Clinical trial results:
A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Pegfilgrastim Administered to Subjects With Newly Diagnosed, Locally-advanced or Metastatic Colorectal Cancer Treated With Bevacizumab and Either 5-fluorouracil, Oxaliplatin, Leucovorin (FOLFOX) or 5-fluorouracil, Irinotecan, Leucovorin (FOLFIRI)

Summary

EudraCT number	2009-011899-30
Trial protocol	LV HU CZ BE IE IT FR SK BG
Global end of trial date	02 January 2015

Results information

Result version number	v1 (current)
This version publication date	25 June 2016
First version publication date	25 June 2016

Trial information

Trial identification

Sponsor protocol code	20080259

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00911170
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen, Inc
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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	02 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the efficacy of pegfilgrastim, as compared with placebo in reducing the incidence of grade 3/4 febrile neutropenia in subjects with newly diagnosed, locally-advanced or metastatic colorectal cancer (mCRC) treated with bevacizumab and either FOLFOX or FOLFIRI.
This study will also investigate the effect of adding pegfilgrastim to bevacizumab and either FOLFOX or FOLFIRI on overall survival, progression-free survival, and overall response rate.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
The protocol, informed consent form (ICF), other written subject information were submitted to the Independent Ethics Committee / Institutional Review Board for written approval. Written approval of the protocol and ICF were received by Amgen before recruitment of subjects into the study and shipment of the investigational product (IP).
Informed consent forms were signed by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 November 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	36 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 124
Country: Number of subjects enrolled	Canada: 33
Country: Number of subjects enrolled	Australia: 27
Country: Number of subjects enrolled	Belgium: 22
Country: Number of subjects enrolled	Bulgaria: 25
Country: Number of subjects enrolled	Czech Republic: 87
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Hungary: 162
Country: Number of subjects enrolled	Ireland: 35
Country: Number of subjects enrolled	Italy: 28
Country: Number of subjects enrolled	Latvia: 65
Country: Number of subjects enrolled	Mexico: 9

Country: Number of subjects enrolled	Poland: 74
Country: Number of subjects enrolled	Romania: 27
Country: Number of subjects enrolled	Russian Federation: 23
Country: Number of subjects enrolled	Slovakia: 13
Country: Number of subjects enrolled	Ukraine: 82
Worldwide total number of subjects	847
EEA total number of subjects	549

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)	534
From 65 to 84 years	311
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The first participant was enrolled into the study on 03 November 2009 and the last participant on 03 January 2012 at 114 centers worldwide.
This study included a study treatment period (approximately 8 weeks), and a long-term follow-up period (up to 36 months after the last subject enrolled).

Pre-assignment

Screening details:

A total of 1038 subjects were screened, 191 screen-failed and and 847 subjects were enrolled. Randomization was stratified by region (North America vs Rest of World), subject disease status (locally-advanced vs metastatic), and chemotherapy regimen (bevacizumab plus FOLFOX vs bevacizumab plus FOLFIRI).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received standard chemotherapy (FOLFOX or FOLFIRI) on Days 1-2, and bevacizumab 5 mg/kg intravenous (IV) infusion on Day 1 of each 14-day cycle, plus placebo subcutaneous injection once per cycle, for a maximum of 4 cycles, 24 hours after chemotherapy (Day 4). During the long-term follow-up period, further chemotherapy and/or biologic agents (for example, bevacizumab) were to continue at the discretion of the treating physician.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered as a single subcutaneous injection

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mg/kg by intravenous (IV) infusion on day 1 of each 14-day cycle.

Investigational medicinal product name	Standard Chemotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Each participant received one of the following chemotherapy regimens at the discretion of treating physician:

FOLFOX: Oxaliplatin, leucovorin, and 5-fluorouracil;
FOLFIRI: Irinotecan, leucovorin and 5-flurouracil.

Arm title	Pegfilgrastim

Arm description:

Participants received standard chemotherapy (FOLFOX or FOLFIRI) on Days 1-2 and bevacizumab 5 mg/kg intravenous (IV) infusion on Day 1 of each 14-day cycle plus pegfilgrastim 6 mg administered as a single subcutaneous injection once per cycle, for a maximum of 4 cycles, 24 hours after chemotherapy (Day 4). During the long-term follow-up period, further chemotherapy and/or biologic agents (for example, bevacizumab) were to continue at the discretion of the treating physician.

Arm type	Placebo
Investigational medicinal product name	Pegfilgrastim
Investigational medicinal product code	
Other name	Neulasta®
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered as a single 6 mg subcutaneous injection

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mg/kg by intravenous (IV) infusion on day 1 of each 14-day cycle.

Investigational medicinal product name	Standard Chemotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Each participant received one of the following chemotherapy regimens at the discretion of treating physician:
FOLFOX: Oxaliplatin, leucovorin, and 5-fluorouracil;
FOLFIRI: Irinotecan, leucovorin and 5-flurouracil.

Number of subjects in period 1	Placebo	Pegfilgrastim
Started	424	423
Received chemotherapy	423	422
Received bevacizumab	423	420
Received investigational product	422	419
Completed	397	386
Not completed	27	37
Adverse event, serious fatal	6	9
Randomized in error	1	1

Consent withdrawn by subject	4	4
Physician decision	5	5
Disease progression	-	2
Adverse event, non-fatal	9	10
Protocol deviation	1	2
Ineligibility determined	1	3
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received standard chemotherapy (FOLFOX or FOLFIRI) on Days 1-2, and bevacizumab 5 mg/kg intravenous (IV) infusion on Day 1 of each 14-day cycle, plus placebo subcutaneous injection once per cycle, for a maximum of 4 cycles, 24 hours after chemotherapy (Day 4). During the long-term follow-up period, further chemotherapy and/or biologic agents (for example, bevacizumab) were to continue at the discretion of the treating physician.	
Reporting group title	Pegfilgrastim
Reporting group description:	
Participants received standard chemotherapy (FOLFOX or FOLFIRI) on Days 1-2 and bevacizumab 5 mg/kg intravenous (IV) infusion on Day 1 of each 14-day cycle plus pegfilgrastim 6 mg administered as a single subcutaneous injection once per cycle, for a maximum of 4 cycles, 24 hours after chemotherapy (Day 4). During the long-term follow-up period, further chemotherapy and/or biologic agents (for example, bevacizumab) were to continue at the discretion of the treating physician.	

Reporting group values	Placebo	Pegfilgrastim	Total
Number of subjects	424	423	847
Age categorical Units: Subjects			
< 65 years	267	267	534
≥ 65 years	157	156	313
Age Continuous Units: years			
arithmetic mean	60.6	60.7	
standard deviation	± 10.7	± 10.4	-
Gender, Male/Female Units: participants			
Female	159	174	333
Male	265	249	514
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	3	2	5
Black or African American	6	4	10
Hispanic or Latino	8	11	19
Japanese	0	2	2
Native Hawaiian or Other Pacific Islander	2	0	2
White	405	403	808
Chemotherapy Regimen Units: Subjects			
FOLFOX	207	207	414
FOLFIRI	217	216	433
Region			
North America (Canada and the US) and the Rest of World (Australia, Belgium, Bulgaria, Czech Republic, France, Hungary, Ireland, Italy, Latvia, Mexico, Poland, Romania, Russian Federation, Slovakia, and Ukraine)			
Units: Subjects			
North America	79	78	157

Rest of World	345	345	690
Disease Status Units: Subjects			
Locally Advanced	18	18	36
Metastatic	406	405	811
Primary Tumor Diagnosis Units: Subjects			
Colon	284	291	575
Rectum	139	132	271
Missing	1	0	1

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received standard chemotherapy (FOLFOX or FOLFIRI) on Days 1-2, and bevacizumab 5 mg/kg intravenous (IV) infusion on Day 1 of each 14-day cycle, plus placebo subcutaneous injection once per cycle, for a maximum of 4 cycles, 24 hours after chemotherapy (Day 4). During the long-term follow-up period, further chemotherapy and/or biologic agents (for example, bevacizumab) were to continue at the discretion of the treating physician.

Reporting group title	Pegfilgrastim

Reporting group description:

Participants received standard chemotherapy (FOLFOX or FOLFIRI) on Days 1-2 and bevacizumab 5 mg/kg intravenous (IV) infusion on Day 1 of each 14-day cycle plus pegfilgrastim 6 mg administered as a single subcutaneous injection once per cycle, for a maximum of 4 cycles, 24 hours after chemotherapy (Day 4). During the long-term follow-up period, further chemotherapy and/or biologic agents (for example, bevacizumab) were to continue at the discretion of the treating physician.

Primary: Percentage of Participants with Grade 3/4 Febrile Neutropenia Across the First 4 Cycles of Chemotherapy

End point title	Percentage of Participants with Grade 3/4 Febrile Neutropenia Across the First 4 Cycles of Chemotherapy

End point description:

Grade 3/4 febrile neutropenia (FN) is defined as:
• A temperature ≥ 38.0°C (≥ 100.4°F) and absolute neutrophil count (ANC) < 1.0 × 10^9/L, where ANC was measured the same day or within ± 1 calendar day of a temperature ≥ 38.0°C (≥ 100.4°F), or
• An ANC < 1.0 × 10^9/L in combination with:
– documented sepsis or infection, OR
– neutropenia-related hospitalization where ANC was measured the same day or within ± 1 calendar day.
Participants monitored their oral temperatures and maintained diaries to record their temperature twice per day: once in the morning and once in the evening, as well as whenever they suspect they had fever throughout the first 4 cycles of chemotherapy treatment.
This analysis was performed in the primary analysis set which included all participants with a signed informed consent, and who were randomized and received at least 1 dose of protocol-specified study treatment (chemotherapy, bevacizumab, or investigational product).

End point type	Primary

End point timeframe:

Approximately 2 months duration (daily for 4 cycles of treatment; 2 weeks per cycle)

End point values	Placebo	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	423	422		
Units: percentage of participants				
number (confidence interval 95%)	5.7 (3.7 to 8.3)	2.4 (1.1 to 4.3)		

Statistical analyses

Statistical analysis title	Analysis of Grade 3/4 Febrile Neutropenia

Statistical analysis description:

The Cochran-Mantel-Haenszel (CMH) test, stratified by the IVRS-recorded randomization factors (geographic region, disease stage, and chemotherapy), was used to test the difference between treatment arms in the proportion of subjects who experienced grade 3/4 FN during the treatment period.
The odds ratio (pegfilgrastim to placebo) is adjusted for the randomization stratification factors. An OR < 1.0 indicates a lower event rate for the pegfilgrastim arm relative to the placebo arm.

Comparison groups	Placebo v Pegfilgrastim
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.014 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	0.86

Notes:

[1] - The primary hypothesis was that the percentage of participants treated with study chemotherapy and bevacizumab who experience grade 3/4 febrile neutropenia (FN) would be lower in participants randomized to the pegfilgrastim arm compared to placebo arm. The study was designed to have at least 90% power at the 2-sided 0.05 significance level to detect a 6% difference in incidence of grade 3/4 FN from 9% to 3%, which is approximately a 66.7% relative reduction.
[2] - The p-value is adjusted for the randomization stratification factors (chemotherapy regimen, geographic region, disease stage).

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Median time from randomization to date of death caclulated using the Kaplan-Meier method. Participants were censored on the date of last contact (i.e., the date the participant was last known to be alive) if they were not known to have died.

End point type	Secondary

End point timeframe:

From randomization to the end of study. Median time on study was 21.4 months and the maximum was 57.9 months.

End point values	Placebo	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	423	422		
Units: months				
median (confidence interval 95%)	23.1 (21.2 to 24.6)	24 (21.6 to 26.3)		

Statistical analyses

Statistical analysis title	Analysis of Overall Survival

Statistical analysis description:

Hazard ratio for treatment is estimated based on Cox proportional Hazard model stratified by the stratification factors at randomization. Stratification factors are: chemotherapy regimen (FOLFOX vs. FOLFIRI); region (North America vs. Rest of World) and disease status (Metastatic vs. Locally Advanced). A hazard ratio < 1.0 indicates a lower average event rate and a longer survival time for the pegfilgrastim arm relative to the placebo arm.

Comparison groups	Placebo v Pegfilgrastim
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.398 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.09

Notes:

[3] - P-value based on the log-rank test statistic from the Kaplan-Meier survival analysis stratified by the 3 randomization factors.

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

Time from randomization to the date of radiological disease progression or death from any cause, whichever event occurs first, calculated using the Kaplan-Meier method. Participants without either event by the analysis data cutoff date were censored on the date of their last evaluable disease assessment. Disease progression based on the investigator's assessment of radiographic scans using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Clinical progression without radiological assessment was not be considered a disease progression in this analysis. Progression defined as at least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study recorded since the treatment started or the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

End point type	Secondary

End point timeframe:

From randomization to the end of study. Median time on study was 21.4 months and the maximum was 57.9 months.

End point values	Placebo	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	423	422		
Units: months				
median (confidence interval 95%)	10.4 (9.5 to 11.1)	10.6 (9.4 to 11.2)		

Statistical analyses

Statistical analysis title	Analysis of Progression-free Survival

Statistical analysis description:

Hazard ratio for treatment is estimated based on Cox proportional Hazard model stratified by 3 stratification factors at randomization. Stratification factors are: chemotherapy regimen (FOLFOX vs. FOLFIRI); region (North America vs. Rest of World) and disease status (Metastatic vs. Locally Advanced). A hazard ratio < 1.0 indicates a lower average event rate and a longer survival time for the pegfilgrastim arm relative to the placebo arm.

Comparison groups	Placebo v Pegfilgrastim
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.224 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.06

Notes:

[4] - P-value based on the log-rank test statistic from the Kaplan-Meier survival analysis stratified by the 3 randomization factors.

Secondary: Time to Progression

End point title	Time to Progression

End point description:

Time from randomization to date of radiological disease progression calculated using the Kaplan-Meier method. Participants without progression were censored on the date of their last radiographic tumor assessment. Disease progression based on the investigator's assessment of scans using the RECIST v1.1. Clinical progression without radiological assessment was not considered a disease progression. Progression is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study recorded since the treatment started or the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

End point type	Secondary

End point timeframe:

From randomization to the end of study. Median time on study was 21.4 months and the maximum was 57.9 months.

End point values	Placebo	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	423	422		
Units: months				
median (confidence interval 95%)	12.5 (11.1 to 12.7)	12.1 (11 to 12.7)		

Statistical analyses

Statistical analysis title	Analysis of Time to Progression

Statistical analysis description:

Hazard ratio, stratified by randomization stratification factors at baseline, is estimated based on the proportional subdistribution hazards model proposed by Fine and Gray (1999). Stratification factors are: chemotherapy regimen (FOLFOX vs. FOLFIRI); region (North America vs. Rest of World) and disease status (Metastatic vs. Locally Advanced). A hazard ratio < 1.0 indicates a lower average event rate and a longer survival time for the pegfilgrastim arm relative to the placebo arm.

Comparison groups	Placebo v Pegfilgrastim
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.861 [5]
Method	Fine and Gray Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.15

Notes:

[5] - Stratified by randomization stratification factors

Secondary: Percentage of Participants with an Objective Response

End point title	Percentage of Participants with an Objective Response

End point description:

The percentage of participants with a complete response (CR) or partial response (PR) defined by the RECIST v1.1 criteria at any time during the study. Response was determined by the investigator's assessment of radiographic scans.
CR: Disappearance of all non-nodal target lesions and the disappearance of all non-nodal non-target lesions, and no new lesions. All nodal lesions must have reduction of short axis to < 10 mm.
PR: At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters and no new lesions and/or unequivocal progression of existing non-target lesions, or, the disappearance of all non-nodal target lesions with persistence of one or more non-target lesion(s).

End point type	Secondary

End point timeframe:

From randomization to the end of study. Median time on study was 21.4 months and the maximum was 57.9 months.

End point values	Placebo	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	420[6]	420[7]		
Units: percentage of participants				
number (confidence interval 95%)	57.6 (52.7 to 62.4)	61 (56.1 to 65.6)		

Notes:

[6] - Subjects with measurable disease at baseline

[7] - Subjects with measurable disease at baseline

Statistical analyses

Statistical analysis title	Analysis of Objective Response

Statistical analysis description:

Odds ratio (OR) adjusted for the randomization stratification factors. An OR > 1.0 indicates a higher event rate for the pegfilgrastim arm relative to the placebo arm.

Comparison groups	Placebo v Pegfilgrastim
Number of subjects included in analysis	840
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.33 [8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.51

Notes:

[8] - The p-value is from the Cochran Mantel Haenszel (CMH) test adjusting for the randomization stratification factors.

