Clinical trial results:
A prospective, phase III, controlled, multicentre, randomised clinical trial comparing combination gemcitabine and capecitabine therapy with concurrent and sequential chemoimmunotherapy using a telomerase vaccine in locally advanced and metastatic pancreatic cancer.

Summary

EudraCT number	2006-000461-10
Trial protocol	GB
Global end of trial date	27 May 2012

Results information

Result version number	v1 (current)
This version publication date	28 February 2019
First version publication date	28 February 2019

Trial information

Trial identification

Sponsor protocol code	ISRCTN43482138

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	The Royal Liverpool and Broadgreen University Hospitals NHS Trust
Sponsor organisation address	Prescot Street, Liverpool, United Kingdom, L7 8XP
Public contact	Ms Charlotte Rawcliffe, Liverpool Cancer Trials Unit, University of Liverpool, 0151 794 8167, C.Rawcliffe@liverpool.ac.uk
Scientific contact	Dr Victoria Shaw, GCLP Labs, University of Liverpool, 0151 706 4180, Victoria.Shaw@liverpool.ac.uk

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	25 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 May 2011
Global end of trial reached?	Yes
Global end of trial date	27 May 2012
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy of GV1001 on length of survival when added concurrently or sequentially to the combination gemcitabine and capecitabine in patients with locally advanced or metastatic pancreatic adenocarcinoma.

Protection of trial subjects:

Patients were asked to consent that data are recorded, collected, stored and processed and might be transferred to other countries, in accordance with any national legislation implementing the EU Data Protection Directive (95/46/EC).

Data was processed in accordance with the general terms and conditions of the authorisation from the 'Information Commissioner's Office' to the LCTU, as required, according to national legislation implementing the Data Protection Directive; 95/46/EC.

Background therapy: -

Evidence for comparator:

For patients with locally advanced or metastatic pancreatic cancer, who wish to have, and are fit enough to benefit from, active treatment, chemotherapy with single agent gemcitabine has for several years been the standard of care. The recently reported results of the NCRI GEMCAP trial, a randomised comparison of gemcitabine versus the combination of gemcitabine and capecitabine, and associated meta-analysis demonstrated a statistically significant survival benefit for patients receiving the combined treatment with acceptable levels of toxicity. Therefore all subjects enrolled in this programme will receive the GEM-CAP combination chemotherapy.
The benefits of the combination, though real, are modest and continual efforts to improve our management of this disease are essential. Vaccination of pancreatic cancer patients with the Telomerase vaccine GV1001 has yielded promising results. It has been administered to over 100 subjects and has been well tolerated with no serious adverse events. The most commonly reported adverse events are injection site reactions, chills, nausea and dizziness of which the majority were of mild intensity. It is thus an attractive candidate therapy to add to gemcitabine and capecitabine in order to try and improve outcomes in this disease. This trial will not be placebo controlled as it is not felt to be acceptable to submit patients in the control arm to unnecessary injections.

Actual start date of recruitment	29 March 2007
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	United Kingdom: 1062
Worldwide total number of subjects	1062
EEA total number of subjects	1062

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)	601
From 65 to 84 years	461
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

UK only. First patient, first visit (FPFV; date of randomisation): 29 Mar 2007 and date of close of recruitment of the study: 27 May 2011 (closed early based on the final interim analysis by the Independent Safety and Data Monitoring Committee (ISDMC) as the sequential immunotherapy arm appeared to be inferior), Quality of life, Pain assessment

Pre-assignment

Screening details:

Histology/cytology, Informed consent, Inclusion criteria, Randomisation, Demography & medical history, Physical examination, Vital signs, ECOG Performance status, ECG, Haematology, Serum Chemistry, Genomic/Proteomic Sampling, Blood, Proteomic Sampling - Urine, CT scan (RECIST), CA19-9
1573 patients screened, 108 patients declined, 402 ineligible

Period 1

Period 1 title	Treatment Phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Gemcitabine and Capecitabine Therapy

Arm description:

Gemcitabine will be administered on day 1, 8 and 15 followed by 7 days' rest. Per oral capecitabine will be administered morning and evening for 21 days followed by 7 days' rest. Gemcitabine and capecitabine therapy cycle will be repeated every 4 weeks until withdrawal from trial treatment due to patient choice, intolerable toxicity or disease progression.

Patients will have a CT scan at baseline, week 8 and every 12 weeks until the patient is withdrawn from the study. Upon withdrawal patients will be treated according to local practice and be subject to follow-up every 3 months until death.

Arm type	Active comparator
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	Gemzar
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000mg/m2 gemcitabine must be given as an intravenous infusion over 30 minutes unless haematological toxicity occurs requiring dose adjustment

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

Dosage and administration details:

830 mg/m2 capecitabine must be administered orally morning and evening daily (total daily dose of 1660 mg/m2) unless toxicity occurs requiring dose adjustment

Investigational medicinal product name	GV1001
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

3.5 ml sterile single dosage

Arm title	Gemcitabine and Capecitabine then Sequential GV1001 Therapy

Arm description:

Patients will receive two cycles of combination gemcitabine and capecitabine before Each of the two cycles of combination gemcitabine and capecitabine consists of:

Gemcitabine administered on day 1, 8 and 15 followed by 7 days“ rest. Per oral capecitabine administered morning and evening for 21 days followed by 7 days' rest. Following completion of two cycles of gemcitabine and capecitabine therapy, GV1001 will be administered intradermally on Monday, Wednesday and Friday during week 9 and once weekly during weeks 10, 11, 12 and 14. After that, vaccinations will follow a once monthly schedule until patient choice, intolerable toxicity or disease progression. Granulocytemacrophage colony-stimulating factor (GM-CSF) will be used as an adjuvant, given 10-15 minutes prior to each administration of GV1001.

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

Dosage and administration details:

830 mg/m2 capecitabine must be administered orally morning and evening daily (total daily dose of 1660 mg/m2) unless toxicity occurs requiring dose adjustment as described below.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	Gemzar
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000mg/m2 gemcitabine must be given as an intravenous infusion over 30 minutes unless haematological toxicity occurs requiring dose adjustment

Arm title	Concurrent Gemcitabine, Capecitabine and GV1001 Therapy

Arm description:

Gemcitabine will be administered on day 1, 8 and 15 followed by 7 days' rest. Per oral capecitabine will be administered morning and evening for 21 days followed by 7 days' rest. Gemcitabine and capecitabine therapy cycles will be repeated every 4 weeks until withdrawal from trial treatment due to patient choice, intolerable toxicity or disease progression.

Arm type	Experimental
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	Gemzar
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000mg/m2 gemcitabine must be given as an intravenous infusion over 30 minutes unless haematological toxicity occurs requiring dose adjustment

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

Dosage and administration details:	
830 mg/m2 capecitabine must be administered orally morning and evening daily (total daily dose of 1660 mg/m2) unless toxicity occurs requiring dose adjustment as described below.	
Investigational medicinal product name	GV1001
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intradermal use
Dosage and administration details:	
3.5 ml sterile single dosage	
Investigational medicinal product name	GM-CSF
Investigational medicinal product code	
Other name	Leukine
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Subcutaneous use, Intravenous use
Dosage and administration details:	
Sterile vials containing 250 g lyophilised Leukine	

Number of subjects in period 1	Gemcitabine and Capecitabine Therapy	Gemcitabine and Capecitabine then Sequential GV1001 Therapy	Concurrent Gemcitabine, Capecitabine and GV1001 Therapy
Started	358	350	354
Completed	358	350	354

Baseline characteristics

Reporting groups

Reporting group title	Gemcitabine and Capecitabine Therapy

Reporting group description:

Gemcitabine will be administered on day 1, 8 and 15 followed by 7 days' rest. Per oral capecitabine will be administered morning and evening for 21 days followed by 7 days' rest. Gemcitabine and capecitabine therapy cycle will be repeated every 4 weeks until withdrawal from trial treatment due to patient choice, intolerable toxicity or disease progression.

Patients will have a CT scan at baseline, week 8 and every 12 weeks until the patient is withdrawn from the study. Upon withdrawal patients will be treated according to local practice and be subject to follow-up every 3 months until death.

Reporting group title	Gemcitabine and Capecitabine then Sequential GV1001 Therapy

Reporting group description:

Patients will receive two cycles of combination gemcitabine and capecitabine before Each of the two cycles of combination gemcitabine and capecitabine consists of:

Gemcitabine administered on day 1, 8 and 15 followed by 7 days“ rest. Per oral capecitabine administered morning and evening for 21 days followed by 7 days' rest. Following completion of two cycles of gemcitabine and capecitabine therapy, GV1001 will be administered intradermally on Monday, Wednesday and Friday during week 9 and once weekly during weeks 10, 11, 12 and 14. After that, vaccinations will follow a once monthly schedule until patient choice, intolerable toxicity or disease progression. Granulocytemacrophage colony-stimulating factor (GM-CSF) will be used as an adjuvant, given 10-15 minutes prior to each administration of GV1001.

Reporting group title	Concurrent Gemcitabine, Capecitabine and GV1001 Therapy

Reporting group description:

Gemcitabine will be administered on day 1, 8 and 15 followed by 7 days' rest. Per oral capecitabine will be administered morning and evening for 21 days followed by 7 days' rest. Gemcitabine and capecitabine therapy cycles will be repeated every 4 weeks until withdrawal from trial treatment due to patient choice, intolerable toxicity or disease progression.

Reporting group values	Gemcitabine and Capecitabine Therapy	Gemcitabine and Capecitabine then Sequential GV1001 Therapy	Concurrent Gemcitabine, Capecitabine and GV1001 Therapy
Number of subjects	358	350	354
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	61.9	62.7	62.3
standard deviation	± 9.6	± 9.5	± 9.5

Gender categorical Units: Subjects			
Female	209	203	196
Male	149	147	158

Reporting group values	Total		
Number of subjects	1062		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	608		
Male	454		

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

In order to follow the Intention to Treat (ITT) principle this will consist of all randomised patients excepting for a) patients withdrawing consent between randomisation and starting therapy b) patients withdrawn from the study after randomisation because of irregularities with the consent process.

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who received any trial treatment

Reporting group values	Full Analysis Set	Safety Set	
Number of subjects	1062	1062	
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			

Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	 62.3 ± 9.5	 62.3 ± 9.5	
Gender categorical Units: Subjects			
Female Male	454 608	454 608	

End points

End points reporting groups

Reporting group title	Gemcitabine and Capecitabine Therapy

Reporting group description:

Gemcitabine will be administered on day 1, 8 and 15 followed by 7 days' rest. Per oral capecitabine will be administered morning and evening for 21 days followed by 7 days' rest. Gemcitabine and capecitabine therapy cycle will be repeated every 4 weeks until withdrawal from trial treatment due to patient choice, intolerable toxicity or disease progression.

Patients will have a CT scan at baseline, week 8 and every 12 weeks until the patient is withdrawn from the study. Upon withdrawal patients will be treated according to local practice and be subject to follow-up every 3 months until death.

Reporting group title	Gemcitabine and Capecitabine then Sequential GV1001 Therapy

Reporting group description:

Patients will receive two cycles of combination gemcitabine and capecitabine before Each of the two cycles of combination gemcitabine and capecitabine consists of:

Gemcitabine administered on day 1, 8 and 15 followed by 7 days“ rest. Per oral capecitabine administered morning and evening for 21 days followed by 7 days' rest. Following completion of two cycles of gemcitabine and capecitabine therapy, GV1001 will be administered intradermally on Monday, Wednesday and Friday during week 9 and once weekly during weeks 10, 11, 12 and 14. After that, vaccinations will follow a once monthly schedule until patient choice, intolerable toxicity or disease progression. Granulocytemacrophage colony-stimulating factor (GM-CSF) will be used as an adjuvant, given 10-15 minutes prior to each administration of GV1001.

Reporting group title	Concurrent Gemcitabine, Capecitabine and GV1001 Therapy

Reporting group description:

Gemcitabine will be administered on day 1, 8 and 15 followed by 7 days' rest. Per oral capecitabine will be administered morning and evening for 21 days followed by 7 days' rest. Gemcitabine and capecitabine therapy cycles will be repeated every 4 weeks until withdrawal from trial treatment due to patient choice, intolerable toxicity or disease progression.

Subject analysis set title	Full Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

In order to follow the Intention to Treat (ITT) principle this will consist of all randomised patients excepting for a) patients withdrawing consent between randomisation and starting therapy b) patients withdrawn from the study after randomisation because of irregularities with the consent process.

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who received any trial treatment

Primary: Overall Survival

End point title	Overall Survival

End point description:

End point type	Primary

End point timeframe:

From randomisation until death by any cause

End point values	Gemcitabine and Capecitabine Therapy	Gemcitabine and Capecitabine then Sequential GV1001 Therapy	Concurrent Gemcitabine, Capecitabine and GV1001 Therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	358	350	354	
Units: Subjects				
median (confidence interval 95%)	7.89 (7.07 to 8.85)	6.94 (6.35 to 7.60)	8.36 (7.30 to 9.74)	

Statistical analyses

Statistical analysis title	Primary Efficacy Analysis Arm 1 Vs Arm 2

Statistical analysis description:

Primary efficacy analysis of overall survival between the three treatment arms carried out using Cox Proportional Hazards modelling

Comparison groups	Gemcitabine and Capecitabine then Sequential GV1001 Therapy v Gemcitabine and Capecitabine Therapy
Number of subjects included in analysis	708
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [1]
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	1.19
Confidence interval	
level	Other: 98.25 %
sides	2-sided
lower limit	0.97
upper limit	1.48
Variability estimate	Standard error of the mean

Notes:

[1] - Please note this is a family wise type I error for the full trial which includes multiple comparisons and formal interim analysis. The final P-value to determine significance of an experimental treatment over the control used a P-value of 0.02078.

Statistical analysis title	Primary Efficacy Analysis Arm 1 Vs Arm 3

Statistical analysis description:

Primary efficacy analysis of overall survival between the three treatment arms carried out using Cox Proportional Hazards modelling

Comparison groups	Gemcitabine and Capecitabine Therapy v Concurrent Gemcitabine, Capecitabine and GV1001 Therapy
Number of subjects included in analysis	712
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [2]
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	1.05

Confidence interval	
level	Other: 98.25 %
sides	2-sided
lower limit	0.85
upper limit	1.29
Variability estimate	Standard error of the mean

Notes:

[2] - Please note this is a family wise type I error for the full trial which includes multiple comparisons and formal interim analysis. The final P-value to determine significance of an experimental treatment over the control used a P-value of 0.02078.

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

End point type	Secondary

End point timeframe:

Measured as the time from randomisation until progression or death by any cause

End point values	Gemcitabine and Capecitabine Therapy	Gemcitabine and Capecitabine then Sequential GV1001 Therapy	Concurrent Gemcitabine, Capecitabine and GV1001 Therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	358	350	354	
Units: Subjects				
median (confidence interval 95%)	6.35 (4.77 to 7.07)	4.54 (4.34 to 4.61)	6.58 (5.03 to 7.27)	

Statistical analyses

Statistical analysis title	Progression Free Survival Arm 1 Vs Arm 2
Comparison groups	Gemcitabine and Capecitabine Therapy v Gemcitabine and Capecitabine then Sequential GV1001 Therapy
Number of subjects included in analysis	708
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.26
upper limit	1.78

Variability estimate	Standard error of the mean

Statistical analysis title	Progression Free Survival Arm 1 Vs Arm 3
Comparison groups	Gemcitabine and Capecitabine Therapy v Concurrent Gemcitabine, Capecitabine and GV1001 Therapy
Number of subjects included in analysis	712
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.19
Variability estimate	Standard error of the mean

Secondary: Best Overall Clinical Response

End point title	Best Overall Clinical Response
End point description:	
End point type	Secondary
End point timeframe:	
From randomisation until death or competition of follow-up	

End point values	Gemcitabine and Capecitabine Therapy	Gemcitabine and Capecitabine then Sequential GV1001 Therapy	Concurrent Gemcitabine, Capecitabine and GV1001 Therapy	Full Analysis Set
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	358	350	354	
Units: Subjects				
number (not applicable)				
Missing	28	19	26	73
Dead by 8 weeks	3	6	4	13
Dead other	4	2	2	8
Progressive Disease	106	95	94	295
Stable Disease	154	197	173	524
Partial Response	60	30	52	142
Complete Response	3	1	3	7

Statistical analyses

Statistical analysis title	Analysis of Best Overall Response Arm 1 Vs Arm 2
Comparison groups	Gemcitabine and Capecitabine Therapy v Gemcitabine and Capecitabine then Sequential GV1001 Therapy
Number of subjects included in analysis	708
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.01
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	1.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.33
upper limit	2.98
Variability estimate	Standard error of the mean

Statistical analysis title	Analysis of Best Overall Response Arm 1 Vs Arm 3
Comparison groups	Gemcitabine and Capecitabine Therapy v Concurrent Gemcitabine, Capecitabine and GV1001 Therapy
Number of subjects included in analysis	712
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.58
Variability estimate	Standard error of the mean

Adverse events information

Timeframe for reporting adverse events:

AEs: Consent to last day of IMP administration/final study visit
SAEs (except deaths due to progressive disease): Consent until 28 days after last administration of trial treatment
After reporting period if AE/SAE possibly related to IMP

Adverse event reporting additional description:

ALL AEs recorded on CRF
ALL SAEs reported to ORION PVG via the documented reporting system

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3

Reporting groups

Reporting group title	Gemcitabine and Capecitabine Therapy

Reporting group description:

Gemcitabine will be administered on day 1, 8 and 15 followed by 7 days' rest. Per oral capecitabine will be administered morning and evening for 21 days followed by 7 days' rest. Gemcitabine and capecitabine therapy cycle will be repeated every 4 weeks until withdrawal from trial treatment due to patient choice, intolerable toxicity or disease progression.

Patients will have a CT scan at baseline, week 8 and every 12 weeks until the patient is withdrawn from the study. Upon withdrawal patients will be treated according to local practice and be subject to follow-up every 3 months until death.

Reporting group title	Gemcitabine and Capecitabine then Sequential GV1001 Therapy

Reporting group description:

Patients will receive two cycles of combination gemcitabine and capecitabine before Each of the two cycles of combination gemcitabine and capecitabine consists of:

Gemcitabine administered on day 1, 8 and 15 followed by 7 days“ rest. Per oral capecitabine administered morning and evening for 21 days followed by 7 days' rest. Following completion of two cycles of gemcitabine and capecitabine therapy, GV1001 will be administered intradermally on Monday, Wednesday and Friday during week 9 and once weekly during weeks 10, 11, 12 and 14. After that, vaccinations will follow a once monthly schedule until patient choice, intolerable toxicity or disease progression. Granulocytemacrophage colony-stimulating factor (GM-CSF) will be used as an adjuvant, given 10-15 minutes prior to each administration of GV1001.

Reporting group title	Concurrent Gemcitabine, Capecitabine and GV1001 Therapy

Reporting group description:

Gemcitabine will be administered on day 1, 8 and 15 followed by 7 days' rest. Per oral capecitabine will be administered morning and evening for 21 days followed by 7 days' rest. Gemcitabine and capecitabine therapy cycles will be repeated every 4 weeks until withdrawal from trial treatment due to patient choice, intolerable toxicity or disease progression.

Serious adverse events	Gemcitabine and Capecitabine Therapy	Gemcitabine and Capecitabine then Sequential GV1001 Therapy	Concurrent Gemcitabine, Capecitabine and GV1001 Therapy
Total subjects affected by serious adverse events			
subjects affected / exposed	134 / 358 (37.43%)	147 / 350 (42.00%)	167 / 354 (47.18%)
number of deaths (all causes)	245	268	259
number of deaths resulting from adverse events	10	13	10

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant ascites			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant ovarian cyst			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour invasion			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Circulatory collapse			

subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	2 / 4
Deep vein thrombosis			
subjects affected / exposed	11 / 358 (3.07%)	8 / 350 (2.29%)	7 / 354 (1.98%)
occurrences causally related to treatment / all	10 / 22	14 / 20	14 / 36
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	5 / 354 (1.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 19
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			
subjects affected / exposed	1 / 358 (0.28%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	1 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			

subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vena cava thrombosis			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 4
Surgical and medical procedures			
Pain management			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stent placement			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 358 (0.56%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest discomfort			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	4 / 358 (1.12%)	1 / 350 (0.29%)	4 / 354 (1.13%)
occurrences causally related to treatment / all	1 / 8	0 / 4	1 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chills			
subjects affected / exposed	1 / 358 (0.28%)	3 / 350 (0.86%)	3 / 354 (0.85%)
occurrences causally related to treatment / all	2 / 2	6 / 12	1 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Death			
subjects affected / exposed	1 / 358 (0.28%)	2 / 350 (0.57%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 6	0 / 0
deaths causally related to treatment / all	2 / 2	0 / 6	0 / 0
Device occlusion			
subjects affected / exposed	9 / 358 (2.51%)	22 / 350 (6.29%)	17 / 354 (4.80%)
occurrences causally related to treatment / all	2 / 20	0 / 72	1 / 70
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	25 / 358 (6.98%)	31 / 350 (8.86%)	22 / 354 (6.21%)
occurrences causally related to treatment / all	2 / 51	1 / 112	0 / 86
deaths causally related to treatment / all	0 / 24	0 / 52	0 / 32
Fatigue			
subjects affected / exposed	3 / 358 (0.84%)	2 / 350 (0.57%)	2 / 354 (0.56%)
occurrences causally related to treatment / all	6 / 10	0 / 6	6 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	3 / 358 (0.84%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 0
Influenza like illness			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucosal inflammation			
subjects affected / exposed	1 / 358 (0.28%)	1 / 350 (0.29%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	2 / 2	0 / 2	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			
subjects affected / exposed	0 / 358 (0.00%)	2 / 350 (0.57%)	2 / 354 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 6	2 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			

subjects affected / exposed	7 / 358 (1.96%)	2 / 350 (0.57%)	5 / 354 (1.41%)
occurrences causally related to treatment / all	2 / 14	2 / 4	3 / 24
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	4 / 358 (1.12%)	6 / 350 (1.71%)	4 / 354 (1.13%)
occurrences causally related to treatment / all	0 / 8	0 / 22	0 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	22 / 358 (6.15%)	29 / 350 (8.29%)	37 / 354 (10.45%)
occurrences causally related to treatment / all	25 / 55	41 / 99	71 / 176
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stent malfunction			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	2 / 354 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 8
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 358 (0.00%)	2 / 350 (0.57%)	3 / 354 (0.85%)
occurrences causally related to treatment / all	0 / 0	5 / 8	7 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Scrotal oedema			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	9 / 358 (2.51%)	5 / 350 (1.43%)	4 / 354 (1.13%)
occurrences causally related to treatment / all	5 / 17	0 / 14	5 / 16
deaths causally related to treatment / all	0 / 0	0 / 8	0 / 0
Epistaxis			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiccups			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hydropneumothorax			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	6 / 358 (1.68%)	3 / 350 (0.86%)	3 / 354 (0.85%)
occurrences causally related to treatment / all	2 / 14	0 / 16	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 358 (0.28%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	1 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	19 / 358 (5.31%)	26 / 350 (7.43%)	16 / 354 (4.52%)
occurrences causally related to treatment / all	11 / 40	19 / 82	14 / 64
deaths causally related to treatment / all	0 / 0	1 / 8	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary thrombosis			

subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	3 / 358 (0.84%)	3 / 350 (0.86%)	4 / 354 (1.13%)
occurrences causally related to treatment / all	0 / 6	2 / 6	0 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mood altered			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood albumin decreased			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	4 / 354 (1.13%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood glucose increased			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Body temperature increased			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	3 / 354 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio increased			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test abnormal			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urine output decreased			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count increased			

subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Afferent loop syndrome			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 358 (0.00%)	2 / 350 (0.57%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Narcotic intoxication			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural bile leak			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haematoma			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubis fracture			

subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stent occlusion			
subjects affected / exposed	0 / 358 (0.00%)	2 / 350 (0.57%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transfusion reaction			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound complication			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	2 / 354 (0.56%)
occurrences causally related to treatment / all	0 / 0	1 / 2	2 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 4
Arteriospasm coronary			

subjects affected / exposed	2 / 358 (0.56%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	2 / 354 (0.56%)
occurrences causally related to treatment / all	0 / 2	0 / 0	2 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 4
Coronary artery occlusion			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	5 / 358 (1.40%)	1 / 350 (0.29%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	5 / 10	1 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 358 (0.28%)	1 / 350 (0.29%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	2 / 2	0 / 2	1 / 4
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
Palpitations			

subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	3 / 358 (0.84%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	2 / 358 (0.56%)	1 / 350 (0.29%)	2 / 354 (0.56%)
occurrences causally related to treatment / all	0 / 4	0 / 4	2 / 8
deaths causally related to treatment / all	0 / 2	0 / 4	2 / 4
Depressed level of consciousness			

subjects affected / exposed	1 / 358 (0.28%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial palsy			
subjects affected / exposed	0 / 358 (0.00%)	2 / 350 (0.57%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial spasm			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lethargy			
subjects affected / exposed	2 / 358 (0.56%)	1 / 350 (0.29%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 4	0 / 4	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinsonism			

subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 358 (0.28%)	1 / 350 (0.29%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	1 / 358 (0.28%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 358 (0.28%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Unresponsive to stimuli			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	13 / 358 (3.63%)	10 / 350 (2.86%)	14 / 354 (3.95%)
occurrences causally related to treatment / all	21 / 28	9 / 28	21 / 64
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			

subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	2 / 358 (0.56%)	3 / 350 (0.86%)	3 / 354 (0.85%)
occurrences causally related to treatment / all	4 / 4	6 / 6	6 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	4 / 358 (1.12%)	5 / 350 (1.43%)	8 / 354 (2.26%)
occurrences causally related to treatment / all	8 / 8	9 / 14	20 / 32
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	5 / 358 (1.40%)	2 / 350 (0.57%)	6 / 354 (1.69%)
occurrences causally related to treatment / all	11 / 12	4 / 4	13 / 24
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 358 (0.28%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	27 / 358 (7.54%)	25 / 350 (7.14%)	26 / 354 (7.34%)
occurrences causally related to treatment / all	5 / 56	4 / 98	7 / 116
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			

subjects affected / exposed	5 / 358 (1.40%)	1 / 350 (0.29%)	4 / 354 (1.13%)
occurrences causally related to treatment / all	2 / 10	0 / 4	1 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	20 / 358 (5.59%)	20 / 350 (5.71%)	17 / 354 (4.80%)
occurrences causally related to treatment / all	0 / 43	2 / 88	0 / 92
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic pseudo-obstruction			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	13 / 358 (3.63%)	10 / 350 (2.86%)	12 / 354 (3.39%)
occurrences causally related to treatment / all	8 / 30	6 / 28	2 / 52
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	12 / 358 (3.35%)	16 / 350 (4.57%)	16 / 354 (4.52%)
occurrences causally related to treatment / all	13 / 26	27 / 42	25 / 67
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal obstruction			
subjects affected / exposed	0 / 358 (0.00%)	4 / 350 (1.14%)	6 / 354 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 14	0 / 24
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal stenosis			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	2 / 354 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			

subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	2 / 2	0 / 0
Eructation			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal fistula			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 358 (0.84%)	7 / 350 (2.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 6	1 / 20	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal obstruction			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal perforation			

subjects affected / exposed	0 / 358 (0.00%)	2 / 350 (0.57%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 4
Impaired gastric emptying			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal infarction			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	3 / 358 (0.84%)	1 / 350 (0.29%)	3 / 354 (0.85%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 4
Large intestinal obstruction			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 358 (0.00%)	2 / 350 (0.57%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mesenteric vein thrombosis			

subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	8 / 358 (2.23%)	18 / 350 (5.14%)	17 / 354 (4.80%)
occurrences causally related to treatment / all	11 / 16	29 / 61	22 / 71
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction gastric			
subjects affected / exposed	5 / 358 (1.40%)	10 / 350 (2.86%)	5 / 354 (1.41%)
occurrences causally related to treatment / all	0 / 10	0 / 40	0 / 20
deaths causally related to treatment / all	0 / 0	0 / 8	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 358 (0.28%)	2 / 350 (0.57%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 0
Peptic ulcer perforation			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 0
Peritoneal perforation			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 358 (0.28%)	3 / 350 (0.86%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal haemorrhage			

subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	4 / 358 (1.12%)	1 / 350 (0.29%)	4 / 354 (1.13%)
occurrences causally related to treatment / all	0 / 8	0 / 4	0 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	3 / 358 (0.84%)	1 / 350 (0.29%)	2 / 354 (0.56%)
occurrences causally related to treatment / all	6 / 6	2 / 4	2 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	3 / 358 (0.84%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Vomiting			
subjects affected / exposed	28 / 358 (7.82%)	25 / 350 (7.14%)	33 / 354 (9.32%)
occurrences causally related to treatment / all	26 / 59	27 / 95	43 / 144
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	8 / 358 (2.23%)	7 / 350 (2.00%)	7 / 354 (1.98%)
occurrences causally related to treatment / all	0 / 16	0 / 30	0 / 32
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stenosis			
subjects affected / exposed	1 / 358 (0.28%)	4 / 350 (1.14%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 2	0 / 14	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary dilatation			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	4 / 354 (1.13%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			

subjects affected / exposed	12 / 358 (3.35%)	9 / 350 (2.57%)	11 / 354 (3.11%)
occurrences causally related to treatment / all	8 / 26	0 / 38	0 / 50
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 358 (0.28%)	3 / 350 (0.86%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 2	0 / 8	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder obstruction			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Hepatic function abnormal			
subjects affected / exposed	1 / 358 (0.28%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic pain			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	6 / 358 (1.68%)	4 / 350 (1.14%)	2 / 354 (0.56%)
occurrences causally related to treatment / all	0 / 16	0 / 14	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			

subjects affected / exposed	3 / 358 (0.84%)	0 / 350 (0.00%)	3 / 354 (0.85%)
occurrences causally related to treatment / all	0 / 6	0 / 0	1 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	3 / 358 (0.84%)	6 / 350 (1.71%)	8 / 354 (2.26%)
occurrences causally related to treatment / all	0 / 6	0 / 20	0 / 36
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 0
Liver disorder			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perforation bile duct			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Portal vein thrombosis			
subjects affected / exposed	2 / 358 (0.56%)	2 / 350 (0.57%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	2 / 4	2 / 10	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 358 (0.28%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	2 / 2	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panniculitis			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plantar erythema			

subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	1 / 358 (0.28%)	3 / 350 (0.86%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	2 / 2	5 / 8	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash generalised			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash pruritic			
subjects affected / exposed	0 / 358 (0.00%)	2 / 350 (0.57%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	3 / 4	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Swelling face			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	3 / 358 (0.84%)	0 / 350 (0.00%)	2 / 354 (0.56%)
occurrences causally related to treatment / all	1 / 6	0 / 0	1 / 8
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 4
Renal failure acute			
subjects affected / exposed	1 / 358 (0.28%)	2 / 350 (0.57%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			

subjects affected / exposed	2 / 358 (0.56%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 358 (0.56%)	2 / 350 (0.57%)	4 / 354 (1.13%)
occurrences causally related to treatment / all	0 / 4	0 / 6	0 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	1 / 358 (0.28%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 0
Anal abscess			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bacteraemia			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial infection			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary sepsis			
subjects affected / exposed	16 / 358 (4.47%)	16 / 350 (4.57%)	16 / 354 (4.52%)
occurrences causally related to treatment / all	2 / 40	12 / 72	4 / 98
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 4
Biliary tract infection			
subjects affected / exposed	3 / 358 (0.84%)	1 / 350 (0.29%)	2 / 354 (0.56%)
occurrences causally related to treatment / all	4 / 6	0 / 2	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	2 / 2	0 / 0
Cellulitis			
subjects affected / exposed	12 / 358 (3.35%)	4 / 350 (1.14%)	6 / 354 (1.69%)
occurrences causally related to treatment / all	5 / 26	6 / 10	5 / 23
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis suppurative			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Clostridial infection			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			

subjects affected / exposed	0 / 358 (0.00%)	2 / 350 (0.57%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 8	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 358 (0.00%)	3 / 350 (0.86%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 12	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder abscess			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	16 / 358 (4.47%)	4 / 350 (1.14%)	12 / 354 (3.39%)
occurrences causally related to treatment / all	20 / 36	1 / 18	9 / 56
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious peritonitis			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella infection			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella sepsis			

subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	1 / 358 (0.28%)	2 / 350 (0.57%)	3 / 354 (0.85%)
occurrences causally related to treatment / all	0 / 2	0 / 8	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 4
Lower respiratory tract infection			
subjects affected / exposed	6 / 358 (1.68%)	11 / 350 (3.14%)	9 / 354 (2.54%)
occurrences causally related to treatment / all	10 / 12	8 / 34	10 / 44
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 0
Mastoiditis			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic infection			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	8 / 358 (2.23%)	3 / 350 (0.86%)	2 / 354 (0.56%)
occurrences causally related to treatment / all	16 / 16	6 / 8	4 / 8
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
Opportunistic infection			
subjects affected / exposed	1 / 358 (0.28%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 4	0 / 0
Oral candidiasis			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paronychia			

subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis bacterial			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 358 (0.84%)	5 / 350 (1.43%)	4 / 354 (1.13%)
occurrences causally related to treatment / all	2 / 6	3 / 16	4 / 20
deaths causally related to treatment / all	0 / 0	0 / 6	0 / 0
Pneumonia klebsiella			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural infection			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonas infection			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			

subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	2 / 354 (0.56%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	6 / 358 (1.68%)	8 / 350 (2.29%)	13 / 354 (3.67%)
occurrences causally related to treatment / all	0 / 12	10 / 20	9 / 56
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 8
Septic shock			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 4
Skin infection			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stent related infection			
subjects affected / exposed	2 / 358 (0.56%)	4 / 350 (1.14%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 4	0 / 10	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 4
Streptococcal sepsis			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			

subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	1 / 2	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	3 / 358 (0.84%)	3 / 350 (0.86%)	3 / 354 (0.85%)
occurrences causally related to treatment / all	3 / 6	2 / 10	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 2	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound abscess			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	4 / 358 (1.12%)	3 / 350 (0.86%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	4 / 8	0 / 10	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	5 / 358 (1.40%)	10 / 350 (2.86%)	4 / 354 (1.13%)
occurrences causally related to treatment / all	4 / 10	6 / 32	0 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			

subjects affected / exposed	0 / 358 (0.00%)	1 / 350 (0.29%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	2 / 358 (0.56%)	1 / 350 (0.29%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	1 / 4	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Gout			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	3 / 358 (0.84%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 4
Hyperglycaemia			
subjects affected / exposed	1 / 358 (0.28%)	7 / 350 (2.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	4 / 20	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	2 / 358 (0.56%)	3 / 350 (0.86%)	2 / 354 (0.56%)
occurrences causally related to treatment / all	0 / 4	0 / 10	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	2 / 354 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	2 / 358 (0.56%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemic syndrome			

subjects affected / exposed	1 / 358 (0.28%)	0 / 350 (0.00%)	0 / 354 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral intake reduced			
subjects affected / exposed	0 / 358 (0.00%)	0 / 350 (0.00%)	1 / 354 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Gemcitabine and Capecitabine Therapy	Gemcitabine and Capecitabine then Sequential GV1001 Therapy	Concurrent Gemcitabine, Capecitabine and GV1001 Therapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	320 / 358 (89.39%)	306 / 350 (87.43%)	325 / 354 (91.81%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	69 / 358 (19.27%)	63 / 350 (18.00%)	61 / 354 (17.23%)
occurrences (all)	105	103	105
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	60 / 358 (16.76%)	52 / 350 (14.86%)	57 / 354 (16.10%)
occurrences (all)	101	87	99

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 January 2007	SUBSTANTIAL AMENDMENT (MREC 01) - Change in the content of clinical Kit 1 (include one more vial of Leukine (GM-CSF) and one less vial of Bacteriostatic Water) - Change in label text to clarify the storage conditions and in-use shelf-life for GV1001 and Leukine after reconstitution Both reflected in minor changes in the protocol
05 March 2007	SUBSTANTIAL AMENDMENT (MREC 02) - Changes to the protocol - Submission of Investigators Brochure (IB) to replace SmPC
05 March 2007	SUBSTANTIAL AMENDMENT (MREC 03) - Changes to Protocol (Submitted to both MHRA and MREC in order to seek approval of amendment 2 to Protocol version 5) - Change in Clinical Trial Agreement (Chief Investigator changed from Professor J Neoptolemos to Dr G Middleton, Principal Investigator has changed from Dr G Middleton to Professor J Neoptolemos)
08 March 2007	SUBSTANTIAL AMENDMENT (MREC 04) Protocol Changes - Deletion of University as a co-sponsor - Deletion of University as a co-sponsor on Patient Information Sheet Clinical Trial Agreement Changes - Deletion of University as a co-sponsor
06 July 2007	SUBSTANTIAL AMENDMENT (MREC 06) - Changes to the Protocol - Change in the Clinical Trial Application - Change in the MREC Parts A&B - Change of Investigators - Addition of new sites - Update of IMPD of GV1001 to extend the shelf-life and change of the specifications
20 December 2007	SUBSTANTIAL AMENDMENT (MREC 07) - Changes to the Protocol: Change in GV1001 Kit 1 design Change of sample schedule for immunomonitoring Change of type of documents to be reviewed by LCTU before randomisation of a patient - Change in the Clinical Trial Application – Addition of new sites - Change in the MREC Parts A&B – Addition of new sites
01 May 2008	SUBSTANTIAL AMENDMENT (MREC 08) - Change of PI due to maternity leave – Dr Pippa Corrie from Addenbrooke's hospital will be on maternity leave from the 06/05/2008 to the 04/01/2008. The new PI for the site will be Dr Hugo Ford. - Addition of new site – Weston General Hospital in Weston-Super-Mare has joined the list of sites on the TeloVac trial. The PI for this site is Dr Serena Hilman.
20 May 2008	SUBSTANTIAL AMENDMENT (MREC 09) - Change of PI due to maternity leave - Dr Archer from Portsmouth Hospital will be on maternity leave until October. The new PI will be Ann O'Callaghan - Change of PI due to Dr Ostrowski retiring 0 Dr Ostrowski will be replaced by Dr Stubbings at Norfolk and Norwich

10 July 2008	SUBSTANTIAL AMENDMENT (MREC 10) - Change of PI at James Paget Hospital - Addition of site namely Alexandra Hospital - Notification of update to the GV1001 IB (for information only)
17 November 2008	SUBSTANTIAL AMENDMENT (MREC 11) - Notification of update to the Xeloda (capecitabine) IB - Notification of change of Principal Investigator
27 February 2009	MINOR AMENDMENT (MREC) 12 - Information only - Submission of additional label text provided for capecitabine by Roche
05 August 2009	SUBSTANTIAL AMENDMENT (MREC 13) - Change in PI at 3 sites: Norfolk and Norwich, Churchill and Yeovil District Hospital
18 January 2010	MINOR AMENDMENT (MREC 14) - Updated IBs (information only): Xeloda v10 and v11
02 February 2010	SUBSTANTIAL AMENDMENT (MREC 15&16) - Change to Patient Diary and Skin Test Ruler - Change in PI at Torbay Hospital
24 June 2010	MINOR AMENDMENT (MREC 17) - Information Only - Capecitabine diary footer altered to state version 3 - GV1001 IB v6 submitted for information
04 August 2010	SUBSTANTIAL AMENDMENT (MREC 18) - Protocol amended to allow for treatment breaks for patients - Administrative changes for protocol (re-ordering sections). - Notification of change of name from Cookridge Hospital to St James (named as Cookridge on original CTA). - Information sheet and informed consent form re-numbered as version 8 to avoid confusion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 May 2011	There was evidence that patients receiving vaccine treatment alone (Arm 2) had a poorer outcome than patients receiving standard chemotherapy treatment and there was no evidence of a a survival benefit from the addition of vaccine to chemotherapy compared to chemotherapy alone. The MHRA and Ethics were first informed of Urgent Safety Measures taken on 24/05/2011 that resulted in suspension of recruitment to Arm 2 of the trial. Given the advanced stage of the trial and the relatively small number of patients needed to completed target recruitment, the recommendation of the DMC and TSC (26/05/2011) was to close the TeloVac trial to further recruitment on 27/05/2011.	-

Notes:

Limitations and caveats

None reported