# Clinical trial results:
# 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

## Summary

| | |
|---|---|
| EudraCT number | 2012-002888-10 |
| Trial protocol | GB DE FR LT NO AT |
| Global end of trial date | 21 February 2019 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 23 May 2021 |
| First version publication date | 23 May 2021 |
| Summary attachment (see zip file) | PCI-A202-12 CSR synopsis (PCI-A202-12-synopsis.pdf) |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | PCI A202/12 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01900158 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | PCI Biotech AS |
| Sponsor organisation address | Ullernchausséen 64, Oslo, Norway, N-0379 |
| Public contact | Regulatory Affairs, Theradex (Europe) Ltd, +44 01293510319, regulatory@theradex.co.uk |
| Scientific contact | Clinical Trial Disclosure Desk, PCI Biotech AS, +47 67 11 54 00, |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 17 November 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 21 February 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 21 February 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Phase I Dose Escalation
• 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

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 cholangiocarcinoma

Please note, as the Phase II part of the study was not conducted as planned, therefore the main objective for this part have not been included. A separate Protocol for the modified part of the Phase II study has been prepared.

Protection of trial subjects:

Photosensitivity following PCI treatment. Patients could be sensitive to light for a period after exposure to fimaporfin, and patients are therefor advised to take precautions to prevent skin and eye sensitivity reactions. Patients receive detailed information about possible reactions, how to protect themselves and how they should gradually increase their light exposure and additionally on how and when to test their degree of photosensitivity.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 15 November 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Norway: 2 |
| Country: Number of subjects enrolled | United Kingdom: 3 |
| Country: Number of subjects enrolled | Germany: 19 |
| Worldwide total number of subjects | 24 |
| EEA total number of subjects | 24 |

Notes:

| Subjects enrolled per age group | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 13 |
| From 65 to 84 years | 11 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

First patient enrolled: 16 January 2014
Last patient last visit: 21 February 2019
Patients recruited at eight centres; six centres in Germany, one centre in the UK, and one centre in Norway

### Pre-assignment

Screening details:

Patients had to be ≥18 years, have an estimated life expectancy ≥12 weeks and had to have histopathologically/cytologically (C5) verified adenocarcinoma consistent with CCA.

### Period 1

| | |
|---|---|
| Period 1 title | Dose escalation phase (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

None

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Cohort 1: 0.06 / 15 |

Arm description:

Patients were treated with a single PCI treatment (Amphinex 0.06 mg/kg + gemcitabine 1000 mg/m2 and intraluminal laser light 15 J/cm) followed by recognised standard of care treatment for this indication: systemic chemotherapy consisting of up to eight cycles of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2. Amphinex and gemcitabine were considered IMPs in this study.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Amphinex |
| Investigational medicinal product code | Not Applicable |
| Other name | Fimaporfin |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Amphinex solution for injection was administered at a dose of 0.06 mg/kg intravenously on Day 0.

| | |
|---|---|
| Investigational medicinal product name | Gemcitabine |
| Investigational medicinal product code | Not Applicable |
| Other name | Not Applicable |
| Pharmaceutical forms | Powder for solution for infusion, Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A single gemcitabine infusion was administered at a dose of 1000 mg/m2 intravenously on Day 4.

| | |
|---|---|
| **Arm title** | Cohort 2: 0.06 / 30 |

Arm description:

Patients were treated with a single PCI treatment (Amphinex 0.06 mg/kg + gemcitabine 1000 mg/m2 and intraluminal laser light 30 J/cm) followed by recognised standard of care treatment for this indication: systemic chemotherapy consisting of up to eight cycles of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2. Amphinex and gemcitabine were considered IMPs in this study.

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | Amphinex |
| Investigational medicinal product code | Not Applicable |
| Other name | Fimaporfin |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Amphinex solution for injection was administered at a dose of 0.06 mg/kg intravenously on Day 0.

| | |
|---|---|
| Investigational medicinal product name | Gemcitabine |
| Investigational medicinal product code | Not Applicable |
| Other name | Not Applicable |
| Pharmaceutical forms | Powder for solution for infusion, Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A single gemcitabine infusion was administered at a dose of 1000 mg/m2 intravenously on Day 4.

| | |
|---|---|
| **Arm title** | Cohort 3: 0.12 / 30 |

Arm description:

Patients were treated with a single PCI treatment (Amphinex 0.12 mg/kg + gemcitabine 1000 mg/m2 and intraluminal laser light 30 J/cm) followed by recognised standard of care treatment for this indication: systemic chemotherapy consisting of up to eight cycles of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2. Amphinex and gemcitabine were considered IMPs in this study.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Amphinex |
| Investigational medicinal product code | Not Applicable |
| Other name | Fimaporfin |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Amphinex solution for injection was administered at a dose of 0.12 mg/kg intravenously on Day 0.

| | |
|---|---|
| Investigational medicinal product name | Gemcitabine |
| Investigational medicinal product code | Not Applicable |
| Other name | Not Applicable |
| Pharmaceutical forms | Powder for solution for infusion, Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A single gemcitabine infusion was administered at a dose of 1000 mg/m2 intravenously on Day 4.

| | |
|---|---|
| **Arm title** | Cohort 4: 0.25 / 30 |

Arm description:

Patients were treated with a single PCI treatment (Amphinex 0.25 mg/kg + gemcitabine 1000 mg/m2 and intraluminal laser light 30 J/cm) followed by recognised standard of care treatment for this indication: systemic chemotherapy consisting of up to eight cycles of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2. Amphinex and gemcitabine were considered IMPs in this study.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Amphinex |
| Investigational medicinal product code | Not Applicable |
| Other name | Fimaporfin |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Amphinex solution for injection was administered at a dose of 0.25 mg/kg intravenously on Day 0.

| | |
|---|---|
| Investigational medicinal product name | Gemcitabine |
| Investigational medicinal product code | Not Applicable |
| Other name | Not Applicable |
| Pharmaceutical forms | Powder for solution for infusion, Solution for infusion |

| | |
|---|---|
| Routes of administration | Intravenous use |

Dosage and administration details:

A single gemcitabine infusion was administered at a dose of 1000 mg/m2 intravenously on Day 4.

| **Arm title** | Cohort 5: 0.25 / 30 (Extended Part) |
|---|---|

Arm description:

Patients were treated with up to two PCI treatments (Amphinex 0.25 mg/kg + gemcitabine 1000 mg/m2 and intraluminal laser light 30 J/cm) with recognised standard of care treatment for this indication: systemic chemotherapy consisting of up to eight cycles of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2. If a patient received a second PCI treatment, the intraluminal laser light and single gemcitabine administration was to take place on the planned Day 1 of Cycle 5 treatment (no cisplatin was given, only gemcitabine as part of the PCI treatment). After the intraluminal laser light, patients resumed the 21-day cycle of treatment with combination chemotherapy on Day 8 of Cycle 5 for up to a total of eight cycles. Amphinex and gemcitabine were considered IMPs in this study.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Amphinex |
| Investigational medicinal product code | Not Applicable |
| Other name | Fimaporfin |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Amphinex solution for injection was administered at a dose of 0.25 mg/kg intravenously on Day 0. Patients could receive a second PCI treatment at the end of Cycle 4 of the combination chemotherapy treatment (gemcitabine/cisplatin). The second PCI treatment included a single intravenous dose of Amphinex on Day 18 of Cycle 4.

| | |
|---|---|
| Investigational medicinal product name | Gemcitabine |
| Investigational medicinal product code | Not Applicable |
| Other name | Not Applicable |
| Pharmaceutical forms | Powder for solution for injection/infusion, Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A gemcitabine infusion was administered at a dose of 1000 mg/m2 intravenously on Day 4. If a patient received a second PCI treatment, a second gemcitabine infusion was administered at a dose of 1000 mg/m2 intravenously 4 days after the second Amphinex dose (Day 1 of Cycle 5).

| **Number of subjects in period 1[1]** | Cohort 1: 0.06 / 15 | Cohort 2: 0.06 / 30 | Cohort 3: 0.12 / 30 |
|---|---|---|---|
| Started | 3 | 3 | 4 |
| Completed | 2 | 3 | 3 |
| Not completed | 1 | 0 | 1 |
| Consent withdrawn by subject | 1 | - | 1 |
| Physician decision | - | - | - |
| Progressive disease | - | - | - |

| **Number of subjects in period 1[1]** | Cohort 4: 0.25 / 30 | Cohort 5: 0.25 / 30 (Extended Part) |
|---|---|---|
| Started | 6 | 7 |