Secondary: Percentage of Participants with Grade 4 Febrile Neutropenia Across the First 4 Cycles of Chemotherapy

End point title	Percentage of Participants with Grade 4 Febrile Neutropenia Across the First 4 Cycles of Chemotherapy

End point description:

Grade 4 febrile neutropenia (FN) is defined as:
• A temperature ≥ 38.0ºC (≥ 100.4ºF) and absolute neutrophil count (ANC) < 0.5 × 10^9/L, where ANC is measured the same day or within +/- 1 calendar day of a temperature ≥ 38.0ºC (≥ 100.4ºF), or
• An ANC < 0.5 × 10^9/L in combination with:
o Documented sepsis or infection, OR
o Neutropenia-related hospitalization where ANC is measured the same day or within +/- 1 calendar day.

End point type	Secondary

End point timeframe:

Approximately 2 months duration (Daily for 4 cycles of treatment; 2 weeks per cycle)

End point values	Placebo	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	423	422		
Units: percentage of participants				
number (confidence interval 95%)	3.5 (2 to 5.8)	2.4 (1.1 to 4.3)		

Statistical analyses

Statistical analysis title	Analysis of Grade 4 Febrile Neutropenia

Statistical analysis description:

Odds ratio (OR) adjusted for the randomization stratification factors. An OR < 1.0 indicates a lower event rate for the pegfilgrastim arm relative to the placebo arm.

Comparison groups	Placebo v Pegfilgrastim
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.312 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.49

Notes:

[9] - The study was not planned nor adequately powered to test the secondary endpoints for statistical significance. Therefore, estimations of these secondary endpoints were provided without formal hypothesis testing; p-values are nominal.
[10] - The p-value is from the Cochran Mantel Haenszel (CMH) test adjusting for the randomization stratification factors.

Secondary: Percentage of Participants with Grade 3/4 Neutropenia Across the First 4 Cycles of Chemotherapy

End point title	Percentage of Participants with Grade 3/4 Neutropenia Across the First 4 Cycles of Chemotherapy

End point description:

Grade 3/4 severe neutropenia is defined as neutropenia with absolute neutrophil count (ANC) < 1.0 x 10^9/L.

End point type	Secondary

End point timeframe:

Approximately 2 months duration (daily for 4 cycles of treatment; 2 weeks per cycle)

End point values	Placebo	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	423	422		
Units: percentage of participants				
number (confidence interval 95%)	17 (13.6 to 20.9)	3.6 (2 to 5.8)		

Statistical analyses

Statistical analysis title	Analysis of Grade 3/4 Severe Neutropenia

Statistical analysis description:

Odds ratio (OR) adjusted for the randomization stratification factors. An OR < 1.0 indicates a lower event rate for the pegfilgrastim arm relative to the placebo arm.

Comparison groups	Placebo v Pegfilgrastim

Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.32

Notes:

[11] - The p-value is from the Cochran Mantel Haenszel (CMH) test adjusting for the randomization stratification factors.

Secondary: Percentage of Participants with Grade 4 Neutropenia Across the First 4 Cycles of Chemotherapy

End point title	Percentage of Participants with Grade 4 Neutropenia Across the First 4 Cycles of Chemotherapy

End point description:

Grade 4 severe neutropenia is defined as neutropenia with absolute neutrophil count (ANC) < 0.5 x 10^9/L.

End point type	Secondary

End point timeframe:

Approximately 2 months duration (daily for 4 cycles of treatment; 2 weeks per cycle)

End point values	Placebo	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	423	422		
Units: percentage of participants				
number (confidence interval 95%)	8.3 (5.8 to 11.3)	2.4 (1.1 to 4.3)		

Statistical analyses

Statistical analysis title	Analysis of Grade 4 Severe Neutropenia

Statistical analysis description:

Odds ratio (OR) adjusted for the randomization stratification factors. An OR < 1.0 indicates a lower event rate for the pegfilgrastim arm relative to the placebo arm.

Comparison groups	Placebo v Pegfilgrastim
Number of subjects included in analysis	845
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.27

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	0.56

Notes:

[12] - The p-value is from the Cochran Mantel Haenszel (CMH) test adjusting for the randomization stratification factors.

Secondary: Number of Participants With Adverse Events (AEs)

End point title	Number of Participants With Adverse Events (AEs)

End point description:

A serious adverse event (SAE) is defined as an adverse event that
- is fatal;
- is life threatening (places the participant at immediate risk of death);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- other significant medical hazard.

AEs were assessed for severity according to National Cancer Institute, Common Terminology Criteria for Adverse Events, Version 3.0, based on this general guideline: Grade 1 = Mild AE; Grade 2 = Moderate AE; Grade 3 = Severe AE; Grade 4 = Life-threatening or disabling AE; Grade 5 = Death related to AE.

End point type	Secondary

End point timeframe:

Approximately 8 weeks (4 treatment cycles)

End point values	Placebo	Pegfilgrastim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	421	420		
Units: participants				
number (not applicable)				
Any adverse event	355	344		
Worst Grade of ≥ 2	254	240		
Worst Grade of ≥ 3	119	115		
Worst Grade of ≥ 4	45	31		
Serious adverse events	55	68		
Severe adverse events	103	106		
Life-threatening adverse events	43	27		
Fatal adverse events	11	10		
Leading to discontinuation of IP	1	3		
Leading to discontinuation from study treatment	9	8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 8 weeks (4 treatment cycles)

Adverse event reporting additional description:

All participants in the Primary Analysis Set who received at least 1 dose of investigational product were included in the safety analysis set. One participant was randomized to the placebo arm but actually received pegfilgrastim and is included in the pegfilgrastim arm for the safety analyses.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received standard chemotherapy (FOLFOX or FOLFIRI) on Days 1-2, plus bevacizumab 5 mg/kg intravenous (IV) infusion on Day 1 of each 14-day cycle plus placebo subcutaneous injection once per cycle, for a maximum of 4 cycles, 24 hours after chemotherapy (Day 4).

Reporting group title	Pegfilgrastim

Reporting group description:

Participants received standard chemotherapy (FOLFOX or FOLFIRI) on Days 1-2 and bevacizumab 5 mg/kg intravenous (IV) infusion on Day 1 of each 14-day cycle plus pegfilgrastim 6 mg administered as a single subcutaneous injection once per cycle, for a maximum of 4 cycles, 24 hours after chemotherapy (Day 4).

Serious adverse events	Placebo	Pegfilgrastim	
Total subjects affected by serious adverse events			
subjects affected / exposed	55 / 421 (13.06%)	68 / 420 (16.19%)	
number of deaths (all causes)	116	120	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour necrosis			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	3 / 421 (0.71%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism venous			

subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 421 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis deep			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			

subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 421 (0.00%)	3 / 420 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 421 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 421 (0.48%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 421 (0.48%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Hernia			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Local swelling			

subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device complication			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (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	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	4 / 421 (0.95%)	5 / 420 (1.19%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 421 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
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			
Dyspnoea			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Epistaxis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 421 (0.71%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 421 (0.48%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			

subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (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 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (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 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 421 (0.24%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	

Cardio-respiratory arrest			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (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 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lethargy			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
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			
Agranulocytosis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 421 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Coagulopathy			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 421 (0.24%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granulocytopenia			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 421 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	4 / 421 (0.95%)	3 / 420 (0.71%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 421 (0.71%)	5 / 420 (1.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			

subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 421 (0.00%)	3 / 420 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic obstruction			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic stenosis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 421 (0.24%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	5 / 421 (1.19%)	10 / 420 (2.38%)	
occurrences causally related to treatment / all	0 / 5	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
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	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (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	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 421 (0.00%)	4 / 420 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal fistula			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 421 (0.48%)	3 / 420 (0.71%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			

subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Large intestine perforation			
subjects affected / exposed	2 / 421 (0.48%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Nausea			
subjects affected / exposed	1 / 421 (0.24%)	3 / 420 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral pain			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	3 / 421 (0.71%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal perforation			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 421 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			

subjects affected / exposed	1 / 421 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vomiting			
subjects affected / exposed	3 / 421 (0.71%)	4 / 420 (0.95%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 421 (0.00%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatorenal failure			
subjects affected / exposed	1 / 421 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess rupture			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bacterial sepsis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candidiasis			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial infection			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	2 / 421 (0.48%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 421 (0.24%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter gastritis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			

subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 421 (0.48%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral fungal infection			
subjects affected / exposed	1 / 421 (0.24%)	0 / 420 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 421 (0.00%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			

subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 421 (0.24%)	4 / 420 (0.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 421 (0.48%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 421 (0.48%)	2 / 420 (0.48%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 421 (0.71%)	5 / 420 (1.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 421 (0.24%)	4 / 420 (0.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			

subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 421 (0.00%)	1 / 420 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Placebo	Pegfilgrastim	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	307 / 421 (72.92%)	290 / 420 (69.05%)	
Investigations			
Weight decreased			
subjects affected / exposed	18 / 421 (4.28%)	25 / 420 (5.95%)	
occurrences (all)	21	27	
Vascular disorders			
Hypertension			
subjects affected / exposed	25 / 421 (5.94%)	33 / 420 (7.86%)	
occurrences (all)	29	38	
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 421 (4.99%)	21 / 420 (5.00%)	
occurrences (all)	25	22	
Neuropathy peripheral			
subjects affected / exposed	24 / 421 (5.70%)	28 / 420 (6.67%)	
occurrences (all)	27	33	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	20 / 421 (4.75%)	31 / 420 (7.38%)	
occurrences (all)	25	42	
Neutropenia			
subjects affected / exposed	115 / 421 (27.32%)	30 / 420 (7.14%)	
occurrences (all)	206	36	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	33 / 421 (7.84%)	30 / 420 (7.14%)	
occurrences (all)	42	37	
Fatigue			
subjects affected / exposed	63 / 421 (14.96%)	67 / 420 (15.95%)	
occurrences (all)	87	101	
Pyrexia			
subjects affected / exposed	30 / 421 (7.13%)	55 / 420 (13.10%)	
occurrences (all)	37	79	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	19 / 421 (4.51%)	24 / 420 (5.71%)	
occurrences (all)	22	30	
Constipation			
subjects affected / exposed	45 / 421 (10.69%)	44 / 420 (10.48%)	
occurrences (all)	52	52	
Diarrhoea			
subjects affected / exposed	103 / 421 (24.47%)	105 / 420 (25.00%)	
occurrences (all)	147	177	
Nausea			
subjects affected / exposed	91 / 421 (21.62%)	113 / 420 (26.90%)	
occurrences (all)	119	160	
Stomatitis			
subjects affected / exposed	24 / 421 (5.70%)	9 / 420 (2.14%)	
occurrences (all)	33	13	
Vomiting			
subjects affected / exposed	45 / 421 (10.69%)	46 / 420 (10.95%)	
occurrences (all)	53	54	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	23 / 421 (5.46%)	30 / 420 (7.14%)	
occurrences (all)	25	33	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	17 / 421 (4.04%)	23 / 420 (5.48%)	
occurrences (all)	17	24	

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	13 / 421 (3.09%)	22 / 420 (5.24%)	
occurrences (all)	15	22	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	31 / 421 (7.36%)	39 / 420 (9.29%)	
occurrences (all)	33	52	
Hypokalaemia			
subjects affected / exposed	15 / 421 (3.56%)	31 / 420 (7.38%)	
occurrences (all)	17	37	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2011	The protocol was updated to include that subjects were required to maintain diaries to record their temperature. The eCRF was also updated to create a field for patient-reported temperature recording. The definition of grade 3/4 FN was expanded to ensure all cases of clinical FN were captured. Chemotherapy Dose Adjustments were updated to notify that the subject had to end all study treatments if all components of chemotherapy were suspended for > 6 weeks Exclusion criteria were updated regarding the use of radiosensitizing chemoradiation and implantation of venous device was removed, as it was not safety concern per Avastin® prescribing information. Updated Study Design and Schedule of Assessments to clarify that routine, non-study specific, screening assessments were allowed if they were completed within 28 days of randomization, and the values did not lie outside of the protocol-specified range. Updated Synopsis, Subject enrollment, Study procedures, and Schedule of assessments to specify that randomization was to take place on or before cycle 1, day 1 to ensure all relevant safety data were captured. Clarified definition of CR in protocol 'Appendix F: Guide to using Revised RECIST guideline'. The time period for measuring temperature was updated in Synopsis and Objective to ensure that primary endpoint was correctly identified in cases where data for the time was missing. PTT assessment was replaced and INR range was updated in inclusion criteria and study procedures as PTTs are not a reliable predictor for bleeding diatheses and were not routinely performed nor recommended for patients receiving Avastin®. Also updated inclusion criteria to clarify that if bleeding diathesis was suspected, a bleeding time was to be performed. Updated Study design to clarify that CBC was to be completed within 7 days before initiating study chemotherapy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported