2 STUDY 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: PC-A11:Amphinex® , bleomycin		
Name of Active Ingredient: Fimaporfin and bleomycin		

TITLE OF STUDY:
An open-label, single arm, multi-center, Phase 2 study to evaluate the safety and efficacy of PC-A11 with superficial and interstitial light application in patients with recurrent head and neck squamous cell carcinoma unsuitable for surgery and radiotherapy.

INVESTIGATORS: Dr Krauss; Dr Betz; Dr Schröder; Dr Karakullukcu; Dr Forster; Dr Dolivet; Dr Plesniene; Dr Lyczek.

STUDY CENTRES: The study was conducted at 8 sites in France, Germany, Lithuania, Poland, The Netherlands and the United Kingdom (UK).

PUBLICATIONS:
None.

STUDY PERIOD:	**DEVELOPMENT PHASE:**
First patient recruited 15 May 2012 Last patient completed 27 August 2015 On 03 June 2015, the Sponsor decided to terminate the study due to increased competition by emerging immunotherapies for this patient population. In addition, optimizing the light dose for interstitial (from now on referred to as intratumoral) light application was more complicated than anticipated. No safety concerns led to the termination of the study and all patients were followed-up until their last scheduled protocol visit.	2

OBJECTIVES:

'Run-in' part:

The 'Run-in' part primary objective:

- To determine a safe light dose for PC-A11 with intratumoral laser light application in patients with recurrent head and neck squamous cell carcinoma unsuitable for surgery and radiotherapy and eligible for intratumoral laser light application.

The 'Run-in' part secondary objective:

- To make a preliminary assessment of efficacy at 3 months.
- To assess the safety and tolerability.
- To characterize the pharmacokinetics (PK).
- To test the Quality of Life (QoL).

The 'Run-in' part exploratory objectives:

- To assess possible predictive biomarkers.
- To assess local tumor response by volumetric measurements.
- To assess immune-modulating effects of Amphinex®.
- To assess skin photosensitivity in a subset of patients.
- To assess fluorescence of tumor tissue in a subset of patients.

'Expansion' part:

The 'Expansion' part primary objective:

- To assess the efficacy of PC-A11 with superficial and/or intratumoral laser light application in patients with recurrent squamous cell carcinoma of the head and neck (SCCHN) by means of local non-progression rates at 6 months.

The 'Expansion' part secondary objectives:

- To assess efficacy by means of:
  - Local non-progression rate at 3 months.
  - Objective Overall Response Rate (ORR).
  - Disease Control Rate (DCR).
  - Progression Free Survival (PFS).
  - Overall Survival (OS).
- To assess the safety and tolerability.
- To characterize the PK.
- To test the QoL.

The 'Expansion' part exploratory objectives:

- To assess possible predictive biomarkers.
- To assess local tumor response by volumetric measurements.
- To evaluate immune-modulating effects of Amphinex.
- To assess skin photosensitivity in a subset of patients.

To assess fluorescence of tumor tissue in a subset of patients.

METHODS:

This study was an open-label, single arm, multi-center Phase 2 study to assess the safety and efficacy of PC-A11 in recurrent SCCHN patients who were unsuitable for surgery and radiotherapy. Patients received a single treatment of PC-A11 (Amphinex solution for injection intravenously and bleomycin solution for injection intravenously, followed by superficial and/or laser light application through laser light emitting fibers.

Under Protocol Version 1, all patients were treated with the same laser light dose, either by a single fiber for treatment of superficial tumors only; or by multiple fibers placed intratumorally; or by both superficial and intratumoral treatment. Protocol Version 2 introduced the 'Run-in' part; a light dose escalation for intratumoral light application. Patients treated with intratumoral laser light dose under Protocol Version 1 and those who received both superficial and intratumoral laser light applications were grouped into a 'Pre-expansion' treatment part.

At the time of termination, the study consisted of the following 2 treatment parts:

- A 'Run-in' part (for patients eligible for treatment with intratumoral illumination):
  - During the 'Run-in' part a safe light dose for intratumoral laser light application with acceptable local toxicity and showing early signs of efficacy were to be established in a small number of patients. It was expected that approximately 18-25 evaluable patients were needed to assess safety and efficacy of PC-A11; however, only 11 patients were treated in this part. An interim analysis was planned once 12 patients from the selected dose had provided efficacy data at 3 months. However, the target number of patients was not reached at a selected dose and the interim analysis was not performed.
- An 'Expansion' part:
  - Patients eligible for superficial laser light application were enrolled in the 'Expansion' part of the study. Patients eligible for intratumoral laser light application were to be recruited in the 'Expansion' part of the study when a light dose was established for intratumoral laser light application in the 'Run-in' part; however, this light dose for intratumoral illumination was never reached so the 'Expansion' part comprised only those patients requiring superficial laser light application. Up to 68 evaluable patients were planned to be enrolled in the 'Expansion' part; however, only 7 patients were treated in this part. .

NUMBER OF PATIENTS:

Planned: 'Run-in' part: 18-25; 'Expansion' part: 60-68
Screened: 40
Total treated : 24
Registered: 'Run-in' part: 11; 'Expansion' part: 7 and 'Pre-expansion' part: 6
Completed: 'Run-in' part: 7; 'Expansion' part: 4 and 'Pre-expansion' part: 3

INDICATION AND MAIN CRITERIA FOR INCLUSION:
Patients must have been aged ≥18 years with a histologically or cytologically confirmed diagnosis of recurrent SCCHN, with or without metastasis, considered unsuitable for surgery and radiotherapy. Patients must have had an Eastern Cooperative Oncology Group (ECOG) Performance status ≤1 and at least 1 measurable target lesion at baseline.

TEST PRODUCT:
Amphinex:
The Amphinex (active substance: fimaporfin) component of PC-A11 was injected intravenously at a fimaporfin fixed dose of 0.25 mg/kg on Day 0. The patient was monitored closely for a minimum of 2 hours following Amphinex administration.
Bleomycin:
The bleomycin component of PC-A11 was administered intravenously at a fixed dose of 15000 IU/m^2 on Day 4 (4 days after Amphinex administration). The patient was monitored closely for a minimum of 2 hours following bleomycin administration.
Laser light application:
Laser light application was performed using the photochemical internalization (PCI)-652 nm red light laser 3 hours (±1 hour) after bleomycin administration. Multiple cylindrical diffuser fibers were used for intratumoral illumination and a single frontal distributor fiber was used for superficial illumination.

COMPARATOR PRODUCT:
Not applicable.

DURATION/FOLLOW-UP:
Patients were screened during a period of 28 days before study entry. Patients were admitted to hospital prior to the administration of Amphinex and remained as an inpatient for approximately 7 days. Patients included in the 'Run-in' part were followed-up to 3 months, and patients in the 'Pre-expansion' part and the 'Expansion' part were followed until disease progression, but no longer than 1 year, or until study discontinuation for any other reason. Survival status was documented in an extended follow-up phase until death for all patients.

CRITERIA FOR EVALUATION:
Safety: Safety was assessed by measurement of physical examination, weight, vital signs, performance status, laboratory evaluations (hematology and biochemistry), electrocardiogram (ECG), pain assessment, recording of concurrent illness/therapy, adverse events (AEs) and dose-limiting toxicity (DLT).
Efficacy: Efficacy was assessed by measurement of Baseline disease and local tumor response using either computed tomography (CT), magnetic resonance imaging (MRI) and/or clinical examination (using caliper or ruler measurements) according to the modified Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria.
Pharmacokinetics: PK in serum were assessed in all patients for Amphinex (fimaporfin) PK and in 6 patients for bleomycin PK. However, data for the first 4 patients were considered sufficient to meet the planned requirements for bleomycin PK.
Other: Other assessments included QoL (European Organisation for Research and Treatment of Cancer [EORTC] QLQ-C30 and QLQ-H&N35), tissue sampling to investigate possible predictive biomarkers, blood sampling to evaluate the immune activity of Amphinex, systematic skin photosensitivity measurements and multi-diameter single fiber reflectance spectroscopy (MDSFR) and single fiber fluorescence spectroscopy (SFFL) measurements (in a subset of patients only).

STATISTICAL METHODS:
As the study was terminated, no formal statistical analyses were performed. Demography and safety data were summarized and listed, and efficacy data was listed only.

RESULTS:
Demographics: In the 'Expansion' part, 4/7 patients (57%) completed the study. Mean age was 70.0 years (range 58 to 78 years). All patients were White and 71% of patients were male. Overall, 5 patients (71%) had previously consumed or currently consume alcohol and all patients had previously smoked or currently smoke. The most common tumor location at first diagnosis was the oropharynx (5 patients [71%]).
In the 'Run-in' part, 7/11 patients (64%) overall completed the study: 1 patient (9%) receiving 10 J/cm light dose, 5 patients (45%) receiving 20 J/cm light dose and 1 patient (9%) receiving 30 J/cm light dose. Overall mean age was 56.9 years (range 43 to 66 years), with patients receiving 20 J/cm older on average than patients in the remaining groups. All patients were White and 55% of patients overall were male. The

majority of patients had previously consumed or currently consume alcohol and previously smoked or currently smoke. The most common tumor location at first diagnosis overall was oral cavity (5 patients [45%]).
In the 'Pre-expansion' part, 3/6 patients (50%) completed the study. Mean age was 53.7 years and all patients were White. There were more males (4 patients [67%]) than females (2 patients [33%]). Approximately two-thirds of patients had previously used alcohol and previously smoked. The most common tumor location at first diagnosis was base of tongue (4 patients [67%]).
Efficacy: In the 'Expansion' part, overall 3 patients (43%) had a best overall response of complete response by Week 24, 1 patient (14%) was not evaluable and 3 patients (43%) did not have a Week 24 measurement recorded. Evaluation of progression-free interval in PCI-treated lesions showed that the percent progression-free rate decreased over time and reached approximately 60% at the last observation. Evaluation of OS showed that OS had decreased to approximately 81% by the last observation.

As of 28 June 2016, OS was as follows:

- In the 'Pre-expansion' part all 6 patients were dead: 5 patients died due to disease progression and 1 patient died from a myocardial infarction. Survival ranged from 3 months to 16.5 months.
- In the 'Run-in' part 3 patients were alive and 8 patients were dead. Of the 8 patients who died, 7 patients died due to disease progression and 1 patient died from pneumonia. Survival ranged from 2.5 months to 19 months.
- In the 'Expansion' part 5 patients were alive and 2 patients had died due to disease progression. Survival ranged from 4 months to 40 months, with a median survival time of 31 months.

No efficacy analyses were performed for the 'Pre-expansion' part or the 'Run-in' part patients as an optimal light dose was not established in these treatment groups.
Pharmacokinetics: Concentrations of fimaporfin in plasma were presented graphically for all patients. The blood concentrations decreased sharply and fell below 1000 ng/mL for most patients by Day 6, representing an 80% reduction compared to the maximum blood concentration measured after 2 to 3 minutes. The results confirmed the earlier findings in a Phase I study (PCI 101/06, Amphinex escalation study). PK results for bleomycin were analyzed for 4 patients in total. Fimaporfin does not seem to influence the PK of bleomycin and the half-life of bleomycin (3 hours) was aligned with the results reported in literature.
Safety: In the 'Expansion' part, 6 patients (86%) experienced treatment-emergent adverse events (TEAEs) that were considered related to study treatment. The most common treatment-related TEAEs were pain and constipation. Five patients (71%) experienced TEAEs that were considered severe in intensity. The most common severe TEAE was pain. In total, 2 patients (29%) experienced SAEs. The SAEs were necrosis, diverticulitis and obstructive airway disorder. There were no deaths, TEAEs leading to discontinuation or serious adverse incidents (SAIs).
There were no clinically meaningful changes observed for ECOG status score, clinical laboratory parameters, vital signs parameters, ECGs or physical examinations.

Overall in the 'Run-in' part with dose escalation in light, there were no observed dose-limiting toxicities (DLTs). TEAEs that were considered severe in intensity were reported for 2 patients (67%) in the PC-A11 10 J/cm, 6 patients (86%) in the PC-A11 20 J/cm and 1 patient (100%) in the PC-A11 30 J/cm treatment groups. The most common severe TEAE was pain. One patient in the PC-A11 10 J/cm treatment group experienced a TEAE of toxicity to various agents (opioid intoxication) that was considered life threatening. TEAEs that were considered related to study treatment were reported for 3 patients (100%) in the PC-A11 10 J/cm, 7 patients (100%) in the PC-A11 20 J/cm and 1 patient (100%) in the PC-A11 30 J/cm treatment groups. The most common treatment-related TEAE was pain, which was observed more frequently in the PC-A11 20 J/cm treatment group compared with the remaining light dose groups. Overall, 5 patients (45%) experienced SAEs. The most common SAE was soft tissue injury, reported for 2 patients (29%) in the PC-A11 20 J/cm group. There were no deaths, TEAEs leading to discontinuation or SAIs. There were no clinically meaningful changes observed for ECOG status score, clinical laboratory parameters, vital signs parameters, ECGs or physical examinations.

In the 'Pre-expansion' part, 1 patient experienced a TEAE of myocardial infarction that lead to death the same day (99 days after Amphinex administration and considered unrelated) and 1 patient experienced a TEAE of hypoperfusion that was considered life threatening and classed as a suspected unexpected serious adverse reaction (SUSAR). All 6 patients (100%) experienced a TEAE that was considered related to study treatment, the most common of which were face oedema, application site pain and erythema. Five of the treatment-related TEAEs were SUSARs: arthralgia, hypoperfusion and soft tissue injury (3 events in 3 patients). In total, 3 patients (50%) experienced TEAEs that were considered severe in intensity, with the most common severe TEAEs being soft tissue injury and pain. Overall, 5 patients (83%) experienced SAEs, with the most common SAE being soft tissue injury and was reported for 3 patients (50%). There were no clinically meaningful changes observed for ECOG status score, clinical laboratory parameters, vital signs parameters, ECGs or physical examinations.

The TEAEs were further reviewed manually by the medical monitor and categorized as photosensitivity-related TEAEs and procedural-related TEAEs.

For all parts of the study, a total of 16 patients experienced photosensitivity-related TEAEs. For 5 patients, photosensitivity-related TEAEs were ongoing with remaining symptoms and for 1 patient there were remaining symptoms but it was unknown whether the event was ongoing. The most common preferred term for these events was photosensitivity reaction, which was experienced by 5 patients.

The procedural-related TEAEs were further categorized. For all parts of the study, a total of 15 patients (63%) experienced soft tissue swelling-related TEAEs. A worst severity of severe was recorded for 5 patients, moderate for 8 patients and mild for 2 patients. For 5 patients, soft tissue swelling-related TEAEs were ongoing, for 1 patient there were residual side effects and for 1 patient the outcome was unknown. The most commonly reported soft tissue swelling-related TEAE was face oedema reported for 5 patients. For all parts of the study, a total of 21 patients (88%) experienced pain-related TEAEs. A worst severity of severe was recorded for 14 patients, moderate for 6 patients and mild for 1 patient. For 6 patients, pain-related TEAEs were ongoing and for 1 patient there were residual side effects. The duration for pain-related TEAEs that were not ongoing ranged from <1 day to 84 days (median duration 4 days). The majority of these events were considered mild to moderate in severity and manageable with pharmacological intervention. In certain cases it was difficult to differentiate between tumor-related pain and pain that may have been temporarily exacerbated by the PCI procedure. The most commonly reported pain-related TEAE was the general preferred term pain reported for 13 patients. A total of 9 patients (38%) experienced tissue loss-related TEAEs in all 3 parts of the study. A worst severity of severe was recorded for 3 patients all with serious soft tissue injury that was ongoing. A worst severity of moderate was recorded for 6 patients. Hypoperfusion was recorded as a serious TEAE for 1 patient. One patient had a moderate localized infection TEAE, with a concurrent TEAE of fistula and a later TEAE of fistula repair. One patient had severe hypertension and high blood pressure for <1 day.

CONCLUSIONS: The overall conclusions of the study are as follows:

- The severe soft tissue injuries experienced in the 'Pre-expansion' part were considered to be a result of a too strong effect from the use of multiple fibers for intratumoral light application giving a too high total light dose, as there were no such findings in patients with superficial light application. A dose escalation ('Run-in' part) for total light dose was introduced for the intratumoral light application.
- After the introduction of the 'Run-in' part, these strong effects of the treatment were not observed and Amphinex was well tolerated when administered in combination with bleomycin and intratumoral light application to patients with SCCHN.
- For tumors requiring superficial light application only, Amphinex was well tolerated when administered in combination with bleomycin to patients with SCCHN. Thus, no strong effects on soft tissues were seen in these patients.
- Photosensitivity reactions were reported for 16 out of 24 patients treated in this study overall (67%) Most of these events were mild in intensity. Amongst the procedure-related TEAEs, pain was a commonly-reported TEAE in all treatment parts of the study with 15 out of 24 patients (63%) experiencing procedure-related pain. However, no TEAEs of pain we reported for the lowest intratumoral light dose of 10 J/cm per fiber.

- There were no clinically meaningful changes or notable trends for ECOG status score, clinical laboratory test, vital signs, ECG or physical examination parameters.
- Overall, 43% of patients treated with superficial light only ('Expansion' part) had a best overall response of complete response by Week 24. This confirms the results from the preliminary efficacy observed in the Phase 1 study (PCI 101/06).
- Plasma concentrations of fimaporfin decreased sharply after administration and fell below 1000 ng/mL for most patients by approximately Day 6 in all parts of the study, again confirming the results observed in the Phase 1 study (PCI 101/06). However, precautions should be taken to limit exposure to sunlight and bright indoor light after administration based on the photosensitivity reactions experienced by 16 out of 24 patients.

DATE OF FINAL REPORT: 31 August 2016