| | | |
|---|---|---|
| Completed | 3 | 5 |
| Not completed | 3 | 2 |
| Consent withdrawn by subject | - | - |
| Physician decision | 2 | - |
| Progressive disease | 1 | 2 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 23 patients were enrolled and treated. In addition, one patient (Patient 24) was enrolled but not treated; this patient was enrolled in error due to a screeing failure as inclusion criteria were not met.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Cohort 1: 0.06 / 15 |
| Reporting group description: | |
| Patients were treated with a single PCI treatment (Amphinex 0.06 mg/kg + gemcitabine 1000 mg/m2 and intraluminal laser light 15 J/cm) followed by recognised standard of care treatment for this indication: systemic chemotherapy consisting of up to eight cycles of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2. Amphinex and gemcitabine were considered IMPs in this study. | |
| Reporting group title | Cohort 2: 0.06 / 30 |
| Reporting group description: | |
| Patients were treated with a single PCI treatment (Amphinex 0.06 mg/kg + gemcitabine 1000 mg/m2 and intraluminal laser light 30 J/cm) followed by recognised standard of care treatment for this indication: systemic chemotherapy consisting of up to eight cycles of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2. Amphinex and gemcitabine were considered IMPs in this study. | |
| Reporting group title | Cohort 3: 0.12 / 30 |
| Reporting group description: | |
| Patients were treated with a single PCI treatment (Amphinex 0.12 mg/kg + gemcitabine 1000 mg/m2 and intraluminal laser light 30 J/cm) followed by recognised standard of care treatment for this indication: systemic chemotherapy consisting of up to eight cycles of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2. Amphinex and gemcitabine were considered IMPs in this study. | |
| Reporting group title | Cohort 4: 0.25 / 30 |
| Reporting group description: | |
| Patients were treated with a single PCI treatment (Amphinex 0.25 mg/kg + gemcitabine 1000 mg/m2 and intraluminal laser light 30 J/cm) followed by recognised standard of care treatment for this indication: systemic chemotherapy consisting of up to eight cycles of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2. Amphinex and gemcitabine were considered IMPs in this study. | |
| Reporting group title | Cohort 5: 0.25 / 30 (Extended Part) |
| Reporting group description: | |
| Patients were treated with up to two PCI treatments (Amphinex 0.25 mg/kg + gemcitabine 1000 mg/m2 and intraluminal laser light 30 J/cm) with recognised standard of care treatment for this indication: systemic chemotherapy consisting of up to eight cycles of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2. If a patient received a second PCI treatment, the intraluminal laser light and single gemcitabine administration was to take place on the planned Day 1 of Cycle 5 treatment (no cisplatin was given, only gemcitabine as part of the PCI treatment). After the intraluminal laser light, patients resumed the 21-day cycle of treatment with combination chemotherapy on Day 8 of Cycle 5 for up to a total of eight cycles. Amphinex and gemcitabine were considered IMPs in this study. | |

| Reporting group values | Cohort 1: 0.06 / 15 | Cohort 2: 0.06 / 30 | Cohort 3: 0.12 / 30 |
|---|---|---|---|
| Number of subjects | 3 | 3 | 4 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 3 | 1 | 1 |
| Adults (65 years and over) | 0 | 2 | 3 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 61.7 | 66.7 | 72.8 |
| standard deviation | ± 3.21 | ± 5.69 | ± 7.14 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 1 | 3 | 3 |
| Male | 2 | 0 | 1 |

| | | | |
|---|---|---|---|
| Race (NIH/OMB)<br>Units: Subjects | | | |
| White | 3 | 3 | 4 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Not Hispanic | 3 | 3 | 4 |
| ECOG Performance Status<br>Units: Subjects | | | |
| equals 0 | 3 | 2 | 4 |
| equals 1 | 0 | 1 | 0 |
| Total sum of longest diameter of target lesions<br>Units: millimeter(s) | | | |
| arithmetic mean | 23.50 | 28.00 | 41.67 |
| standard deviation | ± 12.021 | ± 12.728 | ± 25.968 |

| **Reporting group values** | Cohort 4: 0.25 / 30 | Cohort 5: 0.25 / 30 (Extended Part) | Total |
|---|---|---|---|
| Number of subjects | 6 | 7 | 23 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 5 | 3 | 13 |
| Adults (65 years and over) | 1 | 4 | 10 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 59.0 | 68.3 | |
| standard deviation | ± 9.10 | ± 8.13 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 6 | 7 | 20 |
| Male | 0 | 0 | 3 |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| White | 6 | 7 | 23 |
| Ethnicity (NIH/OMB)<br>Units: Subjects | | | |
| Not Hispanic | 6 | 7 | 23 |
| ECOG Performance Status<br>Units: Subjects | | | |
| equals 0 | 4 | 3 | 16 |
| equals 1 | 2 | 4 | 7 |
| Total sum of longest diameter of target lesions<br>Units: millimeter(s) | | | |
| arithmetic mean | 51.80 | 57.70 | |
| standard deviation | ± 24.722 | ± 33.874 | - |

## End points

### End points reporting groups

| Reporting group title | Cohort 1: 0.06 / 15 |
|---|---|
| Reporting group description: | |
| Patients were treated with a single PCI treatment (Amphinex 0.06 mg/kg + gemcitabine 1000 mg/m2 and intraluminal laser light 15 J/cm) followed by recognised standard of care treatment for this indication: systemic chemotherapy consisting of up to eight cycles of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2. Amphinex and gemcitabine were considered IMPs in this study. | |
| Reporting group title | Cohort 2: 0.06 / 30 |
| Reporting group description: | |
| Patients were treated with a single PCI treatment (Amphinex 0.06 mg/kg + gemcitabine 1000 mg/m2 and intraluminal laser light 30 J/cm) followed by recognised standard of care treatment for this indication: systemic chemotherapy consisting of up to eight cycles of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2. Amphinex and gemcitabine were considered IMPs in this study. | |
| Reporting group title | Cohort 3: 0.12 / 30 |
| Reporting group description: | |
| Patients were treated with a single PCI treatment (Amphinex 0.12 mg/kg + gemcitabine 1000 mg/m2 and intraluminal laser light 30 J/cm) followed by recognised standard of care treatment for this indication: systemic chemotherapy consisting of up to eight cycles of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2. Amphinex and gemcitabine were considered IMPs in this study. | |
| Reporting group title | Cohort 4: 0.25 / 30 |
| Reporting group description: | |
| Patients were treated with a single PCI treatment (Amphinex 0.25 mg/kg + gemcitabine 1000 mg/m2 and intraluminal laser light 30 J/cm) followed by recognised standard of care treatment for this indication: systemic chemotherapy consisting of up to eight cycles of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2. Amphinex and gemcitabine were considered IMPs in this study. | |
| Reporting group title | Cohort 5: 0.25 / 30 (Extended Part) |
| Reporting group description: | |
| Patients were treated with up to two PCI treatments (Amphinex 0.25 mg/kg + gemcitabine 1000 mg/m2 and intraluminal laser light 30 J/cm) with recognised standard of care treatment for this indication: systemic chemotherapy consisting of up to eight cycles of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2. If a patient received a second PCI treatment, the intraluminal laser light and single gemcitabine administration was to take place on the planned Day 1 of Cycle 5 treatment (no cisplatin was given, only gemcitabine as part of the PCI treatment). After the intraluminal laser light, patients resumed the 21-day cycle of treatment with combination chemotherapy on Day 8 of Cycle 5 for up to a total of eight cycles. Amphinex and gemcitabine were considered IMPs in this study. | |

### Primary: Number of subjects with dose-limiting toxicities (DLTs; Cohorts 1, 2, 3 and 4) or schedule limiting toxicities (SLTs; Cohort 5), treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and discontinuations due to TEAEs

| End point title | Number of subjects with dose-limiting toxicities (DLTs; Cohorts 1, 2, 3 and 4) or schedule limiting toxicities (SLTs; Cohort 5), treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and discontinuations due to TEAEs[1] |
|---|---|

End point description:

DLTs were defined as a clinically significant toxicity or abnormal laboratory value assessed as unrelated to the underlying disease, or concomitant medications, related to either PCI treatment or to the combination of PCI treatment with cisplatin/gemcitabine systemic chemotherapy and met criteria based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02.
An SLT was defined as a clinically significant toxicity or abnormal laboratory value assessed as unrelated to the underlying disease or concomitant medications and met criteria based on the NCI CTCAE Version 4.02.
A TEAE was defined as an AE that started on or after the start day of study treatment until up to 30 days after the last study treatment.
An SAE was any unfavourable medical occurrence that at any dose resulted in any medically important condition considered by the Investigator.

| End point type | Primary |
|---|---|

End point timeframe:

DLTs - start of the first PCI treatment up to the end of the first chemotherapy cycle.
SLTs - start of the second PCI treatment up to the end of the 21-day cycle of treatment with systemic cisplatin and gemcitabine

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The study was not formally statistically powered and no statistical hypotheses were tested. Data were summarised descriptively.

| **End point values** | Cohort 1: 0.06 / 15 | Cohort 2: 0.06 / 30 | Cohort 3: 0.12 / 30 | Cohort 4: 0.25 / 30 |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 3 | 4 | 6 |
| Units: Subjects | | | | |
| DLTs/SLTs | 0 | 0 | 0 | 0 |
| TEAEs | 3 | 3 | 4 | 6 |
| SAEs | 2 | 2 | 4 | 4 |
| Discontinuations due to TEAEs | 0 | 0 | 0 | 0 |

| **End point values** | Cohort 5: 0.25 / 30 (Extended Part) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: Subjects | | | | |
| DLTs/SLTs | 0 | | | |
| TEAEs | 7 | | | |
| SAEs | 6 | | | |
| Discontinuations due to TEAEs | 1 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetic profile of Amphinex (fimaporfin) and gemcitabine in plasma

| End point title | Pharmacokinetic profile of Amphinex (fimaporfin) and gemcitabine in plasma |
|---|---|

End point description:

The following pharmacokinetic parameters were used to determine the PK profile of fimaporfin and gemcitabine: elimination half life, total clearance, volume of distribution, maximum plasma concentration, area under the plasma concentration versus time curve.

| End point type | Secondary |
|---|---|

End point timeframe:

Amphinex PK samples were collected ≤24hrs pre Amphinex administration and at various times after Amphinex administration.
Gemcitabine PK samples were collected ≤24hrs pre Gemcitabine administration and at various times after administration.

| End point values | Cohort 1: 0.06 / 15 | Cohort 2: 0.06 / 30 | Cohort 3: 0.12 / 30 | Cohort 4: 0.25 / 30 |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 3 | 4 | 6 |
| Units: Total | | | | |
| number (not applicable) | 3 | 3 | 4 | 6 |

| End point values | Cohort 5: 0.25 / 30 (Extended Part) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: Total | | | | |
| number (not applicable) | 7 | | | |

| Attachments (see zip file) | Secondary endpoint_Pharmacokinetic Profile.pdf |
|---|---|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-Free Survival

| End point title | Progression-Free Survival |
|---|---|

End point description:

Progression-free survival was defined as the time from registration to documented disease progression (according to RECIST 1.1 criteria) or death from any cause.

| End point type | Secondary |
|---|---|

End point timeframe:

Progression free survival was assessed using 6-month scan data. Sufficient data were not available to perform this analysis based on time to progression or death (per protocol) as only survival data were collected during the follow-up period.

| End point values | Cohort 1: 0.06 / 15 | Cohort 2: 0.06 / 30 | Cohort 3: 0.12 / 30 | Cohort 4: 0.25 / 30 |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 3 | 3 | 4 | 6 |
| Units: Subjects | | | | |
| Subjects evaluable for PFS | 3 | 3 | 4 | 6 |
| PFS at 6-month scan | 2 | 3 | 3 | 4 |

| End point values | Cohort 5: 0.25 / 30 (Extended Part) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 6 | | | |
| Units: Subjects | | | | |
| Subjects evaluable for PFS | 6 | | | |
| PFS at 6-month scan | 3 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Best Overall Response (BOR)

| End point title | Best Overall Response (BOR) |
|---|---|

End point description:

The BOR was defined as the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for Progressive Disease the smallest measurements recorded since the treatment started). The patient's BOR assignment was dependant on findings of both target and non-target disease and also took into consideration the appearance of new lesions. Overall response categories were Complete Response (CR), Partial Response (PR), Stable Disease (SD), Not Evaluable (NE) and Progressive Disease (PD).

| End point type | Secondary |
|---|---|

End point timeframe:

Due to limited data available at 24 weeks, this analysis would not be meaningful. A summary of BOR regardless of timepoint was analysed.

| End point values | Cohort 1: 0.06 / 15 | Cohort 2: 0.06 / 30 | Cohort 3: 0.12 / 30 | Cohort 4: 0.25 / 30 |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 2 | 3 | 3 | 6 |
| Units: Subjects | | | | |
| Subjects evaluable for BOR | 2 | 3 | 3 | 6 |
| Complete Response | 0 | 0 | 1 | 0 |
| Partial Response | 0 | 0 | 1 | 3 |
| Stable Disease | 2 | 3 | 1 | 1 |
| Progressive Disease | 0 | 0 | 0 | 1 |
| Not Evaluable | 0 | 0 | 0 | 1 |

| End point values | Cohort 5: 0.25 / 30 (Extended Part) | | | |
|---|---|---|---|---|

| Subject group type | Reporting group | | | |
|---|---|---|---|---|
| Number of subjects analysed | 5 | | | |
| Units: Subjects | | | | |
| Subjects evaluable for BOR | 5 | | | |
| Complete Response | 0 | | | |
| Partial Response | 1 | | | |
| Stable Disease | 1 | | | |
| Progressive Disease | 3 | | | |
| Not Evaluable | 0 | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All AEs/SAEs were recorded from time of informed consent until up to 30 days after the study treatment. After 30 days, only AEs/SAEs considered related to the study treatment or significant were reported.

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 15.1+20.1 |

### Reporting groups

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| Reporting group title | Cohort 1: 0.06 / 15 |

Reporting group description:

Patients were treated with a single PCI treatment (Amphinex 0.06 mg/kg + gemcitabine 1000 mg/m2 and intraluminal laser light 15 J/cm) followed by recognised standard of care treatment for this indication: systemic chemotherapy consisting of up to eight cycles of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2. Amphinex and gemcitabine were considered IMPs in this study.

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| Reporting group title | Cohort 2: 0.06 / 30 |

Reporting group description:

Patients were treated with a single PCI treatment (Amphinex 0.06 mg/kg + gemcitabine 1000 mg/m2 and intraluminal laser light 30 J/cm) followed by recognised standard of care treatment for this indication: systemic chemotherapy consisting of up to eight cycles of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2. Amphinex and gemcitabine were considered IMPs in this study.

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| Reporting group title | Cohort 3: 0.12 / 30 |

Reporting group description:

Patients were treated with a single PCI treatment (Amphinex 0.12 mg/kg + gemcitabine 1000 mg/m2 and intraluminal laser light 30 J/cm) followed by recognised standard of care treatment for this indication: systemic chemotherapy consisting of up to eight cycles of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2. Amphinex and gemcitabine were considered IMPs in this study.

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| Reporting group title | Cohort 4: 0.25 / 30 |

Reporting group description:

Patients were treated with a single PCI treatment (Amphinex 0.25 mg/kg + gemcitabine 1000 mg/m2 and intraluminal laser light 30 J/cm) followed by recognised standard of care treatment for this indication: systemic chemotherapy consisting of up to eight cycles of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2. Amphinex and gemcitabine were considered IMPs in this study.

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| Reporting group title | Cohort 5: 0.25 / 30 (Extended Part) |

Reporting group description:

Patients were treated with up to two PCI treatments (Amphinex 0.25 mg/kg + gemcitabine 1000 mg/m2 and intraluminal laser light 30 J/cm) with recognised standard of care treatment for this indication: systemic chemotherapy consisting of up to eight cycles of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2. If a patient received a second PCI treatment, the intraluminal laser light and single gemcitabine administration was to take place on the planned Day 1 of Cycle 5 treatment (no cisplatin was given, only gemcitabine as part of the PCI treatment). After the intraluminal laser light, patients resumed the 21-day cycle of treatment with combination chemotherapy on Day 8 of Cycle 5 for up to a total of eight cycles. Amphinex and gemcitabine were considered IMPs in this study.

| Serious adverse events | Cohort 1: 0.06 / 15 | Cohort 2: 0.06 / 30 | Cohort 3: 0.12 / 30 |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 2 / 3 (66.67%) | 4 / 4 (100.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

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|---|---|---|---|
| Cardiac disorders | | | |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Impaired gastric emptying | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 3 (66.67%) | 3 / 4 (75.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 2 | 0 / 10 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 4 (25.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disease | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abscess | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholangitis infective | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridial infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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|---|---|---|---|
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Cohort 4: 0.25 / 30 | Cohort 5: 0.25 / 30 (Extended Part) | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 6 / 7 (85.71%) | |
| number of deaths (all causes) | 0 | 1 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Cardiac disorders | | | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Impaired gastric emptying | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 6 / 7 (85.71%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disease | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |

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|---|---|---|---|
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abscess | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangitis infective | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridial infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | Cohort 1: 0.06 / 15 | Cohort 2: 0.06 / 30 | Cohort 3: 0.12 / 30 |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 3 / 3 (100.00%) | 4 / 4 (100.00%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Surgical and medical procedures | | | |
| Cholangiostomy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 2 / 3 (66.67%) | 2 / 4 (50.00%) |
| occurrences (all) | 3 | 4 | 2 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Swelling | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

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|---|---|---|---|
| Chills | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Disease progression | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Productive cough | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Wheezing | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mental disorder | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Product issues | | | |

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|---|---|---|---|
| Device occlusion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 1 | 0 | 1 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Body temperature | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haematocrit decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood magnesium decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood potassium decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood urea increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Electrocardiogram abnormal | | | |

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| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Monocyte count increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Troponin T increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Vascular access complication | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Burns second degree | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tooth fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Polyneuropathy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Neuropathy peripheral | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypertonia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 3 / 4 (75.00%) |
| occurrences (all) | 6 | 3 | 6 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 2 / 4 (50.00%) |
| occurrences (all) | 0 | 3 | 2 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Anaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Thrombocytosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 1 / 3 (33.33%) | 1 / 4 (25.00%) |
| occurrences (all) | 4 | 1 | 1 |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 1 / 3 (33.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 6 | 1 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 3 (66.67%) | 1 / 4 (25.00%) |
| occurrences (all) | 1 | 2 | 1 |
| Constipation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 2 / 4 (50.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ascites | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Impaired gastric emptying | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 2 / 3 (66.67%) | 3 / 4 (75.00%) |
| occurrences (all) | 4 | 2 | 10 |
| Hepatobiliary disease | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Jaundice | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 3 (33.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Haemobilia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hepatic pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Skin and subcutaneous tissue disorders | | | |
| Photosensitivity reaction | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 2 / 3 (66.67%) | 3 / 4 (75.00%) |
| occurrences (all) | 6 | 7 | 18 |
| Night sweats | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Hyperkeratosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Nail discolouration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nail dystrophy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Sunburn | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Alopecia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal and urinary disorders | | | |

| | | | |
|---|---|---|---|
| Nephropathy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cholangitis infective | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Abscess | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Biliary sepsis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Clostridial infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Ear infection | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal fungal infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Peritonitis bacterial | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Septic shock | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 3 (33.33%) | 0 / 4 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gout | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 3 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| **Non-serious adverse events** | Cohort 4: 0.25 / 30 | Cohort 5: 0.25 / 30 (Extended Part) | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 6 (100.00%) | 7 / 7 (100.00%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 3 / 7 (42.86%) | |
| occurrences (all) | 2 | 3 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Peripheral vascular disorder | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Surgical and medical procedures | | | |
| Cholangiostomy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 4 / 7 (57.14%) | |
| occurrences (all) | 5 | 8 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 7 (14.29%) | |
| occurrences (all) | 1 | 2 | |
| Swelling | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 1 / 7 (14.29%) | |
| occurrences (all) | 2 | 1 | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 2 / 7 (28.57%) | |
| occurrences (all) | 1 | 2 | |
| Chills | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 7 (28.57%) | |
| occurrences (all) | 0 | 3 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 7 (14.29%) | |
| occurrences (all) | 1 | 1 | |
| Chest discomfort | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Disease progression | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| Cough | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 7 (28.57%) | |
| occurrences (all) | 0 | 2 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Productive cough | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Wheezing | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Mental disorder | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Product issues | | | |
| Device occlusion | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 3 / 7 (42.86%) | |
| occurrences (all) | 0 | 6 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 7 (14.29%) | |
| occurrences (all) | 1 | 2 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 7 (14.29%) | |
| occurrences (all) | 2 | 1 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 2 | |

| | | | |
|---|---|---|---|
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 2 | |
| Body temperature | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Haematocrit decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Blood magnesium decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Blood potassium decreased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Blood urea increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Electrocardiogram abnormal | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Monocyte count increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Troponin T increased | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Vascular access complication | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Procedural pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 2 | |
| Burns second degree | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tooth fracture | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Nervous system disorders | | | |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 7 (14.29%) | |
| occurrences (all) | 1 | 1 | |
| Polyneuropathy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Headache | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypertonia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|---|---|---|
| Neutropenia | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 3 / 7 (42.86%) | |
| occurrences (all) | 11 | 6 | |
| Leukopenia | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 1 / 7 (14.29%) | |
| occurrences (all) | 11 | 5 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 3 / 7 (42.86%) | |
| occurrences (all) | 6 | 10 | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 4 / 7 (57.14%) | |
| occurrences (all) | 0 | 6 | |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 7 (14.29%) | |
| occurrences (all) | 2 | 3 | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Thrombocytosis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 2 / 6 (33.33%) | 6 / 7 (85.71%) | |
| occurrences (all) | 2 | 9 | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 4 / 7 (57.14%) | |
| occurrences (all) | 4 | 8 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 3 / 7 (42.86%) | |
| occurrences (all) | 1 | 3 | |
| Constipation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 7 (28.57%) | |
| occurrences (all) | 0 | 2 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 2 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 2 | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Haematochezia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Impaired gastric emptying | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Toothache | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Hepatobiliary disorders | | | |

| | | | |
|---|---|---|---|
| Cholangitis | | | |
| subjects affected / exposed | 3 / 6 (50.00%) | 6 / 7 (85.71%) | |
| occurrences (all) | 4 | 23 | |
| Hepatobiliary disease | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Jaundice | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Haemobilia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hepatic cirrhosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Hepatic pain | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Photosensitivity reaction | | | |
| subjects affected / exposed | 4 / 6 (66.67%) | 6 / 7 (85.71%) | |
| occurrences (all) | 7 | 34 | |
| Night sweats | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 1 / 7 (14.29%) | |
| occurrences (all) | 1 | 1 | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hyperkeratosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nail discolouration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nail dystrophy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Sunburn | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Renal and urinary disorders | | | |
| Nephropathy | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 7 (28.57%) | |
| occurrences (all) | 0 | 2 | |
| Musculoskeletal pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 2 / 7 (28.57%) | |
| occurrences (all) | 0 | 2 | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Infections and infestations | | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 3 | |
| Cholangitis infective | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 2 | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 2 | |
| Abscess | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Biliary sepsis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Clostridial infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|---|---|---|
| Cystitis | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Ear infection | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gastrointestinal fungal infection | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Peritonitis bacterial | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypokalaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Gout | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 23 October 2012 | Exclusion criteria updated. |
| 21 February 2013 | Inclusion criteria revised. Additional cohorts added to the Dose Escalation Part of the study to explore different intraluminal laser light settings. |
| 19 March 2014 | Additional exclusion criteria added: Patients defined as vulnerable according to French law. Addition of definition of vulnerable according to French law added to Section 5.4 of the protocol. |
| 02 May 2014 | Additional details added to describe the composition, role, and ways of functioning of the CRC.<br>Updated for Phase II part of the study (not applicable from this CSR): Details of Independent Data Monitoring Board added. |
| 19 December 2014 | Updated per Amendments 3 and 4 with the exception of details of Independent Data Monitoring Board.<br>Population changed from patients with 'locally advanced inoperable cholangiocarcinomas' to those with 'advanced inoperable cholangiocarcinomas': Patients with metastatic disease were also allowed to enter the study.<br>Addition of exploratory endpoints to evaluate immune-modulating effects of the PCI procedure and presence of Amphinex in faecal samples. |
| 08 June 2016 | Allowed metastatic disease to be confined to the liver only. Primary lesion to be in the perihilar duct region. Serum (total) bilirubin >2.5 x the Upper Limit of Normal (ULN) for the institution, instead of >1.5 x ULN. ECOG was restricted to 0 to 1 (previously 0 to 2).<br><br>Updated for Phase II part of the study (not applicable to this CSR): Addition of two exploratory endpoints, independent central review of CT scans, and a Steering Committee. |
| 24 March 2017 | Addition of Extended Part of Phase I.<br>Clarification that gemcitabine/cisplatin given as systemic chemotherapy are not considered IMPs. |
| 12 September 2017 | Clarification that patients in the Extended Part of Phase I with progressive disease could receive a second PCI treatment if, in the opinion of the Investigator, the patient would benefit from this treatment.<br>Addition of radiological evaluation of tumour prior to second PCI treatment in Extended Part of Phase I. |
| 10 November 2017 | Addition of two exclusion criteria regarding use of photosensitising drugs and amiodarone.<br>Additional detail provided regarding management of potential photosensitivity reactions.<br>Clarification that all patients were to be stented. |

| | |
|---|---|
| 22 March 2018 | Additional detail added regarding choice of light dose and rationale for Extended Part of Phase I.<br>Clarification that patients in the Extended Part of Phase I with progressive disease could receive a second PCI treatment if, in the opinion of the Investigator, the patient would benefit from this treatment.<br>Addition of radiological evaluation of tumour prior to second PCI treatment in Extended Part of Phase I. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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|---|
| None reported |

Notes: