



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
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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
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Arm title	Cohort 1: 0.06 / 15
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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
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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
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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
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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
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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
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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)
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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 screening 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			
Units: Subjects			
Adults (18-64 years)	3	1	1
Adults (65 years and over)	0	2	3
Age continuous			
Units: years			
arithmetic mean	61.7	66.7	72.8
standard deviation	± 3.21	± 5.69	± 7.14
Gender categorical			
Units: Subjects			
Female	1	3	3
Male	2	0	1

Race (NIH/OMB)			
Units: Subjects			
White	3	3	4
Ethnicity (NIH/OMB)			
Units: Subjects			
Not Hispanic	3	3	4
ECOG Performance Status			
Units: Subjects			
equals 0	3	2	4
equals 1	0	1	0
Total sum of longest diameter of target lesions			
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			
Units: Subjects			
Adults (18-64 years)	5	3	13
Adults (65 years and over)	1	4	10
Age continuous			
Units: years			
arithmetic mean	59.0	68.3	-
standard deviation	± 9.10	± 8.13	-
Gender categorical			
Units: Subjects			
Female	6	7	20
Male	0	0	3
Race (NIH/OMB)			
Units: Subjects			
White	6	7	23
Ethnicity (NIH/OMB)			
Units: Subjects			
Not Hispanic	6	7	23
ECOG Performance Status			
Units: Subjects			
equals 0	4	3	16
equals 1	2	4	7
Total sum of longest diameter of target lesions			
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]
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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
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Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival

End point title	Progression-Free Survival
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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
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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)			
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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
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Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1+20.1

Reporting groups

Reporting group title	Cohort 1: 0.06 / 15
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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
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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
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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
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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)
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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

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			

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

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			

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			

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			

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

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			

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

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Monocyte count increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Troponin T increased subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Injury, poisoning and procedural complications			
Vascular access complication subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0
Procedural pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Burns second degree subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Tooth fracture subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Cardiac disorders			
Tachycardia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0
Atrial flutter subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Nervous system disorders			
Paraesthesia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0
Polyneuropathy subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1	1 / 4 (25.00%) 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 occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Renal failure acute subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Infections and infestations Lower respiratory tract infection subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Infection subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Cholangitis infective subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Sepsis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 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 occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Urinary tract infection bacterial subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	1 / 3 (33.33%) 1	0 / 4 (0.00%) 0
Hyperlipidaemia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Hypokalaemia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Gout subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 0
Hypomagnesaemia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	1 / 4 (25.00%) 1
Type 2 diabetes mellitus subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 4 (0.00%) 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 occurrences (all)	2 / 6 (33.33%) 2	3 / 7 (42.86%) 3	
Hypotension subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 7 (14.29%) 1	
Peripheral vascular disorder			

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

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

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

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 7 (0.00%) 0	
Tooth fracture subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 7 (14.29%) 1	
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 7 (14.29%) 1	
Atrial flutter subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 4	0 / 7 (0.00%) 0	
Nervous system disorders Paraesthesia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	1 / 7 (14.29%) 1	
Polyneuropathy subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 7 (14.29%) 1	
Neuropathy peripheral subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 7 (14.29%) 1	
Dizziness subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 7 (14.29%) 1	
Dysgeusia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 7 (0.00%) 0	
Headache subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 7 (0.00%) 0	
Hypertonia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 7 (0.00%) 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. 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. 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. 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). 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. 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. 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. Additional detail provided regarding management of potential photosensitivity reactions. Clarification that all patients were to be stented.

22 March 2018	<p>Additional detail added regarding choice of light dose and rationale for Extended Part of Phase I.</p> <p>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.</p> <p>Addition of radiological evaluation of tumour prior to second PCI treatment in Extended Part of Phase I.</p>
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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.

None reported

Notes: