3; Neutropenia

or thrombocytopenia Grade 4; All other Grade 3 toxicities that were clinically unexpected.

Extended Part of Phase I: Safety was assessed by evaluating the incidence of schedule limiting toxicities (SLTs) and review of the safety profile (AEs, laboratory assessments and physical findings). A SLT was defined as a clinically significant toxicity or abnormal laboratory value assessed as unrelated to the underlying disease or concomitant medications and met any of the following criteria, based on the NCI CTCAE Version 4.02: Photosensitivity Grade 3 outside the treatment area; Clinically significant phototoxicity inside the treatment area; A toxicity of any grade that was clinically unexpected and considered related to the PCI treatment (changes to cisplatin treatment alone were not to be included as part of this assessment).

Efficacy

Progression-free Survival (PFS) defined as the time from registration to documented disease progression (according to RECIST 1.1 criteria) or death from any cause, and Best Overall Response (BOR).

Pharmacokinetics

Review of the PK profile of Amphinex and gemcitabine in plasma.

Statistical Methods:

All AEs were reviewed to determine whether they met the criteria of a DLT/SLT. Number and percentage of patients with AEs (all treatment-emergent AEs [TEAEs], TEAEs by CTCAE grade, AEs of interest, TEAEs by relationship to each IMP, TEAEs leading to discontinuation, SAEs) were summarised by treatment cohort and overall, including the number of AEs. In addition, time to onset and duration were summarised for biliary sepsis and cholangitis. For selected laboratory variables, test results were summarised using descriptive statistics and changes from baseline were also summarised. Results of other safety assessments were also summarised.

PFS was summarised using Kaplan-Meier plots and median PFS values were summarised with 90% confidence intervals. Pre-defined censoring rules were applied.

BOR (number and percentage of patients with complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD] and not evaluable [NE]) was summarised for each treatment cohort and overall. Response categories (CR, PR, SD, PD and NE) documented were used to calculate BOR.

Summary and Conclusions

A total of 23 patients were enrolled and treated. Of these, 16 were enrolled in the Dose Escalation Part of the study at different dose levels of Amphinex and intraluminal laser light (three patients in Cohort 1, three patients in Cohort 2,

four patients in Cohort 3, and six patients in Cohort 4). A further seven patients were enrolled and treated in the Extended Part of Phase I of whom five patients received two and two patients received one PCI treatment(s) at a dose of 0.25 mg/kg Amphinex with intraluminal laser light of 30 J/cm.

Safety results

No DLTs or SLTs were reported. All patients experienced at least one TEAE during the study; a total of 442 TEAEs were reported. The most frequently reported TEAEs were photosensitivity reactions (72 events [16.3%] in 18 patients [78.3%]) and cholangitis (43 events [9.7%] in 16 patients [69.6%]).

The majority of TEAEs were Grade 1 or Grade 2 in severity; overall, 88 of 442 TEAEs (19.9%) reported in 20 patients (87.0%) were Grade 3. The most frequently reported Grade 3 TEAEs were cholangitis and neutropenia. Five Grade 4 TEAEs were reported in four patients (17.4%); these included four events of neutropenia and one event of gamma-glutamyl transferase increased. No Grade 5 TEAEs were reported.

TEAEs considered related to Amphinex, gemcitabine for PCI, and/or intraluminal laser light application were reported in 22 patients (95.7%). The most frequently reported treatment related TEAE was photosensitivity reaction considered related to Amphinex only.

A total of 18 patients (78.3%) had at least one photosensitivity TEAE during the study. All were Grade 1 or Grade 2 in severity, none led to discontinuation of study treatment or study discontinuation/withdrawal and none were reported as SAEs. The majority were considered related exclusively to Amphinex but there did not appear to be a correlation between the incidence of photosensitivity related TEAEs and Amphinex dose.

A total of 18 patients (78.3%) experienced a total of 47 TEAEs of cholangitis, infective cholangitis or biliary sepsis during the study. The majority were Grade 2 or Grade 3 in severity; no Grade 4 or Grade 5 events were reported. The most frequently reported cause of these events was related to biliary stenting (23 of 47 events [48.9%]). One event of cholangitis was considered related to intraluminal laser light and one event of biliary sepsis was considered possibly related to gemcitabine for PCI treatment and biliary stenting. In addition, one patient had a SAE of infective cholangitis (reported term: cholangiosepsis due to mechanical obstruction of the bile duct) which was considered related to Amphinex, gemcitabine for PCI and intraluminal laser light because their use had resulted in the hoped-for outcome of tumour necrosis. The incidence of cholangitis during the Dose Escalation Part of the study (when patients received a single PCI treatment) was similar across the doses (approximately 70%) whereas, in the Extended Part of Phase I, six of the seven patients (85.7%) experienced cholangitis. Of the five patients who received a second administration, two patients experienced cholangitis after the second PCI treatment. None led to discontinuation of study treatment or study

discontinuation/withdrawal. Overall, no correlation between PCI treatment and time to onset of cholangitis was evident.

Overall, 18 patients (78.3%) experienced a total of 49 treatment-emergent serious adverse events (TESAEs); the most frequently reported SAE was cholangitis (14 patients [60.9%]). None of these SAEs led to discontinuation of study treatment or study discontinuation/withdrawal. Four patients in the Extended Part of Phase I had their treatment interrupted due to TESAEs. No patients died due to TEAEs during the study, but one patient died due to underlying disease/cholangiosepsis.

Laboratory test results were generally as expected for this population with cholangiocarcinoma requiring biliary stenting and on cyclic gemcitabine/cisplatin chemotherapy. Overall, there were no unexpected laboratory findings in this study because of the use of PCI.

Efficacy results

The number of patients in each treatment cohort is small so, although a preliminary assessment of efficacy is possible, results should be interpreted with caution, particularly as the cohorts were not randomised and patients had different prognoses at study entry. Overall, 15 of 22 evaluable patients (68.2%) were alive and progression-free at their 6-month scan after the end of the active treatment phase. A total of 19 patients were evaluable for BOR (three patients had no RECIST data entered but had their progression status captured). According to the Investigators, the majority of these patients had BORs of PR (5 of 19 patients; 26.3%) or SD (8 of 19 patient; 42.1%). Overall, six of the 19 evaluable patients had a BOR of confirmed CR or PR resulting in an Overall Response Rate of 31.6%. A total of 14 of the 19 evaluable patients had a BOR of confirmed CR, PR, or SD resulting in a Disease Control Rate of 73.7%.

A reduction or no change in tumour size was evident in 13 of 17 patients (76.5%) with measurable disease at screening.

Pharmacokinetic results

The PK of fimaporfin was characterised by a relatively slow elimination, with elimination half-lives varying from 18 to 107 days. The total clearance of fimaporfin ranged from 0.058 to 0.359 mL/(hrs*kg) and appeared independent of dose. The volume of distribution in the elimination phase varied between 112 and 294 mL/kg and appeared also independent of dose. The increase in maximum plasma concentration (C_{max}) was proportional to the increase in dose while the increase in area under the plasma concentration versus time curve from time 0 to infinity ($AUC_{0\text{-}inf}$) was higher than the increase in dose. However, since the mean parameter values for the two lower dose levels were based on data from only three patients in each dose group, a conclusion on dose-linearity should be drawn with some caution. Fimaporfin was detected in faeces in a subset of patients in the Dose Escalation Part of this study.

There was a large variability in the estimated exposure to gemcitabine (2,2-difluorodeoxycytidine, dFdC) across the patient group. The reason for this is unknown but likely to be influenced by the number of samples available. Most patients in the study had PK parameter values in the same range as published data but occasionally values were found outside of the published ranges. The route of elimination of dFdC is almost entirely by deamination via cytidine deaminase to its primary metabolite 2,2-difluorodeoxyuridine (dFdU) and excretion via the kidneys. It is considered unlikely that this has been affected by fimaporfin which is assumed to be excreted almost entirely via the bile.

Conclusion

- Both a one- and two-administration schedule of Amphinex-induced PCI of gemcitabine followed by systemic gemcitabine/cisplatin chemotherapy were shown to be tolerable as no DLTs or SLTs were reported.
- The most frequently reported TEAEs were photosensitivity reactions and cholangitis.
- All photosensitivity TEAEs were Grade 1 or Grade 2 in severity and none led to discontinuation of study treatment or study discontinuation/withdrawal, and none were reported as SAEs. Overall, most of the photosensitivity reactions resolved quickly; almost half (47.2%) resolved within 2 days.
- The majority of patients had a TEAE of cholangitis; these events were not related to the PCI treatment but to biliary stenting, were all Grade 2 or Grade 3 in severity, generally resolved within 1 to 5 days, and none led to discontinuation of study treatment or study discontinuation/withdrawal.
- Changes in liver function tests and haematology were in line with expectations for this patient population receiving cyclic chemotherapy.
- Serious local reactions like bile duct perforation, were not observed in this study, thus the PCI treatment seems to have a good safety profile with regards to local effects in the bile duct.
- The PK of fimaporfin is characterised by a rapid distribution phase and a relatively slow elimination phase and fimaporfin is believed to be excreted via the bile into faeces.
- Confirmation of efficacy cannot be concluded due to the small number of patients/limited data available. However, a preliminary assessment showed that the majority of patients (68.2%) were alive and progression-free at their 6-month scan after the end of the active treatment phase, and 14 of 19 evaluable patients had a BOR of confirmed CR, PR, or SD resulting in a DCR of 73.7%.
- A reduction or no change in target lesion size was achieved in 13 of 17 patients (76.5%) with measurable disease at screening.

Although efficacy was not a primary objective of this study and the study was uncontrolled, preliminary efficacy data are encouraging.

Date of Report: 17 November 2020