Clinical trial results:
A Phase 3 Randomized, Open-Label Study Comparing Pexa-Vec (Vaccinia GM-CSF / Thymidine Kinase-Deactivated Virus) Followed by Sorafenib Versus Sorafenib in Patients with Advanced Hepatocellular Carcinoma (HCC) Without Prior Systemic Therapy

Summary

EudraCT number	2014-001985-86
Trial protocol	DE PT PL FR IT
Global end of trial date	14 January 2020

Results information

Result version number	v1 (current)
This version publication date	15 August 2020
First version publication date	15 August 2020

Trial information

Trial identification

Sponsor protocol code	JX594-HEP024

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02562755
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	SillaJen Inc.
Sponsor organisation address	475 Sansome St, Suite 740, San Francisco, United States, CA 94111
Public contact	Clinical Trial Information Desk, SillaJen Inc., 1 415 814 9862, clinicaltrialinfo@sillajen.com
Scientific contact	Clinical Trial Information Desk, SillaJen Inc., 1 415 814 9862, clinicaltrialinfo@sillajen.com

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	13 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 January 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine radiographic responses for patients treated with Pexa-Vec followed by sorafenib (Arm A) versus sorafenib alone (Arm B) based on central assessments using mRECIST for HCC for the following endpoints: time to progression (TTP), overall response rate (ORR), disease control rate (DCR), and time to tumor marker elevation (TTME).

Protection of trial subjects:

Written consent was obtained from the patient before he/she could participate in the study. The content and process of obtaining informed consent was in accordance with all applicable regulatory requirements.

Prior to the initiation of any procedures relating to the study, a patient’s consent was obtained using a consent form written in the patient’s native language that was approved by the IRB/IEC and that was signed and personally dated by the patient at the time of consent. The person who conducted the informed consent discussion signed and personally dated the consent form. A copy of the signed and dated informed consent was given to the patient. The Investigator kept each patient’s original, signed and dated consent form on file for inspection by a regulatory authority or authorized party at any time.

Depending on national regulations, an authorized person other than the Investigator could inform the patient, sign and date the consent form.

During the patient’s participation in the study, whenever important new information became available that was relevant to the patient’s consent, the consent form was updated accordingly for IRB/IEC approval. The patient was informed in a timely manner if new information became available that was relevant to the patient’s willingness to continue participation in the study. The communication of this information was documented. The approved revised consent form was signed and dated by the patient.

Background therapy:

Any medications (as well as HCC medications) or significant non-drug therapies (such as prior radiation therapy, prior HCC surgery, prior HCC local-regional therapy) starting and ending before Day 1 was defined as prior medication. Any non-study medication or any therapeutic intervention (eg, surgery, blood transfusion) with a start date on or after Day 1 up to 28 days after the last dose of Pexa-Vec or sorafenib (eg, up to the safety follow-up visit), inclusive, or with a start date before Day 1 and an end date after Day 1 or ongoing, was considered concomitant medication. All anti-cancer therapies given after progressive disease (PD) were coded using the latest WHO Drug version. For patients who prematurely discontinued the study treatment (for another reason other than PD), all further antineoplastic therapies were collected and coded in the same way. Anti-cancer therapies received after the last dose of study treatment were recorded at follow-up visits after EOT, which also included concomitant treatment before the initiation of survival follow-up visits but after EOT date.

Evidence for comparator:

N/A (Open-label study)

Actual start date of recruitment	30 December 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	China: 82
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	New Zealand: 54
Country: Number of subjects enrolled	Singapore: 11
Country: Number of subjects enrolled	Korea, Republic of: 129
Country: Number of subjects enrolled	Taiwan: 23
Country: Number of subjects enrolled	Thailand: 7
Country: Number of subjects enrolled	United States: 74
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Germany: 13
Worldwide total number of subjects	459
EEA total number of subjects	49

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)	281
From 65 to 84 years	178
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

459 patients were randomly assigned to one of the study treatment group (234 patients in the Pexa-Vec followed by sorafenib treatment group and 225 patients in the sorafenib only treatment group).

Pre-assignment

Screening details:

Screening assessments were performed for 756 subjects after the patient had signed the informed consent and a Patient Study Identification Number was generated. The patients could be screened within 21 days from Day 1 visit. 459 patients successfully completed the screening assessments and they were randomly assigned either in Arm A or Arm B.

Period 1

Period 1 title	Period 1 (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open-label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Pexa-Vec followed by sorafenib treatment group. Study treatment was administered according to their treatment schedule as long as the patient clinically benefited from the treatment and at least until radiographic progression or until unacceptable toxicity occurred. After the treatment phase patients were included in survival follow-up phase consisting of patient and/or caregiver contact every 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Pexa-Vec
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intrathecal use

Dosage and administration details:

Pexa-Vec was administered at a dose of 1 × 109 plaque forming units (pfu) (equivalent to 9.0 Log pfu) as 3 bi-weekly IT injections on Day 1, Week 2, and Week 4.

Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Control drug: Sorafenib was administered at dose of 400 mg oral, BID. In Arm A, treatment with sorafenib was initiated at the visit Week 6 or at least 2 weeks after last Pexa Vec IT injection, whichever was later. If not all 3 Pexa Vec IT were performed, sorafenib was started not earlier than Week 6.

Arm title	Arm B

Arm description:

Sorafenib only treatment group. Study treatment was administered according to their treatment schedule as long as the patient clinically benefited from the treatment and at least until radiographic progression or until unacceptable toxicity occurred. After the treatment phase patients were included in survival follow-up phase consisting of patient and/or caregiver contact every 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Sorafenib was administered at dose of 400 mg oral, BID daily from Day 1 onwards.

Number of subjects in period 1	Arm A	Arm B
Started	234	225
Completed	161	153
Not completed	73	72
Clinical progression	7	13
Adverse event, serious fatal	9	5
Consent withdrawn by subject	11	8
Investigator judgement	6	2
Adverse event, non-fatal	2	6
Other	-	1
Radiographic progression	7	7
Lost to follow-up	1	-
Missing	2	-
Study closure	28	30

Baseline characteristics

Reporting groups	
Reporting group title	Arm A

Reporting group description:

Pexa-Vec followed by sorafenib treatment group. Study treatment was administered according to their treatment schedule as long as the patient clinically benefited from the treatment and at least until radiographic progression or until unacceptable toxicity occurred. After the treatment phase patients were included in survival follow-up phase consisting of patient and/or caregiver contact every 4 weeks.

Reporting group title	Arm B

Reporting group description:

Sorafenib only treatment group. Study treatment was administered according to their treatment schedule as long as the patient clinically benefited from the treatment and at least until radiographic progression or until unacceptable toxicity occurred. After the treatment phase patients were included in survival follow-up phase consisting of patient and/or caregiver contact every 4 weeks.

Reporting group values	Arm A	Arm B	Total
Number of subjects	234	225	459
Age categorical Units: Subjects			
Adults (18-64 years)	133	148	281
From 65-84 years	101	77	178
Age continuous Units: years			
arithmetic mean	61.3	60.5	
standard deviation	± 10.05	± 11.06	-
Gender categorical Units: Subjects			
Female	30	43	73
Male	204	182	386

Subject analysis sets	
Subject analysis set title	Intent-to-treat (ITT) population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients randomly assigned to IP. The ITT patients were analyzed according to the treatment and stratum they were assigned to at randomization. The ITT population was the primary population for efficacy analyses and for summaries of demographic and baseline variables. 459 patients were randomized.

Reporting group values	Intent-to-treat (ITT) population		
Number of subjects	459		
Age categorical Units: Subjects			
Adults (18-64 years)	281		
From 65-84 years	178		
Age continuous Units: years			
arithmetic mean	60.9		
standard deviation	± 10.55		

Gender categorical Units: Subjects			
Female	73		
Male	386		

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

Pexa-Vec followed by sorafenib treatment group. Study treatment was administered according to their treatment schedule as long as the patient clinically benefited from the treatment and at least until radiographic progression or until unacceptable toxicity occurred. After the treatment phase patients were included in survival follow-up phase consisting of patient and/or caregiver contact every 4 weeks.

Reporting group title	Arm B

Reporting group description:

Sorafenib only treatment group. Study treatment was administered according to their treatment schedule as long as the patient clinically benefited from the treatment and at least until radiographic progression or until unacceptable toxicity occurred. After the treatment phase patients were included in survival follow-up phase consisting of patient and/or caregiver contact every 4 weeks.

Subject analysis set title	Intent-to-treat (ITT) population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients randomly assigned to IP. The ITT patients were analyzed according to the treatment and stratum they were assigned to at randomization. The ITT population was the primary population for efficacy analyses and for summaries of demographic and baseline variables. 459 patients were randomized.

Primary: Time to Progression (TTP)

End point title	Time to Progression (TTP)

End point description:

The median TTP was 2.0 months (95% CI: 1.77, 2.96) in the Pexa Vec followed by sorafenib treatment group and 4.2 months (95% CI: 2.92, 4.63) in the sorafenib only treatment group. No statistically significant improvement in TTP was observed for Pexa Vec followed by sorafenib treatment over sorafenib only treatment group (P value=0.9270). The HR was 1.196 (95% CI: 0.932, 1.533).

End point type	Primary

End point timeframe:

Time to progression was defined as the time from randomization to the date of first documented radiographic tumor progression.

End point values	Arm A	Arm B	Intent-to-treat (ITT) population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	234	225	459	
Units: months				
median (confidence interval 95%)				
TTP quartiles (months) (95% CI)	2 (1.77 to 2.96)	4.2 (2.92 to 4.63)	3.0 (2.73 to 3.25)	

Statistical analyses

Statistical analysis title	Statistical analysis plan (SAP)

Statistical analysis description:

Statistical analysis plan (SAP), dated 15 Jan 2020

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	459
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.927
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.196
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.932
upper limit	1.533

Notes:

[1] - Time To Progression (TTP) was presented descriptively for each treatment arm separately using Kaplan-Meier curves. Summary statistics from the Kaplan-Meier distributions was determined, including median TTP and 25% and 75% quartiles with corresponding 95% confidence intervals (CIs). The proportions of patients remaining progression free at 3, 6, 9 and 12 months, along with 95% CIs was also provided by treatment arm.

Primary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

The ORR was 19.2% (45 patients) in the Pexa-Vec followed by sorafenib treatment group and 20.9% (47 patients) in the sorafenib only treatment group for the ITT population. No statistically significant difference in ORR was observed for Pexa Vec followed by sorafenib treatment compared with the sorafenib only treatment group (difference of –1.7%, P value=0.6470).

End point type	Primary

End point timeframe:

ORR was defined as the proportion of patients whose best overall response (BOR) during their participation in the study was either complete response (CR) or partial response (PR). The BOR was recorded from the randomization until tumor progression.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	234	225		
Units: Overall Response Rate				
number (not applicable)				
Overall response rate (%)	19.2	20.9		

Statistical analyses

Statistical analysis title	Statistical Analysis Plan

Statistical analysis description:

Statistical Analysis Plan, 15 Jan 2020

Comparison groups	Arm A v Arm B

Number of subjects included in analysis	459
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.647
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.13
upper limit	5.86

Notes:

[2] - Overall Response Rate (ORR) was presented by treatment arm along with exact 95% CIs. Difference in ORR proportions (with 95% CI) was provided. A Cochran-Mantel-Haenszel test was performed to compare the 2 treatment arms with respect to the ORR at a 1-sided 2.5% level of significance. A re-randomization test stratified for region based on the Mantel-Haenszel Chi-square statistic was performed to obtain one-sided p-value.

Primary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

The DCR was 50.0% (117 patients) in the Pexa-Vec followed by sorafenib treatment group and 57.3% (129 patients) in the sorafenib only treatment group for the ITT population. No statistically significant difference in DCR was observed for Pexa Vec followed by sorafenib treatment compared with the sorafenib only treatment group (difference of –7.3% [95% CI: –16.45, 1.95]; P-value=0.0690).

End point type	Primary

End point timeframe:

DCR was defined as the proportion of patients whose BOR during their participation in the study was either CR, PR, or stable disease.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	234	225		
Units: Subjects				
number (confidence interval 95%)				
Disease Control Rate (%)	50.0 (43.42 to 56.58)	57.3 (50.59 to 63.88)		

Statistical analyses

Statistical analysis title	Statistical Analysis Plan

Statistical analysis description:

Statistical Analysis Plan, 15 Jan 2020

Comparison groups	Arm A v Arm B

Number of subjects included in analysis	459
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.069
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-7.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.45
upper limit	1.95

Notes:

[3] - Disease Control Rate (DCR) was presented by treatment arm along with exact 95% CIs. Difference in proportions (with 95% CI) was also provided. A Cochran-Mantel-Haenszel test was performed to compare the 2 treatment arms with respect to the DCR at a 1-sided 2.5% level of significance. A re-randomization test stratified for region based on the Mantel-Haenszel Chi-square statistic was performed to obtain one-sided p-value.

Primary: Time to Tumor Marker Elevation (TTME)

End point title	Time to Tumor Marker Elevation (TTME)

End point description:

If the patient was alive or had no tumor marker increase of >400 ng/mL at the cut-off date for analysis, TTME was censored at the date of last AFP recorded before the cut-off.

End point type	Primary

End point timeframe:

TTME was defined as time from nadir AFP to AFP>400 ng/mL.

End point values	Arm A	Arm B	Intent-to-treat (ITT) population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	234	225	459	
Units: months				
median (confidence interval 95%)				
TTME quartiles (months) (95% CI)	3.3 (1.68 to 10.09)	4.7 (2.0 to 17.28)	4.2 (2.07 to 10.09)	

Statistical analyses

Statistical analysis title	Statistical Analysis Plan

Statistical analysis description:

Statistical Analysis Plan, 15 Jan 2020

Comparison groups	Arm A v Arm B

Number of subjects included in analysis	459
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.9
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.124
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.823
upper limit	1.534

Notes:

[4] - TTME was summarized by treatment arm. A Kaplan-Meier curve was constructed for each treatment arm. Median TTME and 25% and 75% quartiles was presented along with 95% CIs for each treatment arm. The Kaplan-Meier estimates with 95% CIs at 3, 6, 9 and 12 months was presented by treatment arm. Numbers of patients at risk was displayed at monthly intervals below the time axis for each of the two treatment groups and censored observations was marked by notches on the curves.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All TEAEs and serious TEAEs were collected after the initiation of study treatment and up to 28 days after the last dose of study treatment.

Adverse event reporting additional description:

All safety data were listed and those collected later than 28 days after end date of study treatment were flagged in the listings.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Arm A

Reporting group description:

Pexa-Vec followed by sorafenib treatment group. Study treatment was administered according to their treatment schedule as long as the patient clinically benefited from the treatment and at least until radiographic progression or until unacceptable toxicity occurred. After the treatment phase patients were included in survival follow-up phase consisting of patient and/or caregiver contact every 4 weeks.

Reporting group title	Arm B

Reporting group description:

Sorafenib only treatment group. Study treatment was administered according to their treatment schedule as long as the patient clinically benefited from the treatment and at least until radiographic progression or until unacceptable toxicity occurred. After the treatment phase patients were included in survival follow-up phase consisting of patient and/or caregiver contact every 4 weeks.

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	117 / 218 (53.67%)	77 / 217 (35.48%)	
number of deaths (all causes)	33	25	
number of deaths resulting from adverse events	33	25	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	4 / 218 (1.83%)	4 / 217 (1.84%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 3	0 / 4	
Liver carcinoma ruptured			
subjects affected / exposed	3 / 218 (1.38%)	2 / 217 (0.92%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Tumour pain			

subjects affected / exposed	2 / 218 (0.92%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	2 / 218 (0.92%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Tumour rupture			
subjects affected / exposed	2 / 218 (0.92%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Metastases to spine			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangiocarcinoma			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			

subjects affected / exposed	2 / 218 (0.92%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertension			
subjects affected / exposed	1 / 218 (0.46%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	8 / 218 (3.67%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	11 / 13	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	3 / 218 (1.38%)	5 / 217 (2.30%)	
occurrences causally related to treatment / all	1 / 3	1 / 5	
deaths causally related to treatment / all	0 / 1	0 / 2	
General physical health deterioration			
subjects affected / exposed	2 / 218 (0.92%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Fatigue			
subjects affected / exposed	1 / 218 (0.46%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malaise			

subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 218 (0.92%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	3 / 218 (1.38%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary embolism			
subjects affected / exposed	2 / 218 (0.92%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 218 (0.92%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory distress			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 218 (0.46%)	4 / 217 (1.84%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 218 (0.92%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Hepatic rupture			
subjects affected / exposed	3 / 218 (1.38%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 218 (0.46%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Angina pectoris			
subjects affected / exposed	2 / 218 (0.92%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 218 (0.92%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve disease			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 218 (0.46%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	5 / 218 (2.29%)	4 / 217 (1.84%)	
occurrences causally related to treatment / all	1 / 5	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	

Ischaemic stroke			
subjects affected / exposed	0 / 218 (0.00%)	2 / 217 (0.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcoholic seizure			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			

subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 218 (1.83%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	7 / 218 (3.21%)	3 / 217 (1.38%)	
occurrences causally related to treatment / all	1 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	8 / 218 (3.67%)	4 / 217 (1.84%)	
occurrences causally related to treatment / all	1 / 9	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal pain			
subjects affected / exposed	4 / 218 (1.83%)	5 / 217 (2.30%)	
occurrences causally related to treatment / all	2 / 4	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 218 (1.38%)	3 / 217 (1.38%)	
occurrences causally related to treatment / all	2 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal haemorrhage			
subjects affected / exposed	4 / 218 (1.83%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	3 / 5	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	4 / 218 (1.83%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Constipation			
subjects affected / exposed	2 / 218 (0.92%)	2 / 217 (0.92%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	2 / 218 (0.92%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematemesis			
subjects affected / exposed	2 / 218 (0.92%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric varices haemorrhage			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			

subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 218 (0.46%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric antral vascular ectasia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 218 (0.46%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dieulafoy's vascular malformation			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			

subjects affected / exposed	1 / 218 (0.46%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	4 / 218 (1.83%)	3 / 217 (1.38%)	
occurrences causally related to treatment / all	1 / 5	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental caries			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			

subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	11 / 218 (5.05%)	8 / 217 (3.69%)	
occurrences causally related to treatment / all	1 / 11	0 / 8	
deaths causally related to treatment / all	0 / 9	0 / 7	
Hepatic function abnormal			
subjects affected / exposed	3 / 218 (1.38%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	3 / 218 (1.38%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	2 / 218 (0.92%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 218 (0.92%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	2 / 218 (0.92%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			

subjects affected / exposed	1 / 218 (0.46%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 218 (0.46%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary dilatation			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatorenal syndrome			
subjects affected / exposed	2 / 218 (0.92%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			

subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic haemorrhage			
subjects affected / exposed	2 / 218 (0.92%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatic failure			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic pain			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 218 (0.00%)	2 / 217 (0.92%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity vasculitis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			

subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash pruritic			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash generalised			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis exfoliative generalised			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	3 / 218 (1.38%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Back pain			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis reactive			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 218 (1.38%)	4 / 217 (1.84%)	
occurrences causally related to treatment / all	0 / 3	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sepsis			
subjects affected / exposed	1 / 218 (0.46%)	4 / 217 (1.84%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Peritonitis bacterial			
subjects affected / exposed	4 / 218 (1.83%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	2 / 218 (0.92%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia necrotising			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycobacterial infection			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			

subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 218 (0.46%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinitis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			

subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis viral			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Decreased appetite			
subjects affected / exposed	1 / 218 (0.46%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			

subjects affected / exposed	1 / 218 (0.46%)	0 / 217 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 218 (0.46%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 218 (0.46%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	0 / 218 (0.00%)	1 / 217 (0.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	218 / 218 (100.00%)	214 / 217 (98.62%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	44 / 218 (20.18%)	39 / 217 (17.97%)	
occurrences (all)	44	39	
Hypotension			
subjects affected / exposed	35 / 218 (16.06%)	2 / 217 (0.92%)	
occurrences (all)	35	2	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	184 / 218 (84.40%)	28 / 217 (12.90%)	
occurrences (all)	184	28	
Fatigue			
subjects affected / exposed	65 / 218 (29.82%)	64 / 217 (29.49%)	
occurrences (all)	65	64	
Chills			
subjects affected / exposed	71 / 218 (32.57%)	4 / 217 (1.84%)	
occurrences (all)	71	4	
Oedema peripheral			
subjects affected / exposed	27 / 218 (12.39%)	21 / 217 (9.68%)	
occurrences (all)	27	21	
Asthenia			
subjects affected / exposed	22 / 218 (10.09%)	21 / 217 (9.68%)	
occurrences (all)	22	21	
Influenza like illness			
subjects affected / exposed	37 / 218 (16.97%)	5 / 217 (2.30%)	
occurrences (all)	37	5	
Injection site pain			
subjects affected / exposed	27 / 218 (12.39%)	0 / 217 (0.00%)	
occurrences (all)	27	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	31 / 218 (14.22%)	25 / 217 (11.52%)	
occurrences (all)	31	25	
Dyspnoea			
subjects affected / exposed	18 / 218 (8.26%)	11 / 217 (5.07%)	
occurrences (all)	18	11	
Oropharyngeal pain			
subjects affected / exposed	16 / 218 (7.34%)	10 / 217 (4.61%)	
occurrences (all)	16	10	
Dysphonia			
subjects affected / exposed	10 / 218 (4.59%)	12 / 217 (5.53%)	
occurrences (all)	10	12	
Epistaxis			

subjects affected / exposed	13 / 218 (5.96%)	9 / 217 (4.15%)	
occurrences (all)	13	9	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	16 / 218 (7.34%)	20 / 217 (9.22%)	
occurrences (all)	16	20	
Investigations			
Weight decreased			
subjects affected / exposed	58 / 218 (26.61%)	49 / 217 (22.58%)	
occurrences (all)	58	49	
Aspartate aminotransferase increased			
subjects affected / exposed	30 / 218 (13.76%)	39 / 217 (17.97%)	
occurrences (all)	30	39	
Blood bilirubin increased			
subjects affected / exposed	22 / 218 (10.09%)	33 / 217 (15.21%)	
occurrences (all)	22	33	
Alanine aminotransferase increased			
subjects affected / exposed	17 / 218 (7.80%)	29 / 217 (13.36%)	
occurrences (all)	17	29	
Platelet count decreased			
subjects affected / exposed	15 / 218 (6.88%)	15 / 217 (6.91%)	
occurrences (all)	15	15	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	12 / 218 (5.50%)	2 / 217 (0.92%)	
occurrences (all)	12	2	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	13 / 218 (5.96%)	3 / 217 (1.38%)	
occurrences (all)	13	3	
Tachycardia			
subjects affected / exposed	16 / 218 (7.34%)	0 / 217 (0.00%)	
occurrences (all)	16	0	
Nervous system disorders			
Headache			

subjects affected / exposed	33 / 218 (15.14%)	23 / 217 (10.60%)	
occurrences (all)	33	23	
Dizziness			
subjects affected / exposed	20 / 218 (9.17%)	13 / 217 (5.99%)	
occurrences (all)	20	13	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	33 / 218 (15.14%)	23 / 217 (10.60%)	
occurrences (all)	33	23	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	107 / 218 (49.08%)	116 / 217 (53.46%)	
occurrences (all)	107	116	
Nausea			
subjects affected / exposed	74 / 218 (33.94%)	63 / 217 (29.03%)	
occurrences (all)	74	63	
Abdominal pain			
subjects affected / exposed	62 / 218 (28.44%)	60 / 217 (27.65%)	
occurrences (all)	62	60	
Constipation			
subjects affected / exposed	52 / 218 (23.85%)	51 / 217 (23.50%)	
occurrences (all)	52	51	
Vomiting			
subjects affected / exposed	56 / 218 (25.69%)	27 / 217 (12.44%)	
occurrences (all)	56	27	
Ascites			
subjects affected / exposed	46 / 218 (21.10%)	36 / 217 (16.59%)	
occurrences (all)	46	36	
Abdominal pain upper			
subjects affected / exposed	43 / 218 (19.72%)	30 / 217 (13.82%)	
occurrences (all)	43	30	
Abdominal distension			
subjects affected / exposed	26 / 218 (11.93%)	26 / 217 (11.98%)	
occurrences (all)	26	26	
Stomatitis			

subjects affected / exposed	17 / 218 (7.80%)	24 / 217 (11.06%)	
occurrences (all)	17	24	
Dyspepsia			
subjects affected / exposed	15 / 218 (6.88%)	13 / 217 (5.99%)	
occurrences (all)	15	13	
Skin and subcutaneous tissue disorders			
Palmar plantar erythrodysaesthesia syndrome			
subjects affected / exposed	73 / 218 (33.49%)	99 / 217 (45.62%)	
occurrences (all)	73	99	
Alopecia			
subjects affected / exposed	32 / 218 (14.68%)	46 / 217 (21.20%)	
occurrences (all)	32	46	
Rash			
subjects affected / exposed	23 / 218 (10.55%)	28 / 217 (12.90%)	
occurrences (all)	23	28	
Pruritus			
subjects affected / exposed	16 / 218 (7.34%)	17 / 217 (7.83%)	
occurrences (all)	16	17	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	29 / 218 (13.30%)	17 / 217 (7.83%)	
occurrences (all)	29	17	
Arthralgia			
subjects affected / exposed	20 / 218 (9.17%)	15 / 217 (6.91%)	
occurrences (all)	20	15	
Pain in extremity			
subjects affected / exposed	19 / 218 (8.72%)	12 / 217 (5.53%)	
occurrences (all)	19	12	
Musculoskeletal pain			
subjects affected / exposed	14 / 218 (6.42%)	12 / 217 (5.53%)	
occurrences (all)	14	12	
Muscle spasms			
subjects affected / exposed	10 / 218 (4.59%)	12 / 217 (5.53%)	
occurrences (all)	10	12	
Myalgia			

subjects affected / exposed	11 / 218 (5.05%)	8 / 217 (3.69%)	
occurrences (all)	11	8	
Infections and infestations			
Rash pustular			
subjects affected / exposed	39 / 218 (17.89%)	2 / 217 (0.92%)	
occurrences (all)	39	2	
Upper respiratory tract infection			
subjects affected / exposed	17 / 218 (7.80%)	23 / 217 (10.60%)	
occurrences (all)	17	23	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	85 / 218 (38.99%)	64 / 217 (29.49%)	
occurrences (all)	85	64	
Hypokalaemia			
subjects affected / exposed	18 / 218 (8.26%)	19 / 217 (8.76%)	
occurrences (all)	18	19	
Hypoalbuminaemia			
subjects affected / exposed	15 / 218 (6.88%)	11 / 217 (5.07%)	
occurrences (all)	15	11	
Hyponatraemia			
subjects affected / exposed	16 / 218 (7.34%)	10 / 217 (4.61%)	
occurrences (all)	16	10	
Hyperkalaemia			
subjects affected / exposed	14 / 218 (6.42%)	4 / 217 (1.84%)	
occurrences (all)	14	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 October 2017	Protocol Amendment 1, dated 03 Oct 2017 - Added a section for "Notable Safety Findings" to include a brief description of rare but serious adverse events (SAEs) of myocardial infarction and/or cardiac ischemia and portal vein thrombosis, reported in this study (JX594-HEP024) following Pexa Vec treatment.
26 June 2019	Protocol Amendment 2, dated 26 Jun 2019 - was submitted to Food and Drug Administration (FDA). Exclusion criteria was updated to necessitate approval by a medical monitor for study participation of patients with adequately treated basal or squamous cell skin cancer, in situ cervical cancer, and adequately treated cancer from which the patient had been disease-free for at least 3 years. A window period of ±7 days was included in the survival follow-up phase. Once approved by Sponsor, the Screening window for a patient could be extended beyond 21 days. Screen failure patients were allowed to be re-screened for participation in the study if a prior Sponsor approval was granted etc. Due to the early termination of this study, based on IDMC recommendation, it was never submitted to the sites and implemented operationally. Therefore, the sections of this report describe the study conduct as amended in Protocol Amendment 1, dated 03 Oct 2017.

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.

IDMC identified no new safety concerns, however, recommended study discontinuation in view of the interim analysis suggesting that the original primary objective of improvement in overall survival will unlikely be met by the time of final analysis.

Notes: