Clinical trial results:
A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of GS-5745 Combined with mFOLFOX6 as First Line Treatment in Patients with Advanced Gastric or Gastroesophageal Junction Adenocarcinoma

Summary

EudraCT number	2015-001526-42
Trial protocol	GB PL DE HU ES RO CZ FR BE IT
Global end of trial date	15 May 2019

Results information

Result version number	v1
This version publication date	01 May 2020
First version publication date	01 May 2020

Trial information

Trial identification

Sponsor protocol code	GS-US-296-1080

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02545504
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences , GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center , Gilead Sciences , GileadClinicalTrials@gilead.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2019
Global end of trial reached?	Yes
Global end of trial date	15 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the efficacy of andecaliximab (GS-5745) versus placebo in combination with modified fluorouracil (5-FU), leucovorin (LV), and oxaliplatin (OXA) (mFOLFOX6) as measured by overall survival.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.

This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 October 2015
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 States: 106
Country: Number of subjects enrolled	Turkey: 35
Country: Number of subjects enrolled	Australia: 31
Country: Number of subjects enrolled	Chile: 26
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Colombia: 11
Country: Number of subjects enrolled	Peru: 8
Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	Romania: 28
Country: Number of subjects enrolled	Spain: 55
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Czech Republic: 15
Country: Number of subjects enrolled	France: 13

Country: Number of subjects enrolled	Germany: 24
Country: Number of subjects enrolled	Hungary: 26
Worldwide total number of subjects	432
EEA total number of subjects	215

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)	265
From 65 to 84 years	166
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in Australia, Europe, Chile, Colombia, Peru, Turkey, and the United States. The first participant was screened on 13 October 2015. The last study visit occurred on 15 May 2019.

Pre-assignment

Screening details:

635 participants were screened.

Period 1

Period 1 title	Overall (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	Andecaliximab + mFOLFOX6

Arm description:

Participants were randomized to receive andecaliximab 800 mg intravenous (IV) plus mFOLFOX6 [leucovorin (LV)+5-fluorouracil (5-FU) + oxaliplatin (OXA)] IV as per standard of care on Days 1 and 15 of each 28-day treatment cycle during Cycles 1-6, followed by andecaliximab 800 mg IV plus LV+5-FU on Days 1 and 15 during subsequent cycles until disease progression, unacceptable toxicity, consent withdrawal, or the participant's refusal of treatment for up to 135.4 weeks at the time of final analysis for the endpoints and up to 161.7 weeks to the end of study.

Arm type	Experimental
Investigational medicinal product name	Andecaliximab
Investigational medicinal product code	
Other name	GS-5745
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

800 mg administered on Days 1 and 15 of each 28-day treatment cycle

Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered intravenously per standard of care on Days 1 and 15 of each treatment cycle

Investigational medicinal product name	5-fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered intravenously per standard of care on Days 1 and 15 of each treatment cycle

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered intravenously per standard of care on Days 1 and 15 of each treatment cycle

Arm title	Placebo + mFOLFOX6

Arm description:

Participants were randomized to receive placebo IV plus mFOLFOX6 (LV+5-FU+OXA) as per standard of care on Days 1 and 15 of each 28-day treatment cycle during Cycles 1-6, followed by placebo IV plus LV+5-FU on Days 1 and 15 during subsequent cycles until disease progression, unacceptable toxicity, consent withdrawal, or the participant's refusal of treatment for up to 99.7 weeks at the time of final analysis for the endpoints and up to 112.3 weeks to the end of study.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered intravenously on Days 1 and 15 of each treatment cycle

Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered intravenously per standard of care on Days 1 and 15 of each treatment cycle

Investigational medicinal product name	5-fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered intravenously per standard of care on Days 1 and 15 of each treatment cycle

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered intravenously per standard of care on Days 1 and 15 of each treatment cycle

Number of subjects in period 1	Andecaliximab + mFOLFOX6	Placebo + mFOLFOX6
Started	218	214
Completed	0	0
Not completed	218	214
Death	174	168
Unknown reason	30	32

Withdrew consent	9	11
Investigator's discretion	3	1
Lost to follow-up	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Andecaliximab + mFOLFOX6
Reporting group description:	
Participants were randomized to receive andecaliximab 800 mg intravenous (IV) plus mFOLFOX6 [leucovorin (LV)+5-fluorouracil (5-FU) + oxaliplatin (OXA)] IV as per standard of care on Days 1 and 15 of each 28-day treatment cycle during Cycles 1-6, followed by andecaliximab 800 mg IV plus LV+5-FU on Days 1 and 15 during subsequent cycles until disease progression, unacceptable toxicity, consent withdrawal, or the participant's refusal of treatment for up to 135.4 weeks at the time of final analysis for the endpoints and up to 161.7 weeks to the end of study.	
Reporting group title	Placebo + mFOLFOX6
Reporting group description:	
Participants were randomized to receive placebo IV plus mFOLFOX6 (LV+5-FU+OXA) as per standard of care on Days 1 and 15 of each 28-day treatment cycle during Cycles 1-6, followed by placebo IV plus LV+5-FU on Days 1 and 15 during subsequent cycles until disease progression, unacceptable toxicity, consent withdrawal, or the participant's refusal of treatment for up to 99.7 weeks at the time of final analysis for the endpoints and up to 112.3 weeks to the end of study.	

Reporting group values	Andecaliximab + mFOLFOX6	Placebo + mFOLFOX6	Total
Number of subjects	218	214	432
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	60	61	
standard deviation	± 11.9	± 11.4	-
Gender categorical Units: Subjects			
Female	50	61	111
Male	168	153	321
Ethnicity Units: Subjects			
Hispanic or Latino	38	32	70
Not Hispanic or Latino	170	173	343
Not Permitted	10	9	19
Race Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	5	5	10
Black or African American	4	4	8
White	186	184	370
Not Permitted	8	6	14
Other	15	14	29
Region of Enrollment Units: Subjects			
Colombia	5	6	11
Romania	15	13	28
Hungary	11	15	26
United States	47	59	106

Czechia	10	5	15
United Kingdom	5	6	11
Spain	27	28	55
Turkey	17	18	35
Belgium	2	3	5
Poland	13	11	24
Italy	8	6	14
Australia	13	18	31
Chile	15	11	26
France	10	3	13
Peru	4	4	8
Germany	16	8	24
Type of Cancer Units: Subjects			
Gastric	142	143	285
Gastroesophageal junction	76	71	147

End points

End points reporting groups

Reporting group title	Andecaliximab + mFOLFOX6

Reporting group description:

Participants were randomized to receive andecaliximab 800 mg intravenous (IV) plus mFOLFOX6 [leucovorin (LV)+5-fluorouracil (5-FU) + oxaliplatin (OXA)] IV as per standard of care on Days 1 and 15 of each 28-day treatment cycle during Cycles 1-6, followed by andecaliximab 800 mg IV plus LV+5-FU on Days 1 and 15 during subsequent cycles until disease progression, unacceptable toxicity, consent withdrawal, or the participant's refusal of treatment for up to 135.4 weeks at the time of final analysis for the endpoints and up to 161.7 weeks to the end of study.

Reporting group title	Placebo + mFOLFOX6

Reporting group description:

Participants were randomized to receive placebo IV plus mFOLFOX6 (LV+5-FU+OXA) as per standard of care on Days 1 and 15 of each 28-day treatment cycle during Cycles 1-6, followed by placebo IV plus LV+5-FU on Days 1 and 15 during subsequent cycles until disease progression, unacceptable toxicity, consent withdrawal, or the participant's refusal of treatment for up to 99.7 weeks at the time of final analysis for the endpoints and up to 112.3 weeks to the end of study.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time interval from the date of randomization to death from any cause. The Intent-to-Treat (ITT) Analysis Set included all randomized participants.

End point type	Primary

End point timeframe:

Andecaliximab + mFOLFOX6 median follow-up at the time of final analysis: 19.43 months; Placebo + mFOLFOX6 median follow-up at the time of the final analysis: 19.45 months

End point values	Andecaliximab + mFOLFOX6	Placebo + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	214		
Units: months				
median (confidence interval 95%)	12.52 (11.2 to 14.0)	11.76 (10.3 to 13.5)		

Statistical analyses

Statistical analysis title	OS: Andecaliximab + mFOLFOX6 vs Placebo + mFOLFOX6

Statistical analysis description:

The primary and secondary endpoints were tested sequentially in the following gate-keeping order: the primary OS endpoint, then the secondary PFS endpoint, and finally the secondary ORR endpoint.

Comparison groups	Andecaliximab + mFOLFOX6 v Placebo + mFOLFOX6

Number of subjects included in analysis	432
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.5625 [2]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.18

Notes:

[1] - p-value was stratified by Eastern Cooperative Oncology Group (ECOG) status, geographic region and primary tumor site and Hazard ratio (HR) was stratified by ECOG status, geographic region and primary tumor site with treatment arm as a covariate.

[2] - The significance level at final analysis was 0.046 (two-sided). Stratum with < 6 participants or no informative event by combined treatment arms was pooled with the smallest adjacent stratum for stratified analyses.

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS was defined as the interval of time from the date of randomisation to the earlier of the first documentation of definitive disease progression or death from any cause. Participants in the ITT Analysis Set were analysed.

End point type	Secondary

End point timeframe:

Andecaliximab + mFOLFOX6 median follow-up at the time of final analysis: 18.64 months; Placebo + mFOLFOX6 median follow-up at the time of final analysis: 18.74 months

End point values	Andecaliximab + mFOLFOX6	Placebo + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	214		
Units: months				
median (confidence interval 95%)	7.46 (7.29 to 8.41)	7.06 (5.52 to 7.46)		

Statistical analyses

Statistical analysis title	PFS:Andecaliximab + mFOLFOX6 vs Placebo + mFOLFOX6

Statistical analysis description:

The primary and secondary endpoints were tested sequentially in the following gate-keeping order: the primary OS endpoint, then the secondary PFS endpoint, and finally the secondary ORR endpoint. PFS was tested only if OS was significant.The P-value is for display only.

Comparison groups	Placebo + mFOLFOX6 v Andecaliximab + mFOLFOX6

Number of subjects included in analysis	432
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.1031 [4]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.04

Notes:

[3] - p-value was stratified by ECOG status,geographic region and primary tumor site and HR was stratified by ECOG status, geographic region and primary tumor site with treatment arm as a covariate.
[4] - The significance level at final analysis was 0.032 (two-sided). Stratum with < 6 participants or no informative event by combined treatment arms was pooled with the smallest adjacent stratum for stratified analyses.

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR was defined as the percentage of participants who achieve a complete response (CR) or partial response (PR) as assessed by Response Evaluation Criteria In Solid Tumors (RECIST) v1.1. CR was defined as the disappearance of all target lesions and disappearance of all non-target lesions and normalization of tumor marker level. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Participants in the ITT Analysis Set were analysed.

End point type	Secondary

End point timeframe:

Up to 135.4 weeks at the time of final analysis

End point values	Andecaliximab + mFOLFOX6	Placebo + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	214		
Units: percentage of participants				
number (confidence interval 95%)	50.5 (43.6 to 57.3)	41.1 (34.5 to 48.0)		

Statistical analyses

Statistical analysis title	ORR:Andecaliximab + mFOLFOX6 vs Placebo + mFOLFOX6

Statistical analysis description:

The primary and secondary endpoints were tested sequentially in the following gate-keeping order: the primary OS endpoint, then the secondary PFS endpoint, and finally the secondary ORR endpoint. ORR was tested only if OS and PFS were significant.The P-value is for display only.

Comparison groups	Placebo + mFOLFOX6 v Andecaliximab + mFOLFOX6

Number of subjects included in analysis	432
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0493 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	2.15

Notes:

[5] - p-value and Odds Ratio were stratified by ECOG status, geographic region and primary tumor site.

[6] - The significance level at final analysis was 0.032 (two-sided). Stratum with < 6 participants or no informative event by combined treatment arms was pooled with the smallest adjacent stratum for stratified analyses.

Statistical analysis title	ORR:Andecaliximab + mFOLFOX6 vs Placebo + mFOLFOX6

Statistical analysis description:

A Cochran-Mantel-Haenszel Chi-square test for association between treatment and response, after adjusting for stratification factors, was performed to compare the 2 treatment groups. The 2-sided 95% confidence interval (CI) of difference for ORR between the treatment and placebo is calculated based on stratum-adjusted Cochran-Mantel-Haenszel proportion.

Comparison groups	Andecaliximab + mFOLFOX6 v Placebo + mFOLFOX6
Number of subjects included in analysis	432
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	ORR Difference
Point estimate	9.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	18.8

Secondary: Percentage of Participants Experiencing Treatment-emergent Adverse Events (TEAEs)

End point title	Percentage of Participants Experiencing Treatment-emergent Adverse Events (TEAEs)

End point description:

An adverse event (AE) is any untoward medical occurrence in a clinical study participant administered a medicinal product, which does not necessarily have a causal relationship with the treatment. TEAEs are events in a given study period that meet any of the following criteria: Any AE with onset date of on or after andecalizimab/placebo start date and no later than 30 days after permanent discontinuation of all study treatment (andecaliximab/placebo and chemotherapy) or Any AEs with onset date of on or after the andecaliximab/placebo start date and no later than 55 days after permanent discontinuation of andecaliximab/placebo or AEs leading to discontinuation of andecaliximab/placebo. The Safety Analysis Set included all participants who received at least one dose of andecaliximab/placebo.

End point type	Secondary

End point timeframe:

First dose date up to the last dose date (maximum: 161.7 weeks) plus 30 to 55 days

End point values	Andecaliximab + mFOLFOX6	Placebo + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	210		
Units: percentage of participants				
number (not applicable)	99.1	99.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Clinically Relevant Treatment-emergent Laboratory Abnormalities

End point title	Percentage of Participants With Clinically Relevant Treatment-emergent Laboratory Abnormalities

End point description:

Treatment-emergent laboratory abnormalities were graded per Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 where 0=None, 1=Mild, 2=Moderate, 3=Severe, 4=Potentially Life Threatening. Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any post-baseline time point, up to 30 days after the last dose of all study treatment, or 55 days after the last dose of andecaliximab/placebo for participants who permanently discontinued all study treatments. If the relevant baseline laboratory value is missing, then any abnormality of at least Grade 1 was considered treatment-emergent. Participants in the Safety Analysis Set were analysed.

End point type	Secondary

End point timeframe:

First dose date up to the last dose date (maximum: 161.7 weeks) plus 30 to 55 days

End point values	Andecaliximab + mFOLFOX6	Placebo + mFOLFOX6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	210		
Units: percentage of participants				
number (not applicable)				
Hematology	94.4	89.5		
Serum Chemistry	91.7	92.9		
Coagulation	7.4	3.3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose date up to the last dose date (maximum: 161.7 weeks) plus 30 to 55 days

Adverse event reporting additional description:

Serious Adverse Events and Non-Serious Adverse Events: The Safety Analysis Set included all participants who received at least one dose of andecaliximab/placebo. The Number of Deaths (All-causes): The Intent-to-Treat (ITT) Analysis Set included all randomized participants.(N=218, 214)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Andecaliximab + mFOLFOX6

Reporting group description:

Participants received andecaliximab 800 mg intravenous (IV) plus mFOLFOX6 [leucovorin (LV)+5-fluorouracil (5-FU) + oxaliplatin (OXA)] IV as per standard of care on Days 1 and 15 of each 28-day treatment cycle during Cycles 1-6, followed by andecaliximab 800 mg IV plus LV+5-FU on Days 1 and 15 during subsequent cycles until disease progression, unacceptable toxicity, consent withdrawal, or the participant's refusal of treatment for up to 161.7 weeks.

Reporting group title	Placebo + mFOLFOX6

Reporting group description:

Participants received placebo IV plus mFOLFOX6 (LV+5-FU+OXA) as per standard of care on Days 1 and 15 of each 28-day treatment cycle during Cycles 1-6, followed by placebo IV plus LV+5-FU on Days 1 and 15 during subsequent cycles until disease progression, unacceptable toxicity, consent withdrawal, or the participant's refusal of treatment for up to 112.3 weeks.

Serious adverse events	Andecaliximab + mFOLFOX6	Placebo + mFOLFOX6	
Total subjects affected by serious adverse events			
subjects affected / exposed	103 / 216 (47.69%)	108 / 210 (51.43%)	
number of deaths (all causes)	174	168	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 216 (0.46%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			

subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour necrosis			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
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	3 / 216 (1.39%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral venous disease			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poor venous access			
subjects affected / exposed	3 / 216 (1.39%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			

subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 216 (0.46%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	4 / 216 (1.85%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Fatigue			
subjects affected / exposed	0 / 216 (0.00%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	4 / 216 (1.85%)	3 / 210 (1.43%)	
occurrences causally related to treatment / all	0 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Inflammation			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 216 (0.93%)	4 / 210 (1.90%)	
occurrences causally related to treatment / all	3 / 4	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (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	4 / 216 (1.85%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 216 (0.46%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 216 (0.93%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 216 (0.46%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	8 / 216 (3.70%)	13 / 210 (6.19%)	
occurrences causally related to treatment / all	2 / 8	3 / 13	
deaths causally related to treatment / all	0 / 1	1 / 3	
Respiratory distress			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 216 (1.39%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Product issues			
Device dislocation			

subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 216 (0.93%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Body temperature increased			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			

subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Occult blood positive			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 216 (0.46%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic ulcer			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (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	1 / 216 (0.46%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			

subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 216 (0.46%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous haematoma			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			

subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access complication			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 216 (0.46%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 216 (0.46%)	3 / 210 (1.43%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 2	
Cardio-respiratory arrest			
subjects affected / exposed	2 / 216 (0.93%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiovascular disorder			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			

subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid arteriosclerosis			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 216 (0.46%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Headache			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			

subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 216 (0.93%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paralysis			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
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	3 / 216 (1.39%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	0 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	6 / 216 (2.78%)	5 / 210 (2.38%)	
occurrences causally related to treatment / all	6 / 6	4 / 5	
deaths causally related to treatment / all	2 / 2	0 / 0	
Neutropenia			
subjects affected / exposed	4 / 216 (1.85%)	4 / 210 (1.90%)	
occurrences causally related to treatment / all	10 / 10	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 216 (0.93%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 216 (3.24%)	8 / 210 (3.81%)	
occurrences causally related to treatment / all	0 / 7	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 216 (0.93%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	2 / 216 (0.93%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	3 / 216 (1.39%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	3 / 216 (1.39%)	5 / 210 (2.38%)	
occurrences causally related to treatment / all	3 / 4	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	3 / 216 (1.39%)	3 / 210 (1.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 216 (0.46%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastric perforation			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastric stenosis			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	6 / 216 (2.78%)	4 / 210 (1.90%)	
occurrences causally related to treatment / all	1 / 6	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			

subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 216 (0.46%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 216 (0.46%)	4 / 210 (1.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal pseudo-obstruction			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			

subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	2 / 216 (0.93%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	4 / 216 (1.85%)	4 / 210 (1.90%)	
occurrences causally related to treatment / all	2 / 4	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	3 / 216 (1.39%)	6 / 210 (2.86%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal perforation			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 216 (0.46%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	2 / 216 (0.93%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	2 / 216 (0.93%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 216 (0.46%)	4 / 210 (1.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vomiting			
subjects affected / exposed	11 / 216 (5.09%)	8 / 210 (3.81%)	
occurrences causally related to treatment / all	7 / 13	6 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute on chronic liver failure			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			

subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 216 (0.00%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (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			
Rash maculo-papular			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 216 (0.93%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nephritis			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urine flow decreased			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cellulitis			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 216 (0.93%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 216 (3.24%)	5 / 210 (2.38%)	
occurrences causally related to treatment / all	0 / 8	1 / 5	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumonia necrotising			

subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Postoperative wound infection			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 216 (0.93%)	4 / 210 (1.90%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 2	0 / 1	
Septic shock			
subjects affected / exposed	0 / 216 (0.00%)	2 / 210 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	4 / 216 (1.85%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vascular device infection			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (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 / 216 (0.00%)	1 / 210 (0.48%)	
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	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 216 (1.39%)	3 / 210 (1.43%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	1 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			

subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 216 (0.46%)	1 / 210 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 216 (0.00%)	1 / 210 (0.48%)	
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 / 216 (0.46%)	0 / 210 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Andecaliximab + mFOLFOX6	Placebo + mFOLFOX6	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	209 / 216 (96.76%)	203 / 210 (96.67%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	11 / 216 (5.09%)	12 / 210 (5.71%)	
occurrences (all)	20	13	
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 216 (6.02%)	11 / 210 (5.24%)	
occurrences (all)	23	13	
Blood alkaline phosphatase increased			
subjects affected / exposed	15 / 216 (6.94%)	9 / 210 (4.29%)	
occurrences (all)	19	11	
Neutrophil count decreased			
subjects affected / exposed	30 / 216 (13.89%)	25 / 210 (11.90%)	
occurrences (all)	47	37	

Platelet count decreased			
subjects affected / exposed	19 / 216 (8.80%)	17 / 210 (8.10%)	
occurrences (all)	32	26	
Weight decreased			
subjects affected / exposed	29 / 216 (13.43%)	23 / 210 (10.95%)	
occurrences (all)	30	25	
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 216 (4.17%)	11 / 210 (5.24%)	
occurrences (all)	14	17	
Nervous system disorders			
Dizziness			
subjects affected / exposed	19 / 216 (8.80%)	26 / 210 (12.38%)	
occurrences (all)	22	35	
Dysgeusia			
subjects affected / exposed	21 / 216 (9.72%)	15 / 210 (7.14%)	
occurrences (all)	30	16	
Dysaesthesia			
subjects affected / exposed	15 / 216 (6.94%)	12 / 210 (5.71%)	
occurrences (all)	26	26	
Headache			
subjects affected / exposed	18 / 216 (8.33%)	15 / 210 (7.14%)	
occurrences (all)	32	17	
Neuropathy peripheral			
subjects affected / exposed	28 / 216 (12.96%)	21 / 210 (10.00%)	
occurrences (all)	41	23	
Neurotoxicity			
subjects affected / exposed	10 / 216 (4.63%)	11 / 210 (5.24%)	
occurrences (all)	18	19	
Paraesthesia			
subjects affected / exposed	27 / 216 (12.50%)	24 / 210 (11.43%)	
occurrences (all)	31	31	
Peripheral sensory neuropathy			
subjects affected / exposed	73 / 216 (33.80%)	72 / 210 (34.29%)	
occurrences (all)	124	105	
Taste disorder			

subjects affected / exposed	7 / 216 (3.24%)	11 / 210 (5.24%)	
occurrences (all)	7	11	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	61 / 216 (28.24%)	62 / 210 (29.52%)	
occurrences (all)	70	76	
Neutropenia			
subjects affected / exposed	76 / 216 (35.19%)	73 / 210 (34.76%)	
occurrences (all)	141	127	
Thrombocytopenia			
subjects affected / exposed	38 / 216 (17.59%)	32 / 210 (15.24%)	
occurrences (all)	55	60	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	62 / 216 (28.70%)	52 / 210 (24.76%)	
occurrences (all)	144	78	
Chest pain			
subjects affected / exposed	7 / 216 (3.24%)	11 / 210 (5.24%)	
occurrences (all)	8	13	
Fatigue			
subjects affected / exposed	79 / 216 (36.57%)	72 / 210 (34.29%)	
occurrences (all)	124	108	
Mucosal inflammation			
subjects affected / exposed	25 / 216 (11.57%)	26 / 210 (12.38%)	
occurrences (all)	32	49	
Oedema peripheral			
subjects affected / exposed	18 / 216 (8.33%)	20 / 210 (9.52%)	
occurrences (all)	20	23	
Pyrexia			
subjects affected / exposed	25 / 216 (11.57%)	18 / 210 (8.57%)	
occurrences (all)	32	21	
Temperature intolerance			
subjects affected / exposed	12 / 216 (5.56%)	12 / 210 (5.71%)	
occurrences (all)	18	19	
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	14 / 216 (6.48%)	14 / 210 (6.67%)	
occurrences (all)	16	14	
Abdominal pain			
subjects affected / exposed	41 / 216 (18.98%)	37 / 210 (17.62%)	
occurrences (all)	65	48	
Abdominal pain upper			
subjects affected / exposed	19 / 216 (8.80%)	26 / 210 (12.38%)	
occurrences (all)	26	34	
Ascites			
subjects affected / exposed	11 / 216 (5.09%)	13 / 210 (6.19%)	
occurrences (all)	11	14	
Constipation			
subjects affected / exposed	61 / 216 (28.24%)	61 / 210 (29.05%)	
occurrences (all)	84	77	
Diarrhoea			
subjects affected / exposed	87 / 216 (40.28%)	88 / 210 (41.90%)	
occurrences (all)	176	152	
Dry mouth			
subjects affected / exposed	8 / 216 (3.70%)	12 / 210 (5.71%)	
occurrences (all)	8	15	
Dyspepsia			
subjects affected / exposed	20 / 216 (9.26%)	8 / 210 (3.81%)	
occurrences (all)	20	8	
Dysphagia			
subjects affected / exposed	21 / 216 (9.72%)	19 / 210 (9.05%)	
occurrences (all)	26	25	
Flatulence			
subjects affected / exposed	11 / 216 (5.09%)	10 / 210 (4.76%)	
occurrences (all)	12	11	
Gastrooesophageal reflux disease			
subjects affected / exposed	9 / 216 (4.17%)	14 / 210 (6.67%)	
occurrences (all)	11	14	
Nausea			
subjects affected / exposed	106 / 216 (49.07%)	118 / 210 (56.19%)	
occurrences (all)	223	226	

Stomatitis			
subjects affected / exposed	24 / 216 (11.11%)	21 / 210 (10.00%)	
occurrences (all)	30	33	
Vomiting			
subjects affected / exposed	63 / 216 (29.17%)	62 / 210 (29.52%)	
occurrences (all)	125	118	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	25 / 216 (11.57%)	23 / 210 (10.95%)	
occurrences (all)	28	27	
Dyspnoea			
subjects affected / exposed	20 / 216 (9.26%)	22 / 210 (10.48%)	
occurrences (all)	31	26	
Epistaxis			
subjects affected / exposed	16 / 216 (7.41%)	19 / 210 (9.05%)	
occurrences (all)	17	20	
Hiccups			
subjects affected / exposed	11 / 216 (5.09%)	9 / 210 (4.29%)	
occurrences (all)	13	10	
Pulmonary embolism			
subjects affected / exposed	10 / 216 (4.63%)	12 / 210 (5.71%)	
occurrences (all)	10	13	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	14 / 216 (6.48%)	16 / 210 (7.62%)	
occurrences (all)	15	16	
Rash			
subjects affected / exposed	13 / 216 (6.02%)	11 / 210 (5.24%)	
occurrences (all)	14	14	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	27 / 216 (12.50%)	22 / 210 (10.48%)	
occurrences (all)	28	26	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	14 / 216 (6.48%)	10 / 210 (4.76%)	
occurrences (all)	14	12	
Back pain			
subjects affected / exposed	25 / 216 (11.57%)	20 / 210 (9.52%)	
occurrences (all)	28	21	
Musculoskeletal pain			
subjects affected / exposed	12 / 216 (5.56%)	4 / 210 (1.90%)	
occurrences (all)	15	4	
Myalgia			
subjects affected / exposed	11 / 216 (5.09%)	4 / 210 (1.90%)	
occurrences (all)	11	4	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	16 / 216 (7.41%)	8 / 210 (3.81%)	
occurrences (all)	18	12	
Urinary tract infection			
subjects affected / exposed	16 / 216 (7.41%)	11 / 210 (5.24%)	
occurrences (all)	23	16	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	63 / 216 (29.17%)	72 / 210 (34.29%)	
occurrences (all)	106	93	
Dehydration			
subjects affected / exposed	16 / 216 (7.41%)	16 / 210 (7.62%)	
occurrences (all)	17	20	
Hyperglycaemia			
subjects affected / exposed	13 / 216 (6.02%)	6 / 210 (2.86%)	
occurrences (all)	20	8	
Hypoalbuminaemia			
subjects affected / exposed	12 / 216 (5.56%)	8 / 210 (3.81%)	
occurrences (all)	12	8	
Hypokalaemia			
subjects affected / exposed	28 / 216 (12.96%)	22 / 210 (10.48%)	
occurrences (all)	43	29	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2015	Amendment 1: 1. The study phase was changed from Phase 2 to Phase 3. 2. References to enrollment in relation to study procedures was replaced with randomization.
17 August 2015	Amendment 2: 1. The details on the preparation of GS-5745/placebo (study drug) were removed from the protocol. Additional testing to determine a longer duration of stability was conducted and the preparation instructions provided in the protocol were changed. Detailed study drug preparation instructions were provided separately in a pharmacy manual. 2. To correct errors and inconsistencies in the protocol.
14 December 2015	Amendment 3: 1. An additional 55-day phone follow-up was added to the original 30 day safety follow up in multiple sections.
22 June 2016	Amendment 4: 1. Implemented the updated prescribing information for oxaliplatin in the global protocol. These changes were previously implemented in a French specific protocol amendment (version 3.1). 2. Added an exploratory objective and endpoints for the data collected from patient-reported outcomes. 3. Clarified the dosing requirements for mFOLFOX6 and GS-5745/placebo. 4. Corrected the timing for the coagulation tests when determining eligibility. 5. Changed the p-value from 2-sided to 1-sided in the statistical methods for consistency. 6. Clarified procedures for withdrawing consent. 7. Clarified management of toxicities attributed to GS-745/placebo. 8. Added details on the testing for efficacy endpoints for reference. 9. Corrected minor errors and inconsistencies throughout the protocol.
14 December 2016	Amendment 5: 1. Changed the inclusion criterion on creatinine clearance to reflect the current safety profile of GS-5745 and the oxaliplatin label. 2. Clarified the exclusion criterion on radiotherapy. 3. Revised the instructions on cardiac monitoring after oxaliplatin dosing to reflect each country's standard practice by following the prescribing information/summary of product characteristics (SmPC) for oxaliplatin approved at the local country level. 4. Clarified the timing of the first safety review by the data monitoring committee (DMC). 5. Corrected the duration of the collection of AEs and the timing of the scheduling of the 30- and 55-Day Safety Follow Up visits. 6. Provided the flexibility to follow institutional guidance/practices to calculate body surface area (BSA). 7. Added an anti-GS-5745 antibody sample collection time point at the 30-Day Safety Follow Up visit. 8. Increased the window for using CT/MRI scans obtain during standard of care for screening. 9. Corrected minor errors and inconsistencies throughout the protocol.
06 March 2017	Amendment 6: 1. Updated the futility interim analysis. 2. Provided further clarifications on guidelines for dose interruption and reduction. 3. Corrected minor errors and inconsistencies throughout the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported