Clinical trial results:
A Randomized, Double-Blind, Phase III Study of the Efficacy and Safety of Gemcitabine in Combination With TH-302 Compared With Gemcitabine in Combination With Placebo in Previously Untreated Subjects With Metastatic or Locally Advanced Unresectable Pancreatic Adenocarcinoma

Summary

EudraCT number	2012-002957-42
Trial protocol	BE GB CZ DE HU ES SK IT PL FI NL AT
Global end of trial date	04 May 2016

Results information

Result version number	v1 (current)
This version publication date	11 July 2018
First version publication date	11 July 2018

Trial information

Trial identification

Sponsor protocol code	EMR200592-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01746979
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Molecular Templates (formerly Threshold Pharmaceuticals)
Sponsor organisation address	9301 Amberglen Blvd, Suite 100, Austin, United States, TX 78729
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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	04 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to evaluate efficacy, as measured by overall survival (OS), of gemcitabine in combination with TH-302 compared to gemcitabine in combination with placebo in subjects with previously untreated locally advanced unresectable or metastatic pancreatic adenocarcinoma.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Israel: 21
Country: Number of subjects enrolled	Japan: 116
Country: Number of subjects enrolled	Korea, Republic of: 7
Country: Number of subjects enrolled	Romania: 12
Country: Number of subjects enrolled	Russian Federation: 54
Country: Number of subjects enrolled	United States: 81
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Slovakia: 6
Country: Number of subjects enrolled	Spain: 45
Country: Number of subjects enrolled	United Kingdom: 39
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 49
Country: Number of subjects enrolled	Czech Republic: 35
Country: Number of subjects enrolled	Finland: 13
Country: Number of subjects enrolled	France: 58
Country: Number of subjects enrolled	Germany: 24

Country: Number of subjects enrolled	Hungary: 40
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Argentina: 4
Country: Number of subjects enrolled	Australia: 19
Worldwide total number of subjects	693
EEA total number of subjects	371

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)	325
From 65 to 84 years	367
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 969 subjects were screened, out of which 693 subjects were randomized in the study.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Gemcitabine Plus TH-302

Arm description:

TH-302: TH-302 was administered at a dose of 340 milligrams per square meter (mg/m^2) as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.
Gemcitabine: Gemcitabine was administered at a dose of 1000 mg/m^2 as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

Arm type	Active comparator
Investigational medicinal product name	TH-302
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

TH-302 was administered at a dose of 340 mg/m^2 as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine was administered at a dose of 1000 mg/m^2 as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

Arm title	Gemcitabine Plus Placebo

Arm description:

Gemcitabine: Gemcitabine was administered at a dose of 1000 mg/m^2 as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.
Placebo (5 percent dextrose - D5W): TH-302 placebo (5 percent dextrose - D5W) was administered as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

Arm type	Placebo

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine was administered at a dose of 1000 mg/m^2 as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

Investigational medicinal product name	Placebo (5 percent dextrose - D5W)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

TH-302 placebo (5 percent dextrose - D5W) was administered as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

Number of subjects in period 1	Gemcitabine Plus TH-302	Gemcitabine Plus Placebo
Started	346	347
Completed	0	0
Not completed	346	347
Discontinued	346	347

Baseline characteristics

Reporting groups	
Reporting group title	Gemcitabine Plus TH-302

Reporting group description:

TH-302: TH-302 was administered at a dose of 340 milligrams per square meter (mg/m^2) as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.
Gemcitabine: Gemcitabine was administered at a dose of 1000 mg/m^2 as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

Reporting group title	Gemcitabine Plus Placebo

Reporting group description:

Gemcitabine: Gemcitabine was administered at a dose of 1000 mg/m^2 as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.
Placebo (5 percent dextrose - D5W): TH-302 placebo (5 percent dextrose - D5W) was administered as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

Reporting group values	Gemcitabine Plus TH-302	Gemcitabine Plus Placebo	Total
Number of subjects	346	347	693
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 65 ± 9.70	 63.8 ± 9.82	 -
Gender categorical Units: Subjects			
Female	155	168	323
Male	191	179	370

End points

End points reporting groups

Reporting group title	Gemcitabine Plus TH-302
Reporting group description:	
TH-302: TH-302 was administered at a dose of 340 milligrams per square meter (mg/m^2) as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal. Gemcitabine: Gemcitabine was administered at a dose of 1000 mg/m^2 as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.	
Reporting group title	Gemcitabine Plus Placebo
Reporting group description:	
Gemcitabine: Gemcitabine was administered at a dose of 1000 mg/m^2 as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal. Placebo (5 percent dextrose - D5W): TH-302 placebo (5 percent dextrose - D5W) was administered as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.	

Primary: Overall Survival

End point title	Overall Survival
End point description:	
Overall survival is defined as time from randomization to death or last day known to be alive.	
End point type	Primary
End point timeframe:	
From date of randomization until date of death from any cause or last day known to be alive, assessed up to 2 years	

End point values	Gemcitabine Plus TH-302	Gemcitabine Plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	347		
Units: Months				
median (confidence interval 95%)	8.9 (7.6 to 9.9)	7.6 (6.7 to 8.3)		

Statistical analyses

Statistical analysis title	Statistical analysis of Overall Survival
Comparison groups	Gemcitabine Plus TH-302 v Gemcitabine Plus Placebo
Number of subjects included in analysis	693
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0588
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.844

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.708
upper limit	1.006

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

Progression Free Survival is defined as the time from randomization to either first observation of progressive disease or occurrence of death. Progression is defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1), as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions.

End point type	Secondary

End point timeframe:

From date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 2 years

End point values	Gemcitabine Plus TH-302	Gemcitabine Plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	347		
Units: Months				
median (confidence interval 95%)	5.5 (4.8 to 5.6)	3.7 (3.6 to 3.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis of Progression-free Survival
Comparison groups	Gemcitabine Plus TH-302 v Gemcitabine Plus Placebo
Number of subjects included in analysis	693
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0015
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.747
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.623
upper limit	0.895

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Objective response rate defined as the percentage of subjects having achieved complete response (CR: Disappearance of all target lesions) or partial response (PR: At least a 30 percent decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters) as the best overall response according to local unconfirmed radiological assessments from randomization until the end of study treatment.

End point type	Secondary

End point timeframe:

From date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 2 years

End point values	Gemcitabine Plus TH-302	Gemcitabine Plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	347		
Units: Percentage of Subjects				
number (confidence interval 95%)	20.5 (16.4 to 25.2)	17.3 (13.5 to 21.7)		

Statistical analyses

Statistical analysis title	Statistical analysis of Objective Response Rate
Comparison groups	Gemcitabine Plus TH-302 v Gemcitabine Plus Placebo
Number of subjects included in analysis	693
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2757
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.89

Secondary: Disease Control Rate

End point title	Disease Control Rate

End point description:

Disease control rate defined as the percentage of subjects having achieved CR, PR or stable disease (SD) as the best overall response according to local radiological assessments from randomization until the end of study treatment.

End point type	Secondary

End point timeframe:

From date of randomization until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 2 years

End point values	Gemcitabine Plus TH-302	Gemcitabine Plus Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	347		
Units: Percentage of Subjects				
number (confidence interval 95%)	69.1 (63.9 to 73.9)	63.1 (57.8 to 68.2)		

Statistical analyses

Statistical analysis title	Statistical analysis of Disease Control Rate
Comparison groups	Gemcitabine Plus TH-302 v Gemcitabine Plus Placebo
Number of subjects included in analysis	693
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.085
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.83

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline up to 2 years	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Gemcitabine Plus TH-302

Reporting group description:

TH-302: TH-302 was administered at a dose of 340 milligrams per square meter (mg/m^2) as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.
Gemcitabine: Gemcitabine was administered at a dose of 1000 mg/m^2 as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

Reporting group title	Gemcitabine Plus Placebo

Reporting group description:

Gemcitabine: Gemcitabine was administered at a dose of 1000 mg/m^2 as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.
Placebo (5 percent dextrose - D5W): TH-302 placebo (5 percent dextrose - D5W) was administered as intravenous infusion over 30 minutes on Day 1, 8 and 15 of every 28-day cycle until evidence of progressive disease, intolerable toxicity or subject withdrawal.

Serious adverse events	Gemcitabine Plus TH-302	Gemcitabine Plus Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	183 / 338 (54.14%)	177 / 341 (51.91%)	
number of deaths (all causes)	241	260	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	2 / 338 (0.59%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant ascites			
subjects affected / exposed	1 / 338 (0.30%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraneoplastic syndrome			

subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial occlusive disease			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Arterial thrombosis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Axillary vein thrombosis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	7 / 338 (2.07%)	4 / 341 (1.17%)	
occurrences causally related to treatment / all	1 / 7	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 338 (0.00%)	3 / 341 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertension			

subjects affected / exposed	1 / 338 (0.30%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 338 (0.30%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	2 / 338 (0.59%)	0 / 341 (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			
Asthenia			

subjects affected / exposed	4 / 338 (1.18%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chills			
subjects affected / exposed	0 / 338 (0.00%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	3 / 338 (0.89%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	4 / 338 (1.18%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Fatigue			
subjects affected / exposed	2 / 338 (0.59%)	3 / 341 (0.88%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
General physical health deterioration			
subjects affected / exposed	11 / 338 (3.25%)	14 / 341 (4.11%)	
occurrences causally related to treatment / all	1 / 12	1 / 15	
deaths causally related to treatment / all	1 / 7	1 / 9	
Generalised oedema			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site extravasation			

subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site extravasation			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Local swelling			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	2 / 338 (0.59%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 338 (0.30%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	2 / 338 (0.59%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 338 (0.00%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	14 / 338 (4.14%)	11 / 341 (3.23%)	
occurrences causally related to treatment / all	3 / 15	5 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stent malfunction			
subjects affected / exposed	1 / 338 (0.30%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (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			
Acute interstitial pneumonitis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 338 (0.59%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	2 / 338 (0.59%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonitis			

subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	11 / 338 (3.25%)	10 / 341 (2.93%)	
occurrences causally related to treatment / all	1 / 11	2 / 10	
deaths causally related to treatment / all	1 / 1	1 / 1	
Respiratory failure			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 338 (0.30%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	2 / 338 (0.59%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	2 / 338 (0.59%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 338 (0.59%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	3 / 338 (0.89%)	3 / 341 (0.88%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 338 (0.30%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose fluctuation			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 338 (1.18%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			

subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	2 / 338 (0.59%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	8 / 338 (2.37%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	6 / 8	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	2 / 338 (0.59%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	3 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chemical peritonitis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			

subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural bile leak			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prescribed overdose			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemothorax			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Pyloric stenosis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute coronary syndrome			
subjects affected / exposed	2 / 338 (0.59%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 338 (0.30%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aortic valve disease			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 338 (0.00%)	3 / 341 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	1 / 338 (0.30%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 338 (0.00%)	3 / 341 (0.88%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			

subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	2 / 338 (0.59%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Balance disorder			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral artery stenosis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 338 (0.30%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	3 / 338 (0.89%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Coma			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			

subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemianopia			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 338 (0.30%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Spinal cord compression			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (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	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
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	16 / 338 (4.73%)	15 / 341 (4.40%)	
occurrences causally related to treatment / all	8 / 18	4 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	6 / 338 (1.78%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	6 / 7	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	9 / 338 (2.66%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	12 / 13	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 338 (0.59%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic vein thrombosis			

subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	19 / 338 (5.62%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	17 / 25	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Macular hole			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	10 / 338 (2.96%)	7 / 341 (2.05%)	
occurrences causally related to treatment / all	0 / 10	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 338 (0.30%)	3 / 341 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	2 / 338 (0.59%)	5 / 341 (1.47%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Constipation			

subjects affected / exposed	1 / 338 (0.30%)	3 / 341 (0.88%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	8 / 338 (2.37%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	9 / 11	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			
subjects affected / exposed	1 / 338 (0.30%)	4 / 341 (1.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal perforation			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal stenosis			
subjects affected / exposed	3 / 338 (0.89%)	4 / 341 (1.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 338 (0.30%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			

subjects affected / exposed	0 / 338 (0.00%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 338 (0.30%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	0 / 338 (0.00%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			

subjects affected / exposed	1 / 338 (0.30%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	2 / 338 (0.59%)	3 / 341 (0.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal obstruction			
subjects affected / exposed	2 / 338 (0.59%)	3 / 341 (0.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			

subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			
subjects affected / exposed	3 / 338 (0.89%)	4 / 341 (1.17%)	
occurrences causally related to treatment / all	0 / 4	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	0 / 338 (0.00%)	3 / 341 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedematous pancreatitis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal ulcer			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 338 (0.30%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			

subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 338 (0.30%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 338 (0.00%)	3 / 341 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 338 (0.59%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	7 / 338 (2.07%)	13 / 341 (3.81%)	
occurrences causally related to treatment / all	1 / 8	4 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	3 / 338 (0.89%)	6 / 341 (1.76%)	
occurrences causally related to treatment / all	0 / 3	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	5 / 338 (1.48%)	5 / 341 (1.47%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			

subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary dilatation			
subjects affected / exposed	2 / 338 (0.59%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangiectasis acquired			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangiolitis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	12 / 338 (3.55%)	15 / 341 (4.40%)	
occurrences causally related to treatment / all	1 / 12	3 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	1 / 338 (0.30%)	6 / 341 (1.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 338 (0.59%)	3 / 341 (0.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 338 (0.30%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			

subjects affected / exposed	3 / 338 (0.89%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder obstruction			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	3 / 338 (0.89%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	1 / 2	0 / 1	
Hepatic function abnormal			
subjects affected / exposed	4 / 338 (1.18%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatorenal failure			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 338 (0.00%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 338 (0.30%)	4 / 341 (1.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Jaundice cholestatic			
subjects affected / exposed	3 / 338 (0.89%)	6 / 341 (1.76%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal hypertension			

subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin maceration			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Yellow skin			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			

subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 338 (0.59%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal impairment			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 338 (0.89%)	3 / 341 (0.88%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			

subjects affected / exposed	2 / 338 (0.59%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty arthritis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	2 / 338 (0.59%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial prostatitis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	2 / 338 (0.59%)	3 / 341 (0.88%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Biliary tract infection			
subjects affected / exposed	0 / 338 (0.00%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			

subjects affected / exposed	0 / 338 (0.00%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 338 (0.59%)	3 / 341 (0.88%)	
occurrences causally related to treatment / all	2 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 338 (0.59%)	4 / 341 (1.17%)	
occurrences causally related to treatment / all	1 / 2	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 338 (0.00%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gangrene			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal infection			

subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
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 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 338 (0.30%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal oesophagitis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			

subjects affected / exposed	1 / 338 (0.30%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site infection			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (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 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningoencephalitis herpetic			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (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	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal candidiasis			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic abscess			

subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Penile infection			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pharyngitis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	8 / 338 (2.37%)	9 / 341 (2.64%)	
occurrences causally related to treatment / all	2 / 8	1 / 11	
deaths causally related to treatment / all	1 / 1	1 / 3	
Respiratory tract infection			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	5 / 338 (1.48%)	5 / 341 (1.47%)	
occurrences causally related to treatment / all	1 / 5	1 / 5	
deaths causally related to treatment / all	0 / 0	1 / 1	
Septic shock			
subjects affected / exposed	2 / 338 (0.59%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Splenic abscess			

subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 338 (0.00%)	4 / 341 (1.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal infection			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	2 / 338 (0.59%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 338 (0.59%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			

subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 338 (0.59%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 338 (0.00%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 338 (0.30%)	2 / 341 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	1 / 338 (0.30%)	0 / 341 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic disorder			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 338 (0.00%)	1 / 341 (0.29%)	
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	Gemcitabine Plus TH-302	Gemcitabine Plus Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	331 / 338 (97.93%)	328 / 341 (96.19%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	34 / 338 (10.06%)	30 / 341 (8.80%)	
occurrences (all)	86	52	
Aspartate aminotransferase increased			
subjects affected / exposed	29 / 338 (8.58%)	27 / 341 (7.92%)	
occurrences (all)	71	44	
Blood alkaline phosphatase increased			
subjects affected / exposed	20 / 338 (5.92%)	29 / 341 (8.50%)	
occurrences (all)	34	41	
Blood bilirubin increased			
subjects affected / exposed	21 / 338 (6.21%)	22 / 341 (6.45%)	
occurrences (all)	39	36	
Neutrophil count decreased			
subjects affected / exposed	52 / 338 (15.38%)	29 / 341 (8.50%)	
occurrences (all)	301	94	
Platelet count decreased			
subjects affected / exposed	100 / 338 (29.59%)	44 / 341 (12.90%)	
occurrences (all)	476	122	
Weight decreased			
subjects affected / exposed	31 / 338 (9.17%)	34 / 341 (9.97%)	
occurrences (all)	38	38	
White blood cell count decreased			
subjects affected / exposed	55 / 338 (16.27%)	28 / 341 (8.21%)	
occurrences (all)	263	84	
Vascular disorders			
Hypertension			
subjects affected / exposed	16 / 338 (4.73%)	21 / 341 (6.16%)	
occurrences (all)	30	28	
Nervous system disorders			

Dizziness			
subjects affected / exposed	28 / 338 (8.28%)	24 / 341 (7.04%)	
occurrences (all)	38	32	
Dysgeusia			
subjects affected / exposed	46 / 338 (13.61%)	33 / 341 (9.68%)	
occurrences (all)	57	39	
Headache			
subjects affected / exposed	23 / 338 (6.80%)	26 / 341 (7.62%)	
occurrences (all)	29	33	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	164 / 338 (48.52%)	108 / 341 (31.67%)	
occurrences (all)	582	254	
Leukopenia			
subjects affected / exposed	47 / 338 (13.91%)	29 / 341 (8.50%)	
occurrences (all)	198	47	
Neutropenia			
subjects affected / exposed	140 / 338 (41.42%)	94 / 341 (27.57%)	
occurrences (all)	546	248	
Thrombocytopenia			
subjects affected / exposed	158 / 338 (46.75%)	61 / 341 (17.89%)	
occurrences (all)	772	151	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	81 / 338 (23.96%)	71 / 341 (20.82%)	
occurrences (all)	229	165	
Fatigue			
subjects affected / exposed	98 / 338 (28.99%)	106 / 341 (31.09%)	
occurrences (all)	234	219	
Oedema peripheral			
subjects affected / exposed	64 / 338 (18.93%)	72 / 341 (21.11%)	
occurrences (all)	87	104	
Pyrexia			
subjects affected / exposed	64 / 338 (18.93%)	76 / 341 (22.29%)	
occurrences (all)	104	147	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	65 / 338 (19.23%)	70 / 341 (20.53%)	
occurrences (all)	110	149	
Abdominal pain upper			
subjects affected / exposed	44 / 338 (13.02%)	38 / 341 (11.14%)	
occurrences (all)	66	58	
Ascites			
subjects affected / exposed	18 / 338 (5.33%)	29 / 341 (8.50%)	
occurrences (all)	18	42	
Constipation			
subjects affected / exposed	104 / 338 (30.77%)	104 / 341 (30.50%)	
occurrences (all)	171	146	
Diarrhoea			
subjects affected / exposed	112 / 338 (33.14%)	89 / 341 (26.10%)	
occurrences (all)	245	181	
Haemorrhoids			
subjects affected / exposed	39 / 338 (11.54%)	13 / 341 (3.81%)	
occurrences (all)	59	15	
Nausea			
subjects affected / exposed	168 / 338 (49.70%)	150 / 341 (43.99%)	
occurrences (all)	354	320	
Stomatitis			
subjects affected / exposed	86 / 338 (25.44%)	53 / 341 (15.54%)	
occurrences (all)	172	78	
Vomiting			
subjects affected / exposed	109 / 338 (32.25%)	109 / 341 (31.96%)	
occurrences (all)	243	233	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	28 / 338 (8.28%)	27 / 341 (7.92%)	
occurrences (all)	34	30	
Dyspnoea			
subjects affected / exposed	44 / 338 (13.02%)	27 / 341 (7.92%)	
occurrences (all)	55	44	
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	68 / 338 (20.12%)	23 / 341 (6.74%)	
occurrences (all)	81	30	
Dry skin			
subjects affected / exposed	22 / 338 (6.51%)	13 / 341 (3.81%)	
occurrences (all)	30	13	
Erythema			
subjects affected / exposed	25 / 338 (7.40%)	10 / 341 (2.93%)	
occurrences (all)	32	12	
Pruritus			
subjects affected / exposed	23 / 338 (6.80%)	25 / 341 (7.33%)	
occurrences (all)	27	32	
Rash			
subjects affected / exposed	63 / 338 (18.64%)	46 / 341 (13.49%)	
occurrences (all)	104	65	
Skin hyperpigmentation			
subjects affected / exposed	44 / 338 (13.02%)	3 / 341 (0.88%)	
occurrences (all)	59	4	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	25 / 338 (7.40%)	33 / 341 (9.68%)	
occurrences (all)	26	36	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	30 / 338 (8.88%)	45 / 341 (13.20%)	
occurrences (all)	35	58	
Pain in extremity			
subjects affected / exposed	16 / 338 (4.73%)	18 / 341 (5.28%)	
occurrences (all)	27	23	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	30 / 338 (8.88%)	19 / 341 (5.57%)	
occurrences (all)	44	36	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	117 / 338 (34.62%)	116 / 341 (34.02%)	
occurrences (all)	205	184	
Hyperglycaemia			
subjects affected / exposed	27 / 338 (7.99%)	23 / 341 (6.74%)	
occurrences (all)	44	55	
Hypokalaemia			
subjects affected / exposed	22 / 338 (6.51%)	27 / 341 (7.92%)	
occurrences (all)	30	36	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2013	The changes made to Version 3.0 of the clinical trial protocol are as follows: 1. Clarification of the exclusion criteria with respect to alternative treatments (changes previously incorporated in Local Amendment 1 [9 April 2013], which was implemented in Belgium, Czech Republic, France, Germany, Hungary, Romania, Spain, and the United Kingdom). 2. Clarification of the investigator's obligations for emergency unblinding (changes previously incorporated in Local Amendment 1 [9 April 2013], which was implemented in Belgium, Czech Republic, France, Germany, Hungary, Romania, Spain, and the United Kingdom). 3. Minor modification to the "Numerical Rating Scale for Pain". 4. Addition of the trial acronym (MAESTRO: TH-302 in the treatment of Metastatic or locally Advanced unrESectable pancreaTic adenocaRcinOma). 5. Correction of minor typographical errors in the document.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported