Clinical trial results:
A Randomized, Double-blind, Placebo-controlled, Phase 2 Trial of Paclitaxel in Combination With AMG 386 in Subjects With Advanced Recurrent Epithelial Ovarian or Primary Peritoneal Cancer

Summary

EudraCT number	2008-004438-25
Trial protocol	BE
Global end of trial date	09 December 2019

Results information

Result version number	v1 (current)
This version publication date	20 December 2020
First version publication date	20 December 2020

Trial information

Trial identification

Sponsor protocol code	20060342

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00479817
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	09 December 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to estimate the treatment effect as measured by progression-free survival (PFS) in subjects with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving trebananib (either 3 or 10 mg/kg intravenously [IV] once weekly [QW]) in combination with paclitaxel (80 mg/m² IV QW; 3 weeks on/1 week off) compared with subjects receiving paclitaxel (80 mg/m² IV QW; 3 weeks on/1 week off) plus placebo.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
The study protocol and amendments, the proposed informed consent form, and other written subject information were submitted to the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) of each study center for approval. A copy of the IEC/IRB approval was received by the sponsor before recruitment of subjects into the study and shipment of investigational product.
Subjects or their legally authorized representatives were required to sign the informed consent form before any study-specific screening procedures were performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 July 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	48 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 32
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Canada: 40
Country: Number of subjects enrolled	India: 8
Country: Number of subjects enrolled	United States: 71
Worldwide total number of subjects	161
EEA total number of subjects	10

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)	104
From 65 to 84 years	56
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 38 centers in Australia, Belgium, Canada, India, and the United States.

Pre-assignment

Screening details:

Participants were randomly assigned 1:1:1 to 1 of 3 treatment groups using an automated voice response telephone system. Random assignment was stratified by prior anti-vascular endothelial growth factor (VEGF) therapy and disease progression on or within 6 months of the last chemotherapy.

Period 1

Period 1 title	Overall Study (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	Trebananib 3 mg/kg + Paclitaxel

Arm description:

Participants received intravenous (IV) trebananib 3 mg/kg once a week (QW) and paclitaxel 80 mg/m² IV QW (3 weeks on and then 1 week off) until progression, unacceptable toxicity, or withdrawal of consent.

Arm type	Experimental
Investigational medicinal product name	Tebananib
Investigational medicinal product code	AMG 386
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered by intravenous infusion over 60 minutes

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	Taxol®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel 80 mg/m² IV once a week (QW) (3 weeks on/1 week off) administered by intravenous infusion

Arm title	Trebananib 10 mg/kg + Paclitaxel

Arm description:

Participants received intravenous trebananib 10 mg/kg once a week and paclitaxel 80 mg/m² IV QW (3 weeks on and then 1 week off) until progression, unacceptable toxicity, or withdrawal of consent.

Arm type	Experimental
Investigational medicinal product name	Tebananib
Investigational medicinal product code	AMG 386
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:	
Administered by intravenous infusion over 60 minutes	
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	Taxol®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Paclitaxel 80 mg/m² IV once a week (QW) (3 weeks on/1 week off) administered by intravenous infusion	

Arm title	Placebo + Paclitaxel
Arm description:	
Participants received intravenous placebo to trebananib once a week and paclitaxel 80 mg/m² IV QW (3 weeks on and then 1 week off) until progression, unacceptable toxicity, or withdrawal of consent.	
Arm type	Active comparator
Investigational medicinal product name	Placebo to trebananib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Administered by intravenous infusion over 60 minutes	
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	Taxol®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Paclitaxel 80 mg/m² IV once a week (QW) (3 weeks on/1 week off) administered by intravenous infusion	

Number of subjects in period 1	Trebananib 3 mg/kg + Paclitaxel	Trebananib 10 mg/kg + Paclitaxel	Placebo + Paclitaxel
Started	53	53	55
Received Study Drug	53	52	55
Completed	53	52	55
Not completed	0	1	0
Adverse Event Prior to Treatment	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Trebananib 3 mg/kg + Paclitaxel
Reporting group description:	
Participants received intravenous (IV) trebananib 3 mg/kg once a week (QW) and paclitaxel 80 mg/m² IV QW (3 weeks on and then 1 week off) until progression, unacceptable toxicity, or withdrawal of consent.	
Reporting group title	Trebananib 10 mg/kg + Paclitaxel
Reporting group description:	
Participants received intravenous trebananib 10 mg/kg once a week and paclitaxel 80 mg/m² IV QW (3 weeks on and then 1 week off) until progression, unacceptable toxicity, or withdrawal of consent.	
Reporting group title	Placebo + Paclitaxel
Reporting group description:	
Participants received intravenous placebo to trebananib once a week and paclitaxel 80 mg/m² IV QW (3 weeks on and then 1 week off) until progression, unacceptable toxicity, or withdrawal of consent.	

Reporting group values	Trebananib 3 mg/kg + Paclitaxel	Trebananib 10 mg/kg + Paclitaxel	Placebo + Paclitaxel
Number of subjects	53	53	55
Age Categorical Units: participants			
From 18 - 64 years	35	36	33
From 65 - 84 years	17	17	22
85 years and over	1	0	0
Age Continuous Units: years			
median	60.0	59.0	62.0
full range (min-max)	28 to 85	27 to 80	38 to 83
Sex: Female, Male Units: participants			
Female	53	53	55
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
White	49	41	44
Black or African American	1	3	0
Hispanic or Latino	1	2	2
Asian	2	6	6
Japanese	0	0	1
American Indian or Alaska Native	0	0	1
Native Hawaiian or Other Pacific Islander	0	1	1
Region Units: Subjects			
Asia	2	2	4
Australia	12	8	12
Europe	4	4	2
North America	35	39	37
Primary Tumor Type Units: Subjects			

Ovarian cancer	47	46	44
Primary peritoneal cancer	6	7	8
Fallopian tube cancer	0	0	3
Prior Anti-VEGF Therapy Units: Subjects			
Yes	2	3	3
No	51	50	52
Disease Progression Within 6 Months of Last Chemotherapy Regimen Units: Subjects			
Yes	29	29	29
No	24	24	26
Cancer Antigen 125 (CA-125) Level			
CA-125 is a protein that may be found in high amounts in the blood of patients with ovarian cancer. CA-125 is produced on the surface of cells and is released in the blood stream. CA-125 levels can be used to monitor the effectiveness of treatment for ovarian cancer and for detecting disease recurrence after treatment.			
Units: U/mL			
median	215.6	273.1	156.5
full range (min-max)	4 to 5835	4 to 11696	4 to 6000

Reporting group values	Total		
Number of subjects	161		
Age Categorical Units: participants			
From 18 - 64 years	104		
From 65 - 84 years	56		
85 years and over	1		
Age Continuous Units: years median full range (min-max)	-		
Sex: Female, Male Units: participants			
Female	161		
Male	0		
Race/Ethnicity, Customized Units: Subjects			
White	134		
Black or African American	4		
Hispanic or Latino	5		
Asian	14		
Japanese	1		
American Indian or Alaska Native	1		
Native Hawaiian or Other Pacific Islander	2		
Region Units: Subjects			
Asia	8		
Australia	32		
Europe	10		
North America	111		
Primary Tumor Type			

Units: Subjects			
Ovarian cancer	137		
Primary peritoneal cancer	21		
Fallopian tube cancer	3		
Prior Anti-VEGF Therapy Units: Subjects			
Yes	8		
No	153		
Disease Progression Within 6 Months of Last Chemotherapy Regimen Units: Subjects			
Yes	87		
No	74		
Cancer Antigen 125 (CA-125) Level			
CA-125 is a protein that may be found in high amounts in the blood of patients with ovarian cancer. CA-125 is produced on the surface of cells and is released in the blood stream. CA-125 levels can be used to monitor the effectiveness of treatment for ovarian cancer and for detecting disease recurrence after treatment.			
Units: U/mL			
median			
full range (min-max)	-		

Subject analysis sets	
Subject analysis set title	Pooled Trebananib + Paclitaxel
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received IV trebananib 3 mg/kg or 10 mg/kg once a week and paclitaxel 80 mg/m² IV QW (3 weeks on and then 1 week off) until progression, unacceptable toxicity, or withdrawal of consent.

Reporting group values	Pooled Trebananib + Paclitaxel		
Number of subjects	106		
Age Categorical Units: participants			
From 18 - 64 years	71		
From 65 - 84 years	34		
85 years and over	1		
Age Continuous Units: years			
median	59.5		
full range (min-max)	27 to 85		
Sex: Female, Male Units: participants			
Female	106		
Male	0		
Race/Ethnicity, Customized Units: Subjects			
White	90		
Black or African American	4		
Hispanic or Latino	3		
Asian	8		
Japanese	0		

American Indian or Alaska Native	0		
Native Hawaiian or Other Pacific Islander	1		
Region Units: Subjects			
Asia	4		
Australia	20		
Europe	8		
North America	74		
Primary Tumor Type Units: Subjects			
Ovarian cancer	93		
Primary peritoneal cancer	13		
Fallopian tube cancer	0		
Prior Anti-VEGF Therapy Units: Subjects			
Yes	5		
No	101		
Disease Progression Within 6 Months of Last Chemotherapy Regimen Units: Subjects			
Yes	58		
No	48		
Cancer Antigen 125 (CA-125) Level			
CA-125 is a protein that may be found in high amounts in the blood of patients with ovarian cancer. CA-125 is produced on the surface of cells and is released in the blood stream. CA-125 levels can be used to monitor the effectiveness of treatment for ovarian cancer and for detecting disease recurrence after treatment.			
Units: U/mL			
median	219.8		
full range (min-max)	4 to 11696		

End points

End points reporting groups

Reporting group title	Trebananib 3 mg/kg + Paclitaxel
Reporting group description:	
Participants received intravenous (IV) trebananib 3 mg/kg once a week (QW) and paclitaxel 80 mg/m² IV QW (3 weeks on and then 1 week off) until progression, unacceptable toxicity, or withdrawal of consent.	
Reporting group title	Trebananib 10 mg/kg + Paclitaxel
Reporting group description:	
Participants received intravenous trebananib 10 mg/kg once a week and paclitaxel 80 mg/m² IV QW (3 weeks on and then 1 week off) until progression, unacceptable toxicity, or withdrawal of consent.	
Reporting group title	Placebo + Paclitaxel
Reporting group description:	
Participants received intravenous placebo to trebananib once a week and paclitaxel 80 mg/m² IV QW (3 weeks on and then 1 week off) until progression, unacceptable toxicity, or withdrawal of consent.	
Subject analysis set title	Pooled Trebananib + Paclitaxel
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants received IV trebananib 3 mg/kg or 10 mg/kg once a week and paclitaxel 80 mg/m² IV QW (3 weeks on and then 1 week off) until progression, unacceptable toxicity, or withdrawal of consent.	

Primary: Progression-free Survival

End point title	Progression-free Survival
End point description:	
Progression-free survival (PFS) was calculated using Kaplan-Meier methods as the time from the date of randomization to the earliest of the dates of first disease progression per modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria, clinical progression (per investigator), CA-125 progression per Gynecologic Cancer Intergroup (GCIG) criteria, or death from any cause. Participants not meeting these criteria by the analysis data cut-off date were censored at their last evaluable disease assessment date. Disease progression per RECIST was defined as at least a 20% increase in the size of target lesions, any new lesions and/or unequivocal progression of non-target lesions. CA-125 progression is defined as CA-125 ≥ 2 x upper limit of normal (ULN) for participants with baseline CA-125 < ULN, or CA-125 ≥ 2 x nadir value for participants with baseline CA-125 ≥ ULN, confirmed with a second sample no less than 28 days after the criteria for progression were first met.	
End point type	Primary
End point timeframe:	
From randomization to the final analysis data cut-off date of 09 December 2019; median time on follow-up was 89 weeks.	

End point values	Trebananib 3 mg/kg + Paclitaxel	Trebananib 10 mg/kg + Paclitaxel	Placebo + Paclitaxel	Pooled Trebananib + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	53	53	55	106
Units: months				
median (confidence interval 80%)	5.5 (4.6 to 8.0)	7.1 (6.0 to 7.4)	3.6 (2.0 to 5.0)	6.5 (5.5 to 7.4)

Statistical analyses

Statistical analysis title	Primary Analysis of PFS

Statistical analysis description:

The primary analysis of PFS used a Cox regression model stratified by the stratification factors (prior VEGF therapy, disease progression on or within 6 months of the last chemotherapy regimen) to estimate the PFS hazard ratio and two-sided 80% confidence interval for comparison of both trebananib treatment groups (combined) versus placebo.

Comparison groups	Placebo + Paclitaxel v Pooled Trebananib + Paclitaxel
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.027
Method	Stratified Cox Model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.662
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.522
upper limit	0.841

Notes:

[1] - This study was to provide an estimate and corresponding 2 sided 80% CI with an approximate maximum half width of 0.22 of the efficacy, as measured by the PFS hazard ratio of trebananib in combination with paclitaxel versus paclitaxel alone for 2 pooled dose groups of trebananib (10 and 3 mg/kg QW) in combination with paclitaxel versus the paclitaxel plus placebo group.

Statistical analysis title	Pairwise Comparison of PFS
Comparison groups	Trebananib 10 mg/kg + Paclitaxel v Placebo + Paclitaxel
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.059 [2]
Method	Stratified Cox model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.661
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.499
upper limit	0.875

Notes:

[2] - Stratified by prior VEGF therapy and disease progression on or within 6 months of the last chemotherapy regimen.

Statistical analysis title	Pairwise Comparison of PFS
Comparison groups	Trebananib 3 mg/kg + Paclitaxel v Placebo + Paclitaxel
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.048 [3]
Method	Stratified Cox Model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.653

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.495
upper limit	0.861

Notes:

[3] - Stratified by prior VEGF therapy and disease progression on or within 6 months of the last chemotherapy regimen.

Statistical analysis title	Dose-response Test

Statistical analysis description:

Dose-response effects were tested using a Tarone's test (stratified by the randomization factors) designed to assess improvement in PFS in at least 1 trebananib group versus placebo across the 3 treatment groups.

Comparison groups	Trebananib 3 mg/kg + Paclitaxel v Trebananib 10 mg/kg + Paclitaxel v Placebo + Paclitaxel
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.008
Method	Tarone's Test

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis was performed every 8 weeks during the study. Tumor responses per modified RECIST were determined by the investigator.

Objective response rate (ORR) was defined as the percentage of participants with either a confirmed complete response (CR) or partial response (PR) per modified RECIST criteria.
Complete response: Disappearance of all target and non-target lesions, and no new lesions.
Partial response: At least a 30% decrease in the size of target lesions with no new lesions or progression of non-target lesions, or, disappearance of all target lesions with persistence of one or more non-target lesions. Response must have been confirmed by consecutive assessments performed no less than 28 days after the criteria for response were first met.

End point type	Secondary

End point timeframe:

Assessed every 8 weeks throughout the study; analysis includes data up to the cut-off date of 09 December 2019; median time on follow-up was 89 weeks.

End point values	Trebananib 3 mg/kg + Paclitaxel	Trebananib 10 mg/kg + Paclitaxel	Placebo + Paclitaxel	Pooled Trebananib + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	47[4]	46[5]	52[6]	93[7]
Units: percentage of participants				
number (confidence interval 80%)	21.3 (13.7 to 30.9)	37.0 (27.4 to 47.5)	23.1 (15.6 to 32.3)	29.0 (22.9 to 35.9)

Notes:

[4] - Participants with measurable disease at baseline

[5] - Participants with measurable disease at baseline

[6] - Participants with measurable disease at baseline

[7] - Participants with measurable disease at baseline

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

Duration of response was measured as the time from the first objective response (subsequently confirmed within no less than 4 weeks) to first observed disease progression per modified RECIST criteria or death due to any cause. Participants not meeting these criteria by the analysis data cut-off date were censored at their last evaluable disease assessment date. DOR was calculated using Kaplan-Meier methods.
Disease progression per modified RECIST criteria was defined as at least a 20% increase in the size of target lesions, the appearance of one or more new lesions and/or unequivocal progression of non-target lesions.

End point type	Secondary

End point timeframe:

From randomization to the data cut-off date of 9 December 2019; median time on follow-up was 89 weeks.

End point values	Trebananib 3 mg/kg + Paclitaxel	Trebananib 10 mg/kg + Paclitaxel	Placebo + Paclitaxel	Pooled Trebananib + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	10[8]	17[9]	12[10]	27[11]
Units: months				
median (confidence interval 80%)	11.3 (5.8 to 18.8)	5.4 (3.7 to 5.6)	6.5 (3.7 to 9.1)	5.8 (4.7 to 8.9)

Notes:

[8] - Participants with measurable disease at baseline who had a confirmed objective response

[9] - Participants with measurable disease at baseline who had a confirmed objective response

[10] - Participants with measurable disease at baseline who had a confirmed objective response

[11] - Participants with measurable disease at baseline who had a confirmed objective response

Statistical analyses

No statistical analyses for this end point

Secondary: CA-125 Progression-Free Survival

End point title	CA-125 Progression-Free Survival

End point description:

CA-125 PFS was calculated using Kaplan-Meier methods as the time from the randomization date to the earliest of the dates of first disease progression per CA-125 criteria or death from any cause. Participants not meeting these criteria by the analysis data cut-off date were censored at their last evaluable CA-125 assessment date.
CA-125 progression is defined as CA-125 ≥ 2 × upper limit of normal (ULN) for participants with CA-125 < ULN at baseline, or CA-125 ≥ 2 × nadir value for participants with CA-125 ≥ ULN at baseline,

confirmed with a second sample no less than 28 days after the criteria for progression were first met.

End point type	Secondary

End point timeframe:

From randomization until the primary analysis data cut-off date of 21 October 2009; median time on follow-up was 46 weeks.

End point values	Trebananib 3 mg/kg + Paclitaxel	Trebananib 10 mg/kg + Paclitaxel	Placebo + Paclitaxel	Pooled Trebananib + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	53[12]	53[13]	54[14]	106[15]
Units: months				
median (confidence interval 80%)	10.6 (8.7 to 13.1)	20.4 (8.4 to 20.4)	8.4 (6.1 to 11.3)	10.6 (9.0 to 18.3)

Notes:

[12] - Participants in the ITT population with available baseline CA-125 data

[13] - Participants in the ITT population with available baseline CA-125 data

[14] - Participants in the ITT population with available baseline CA-125 data

[15] - Participants in the ITT population with available baseline CA-125 data

Statistical analyses

No statistical analyses for this end point

Secondary: CA-125 Response Rate

End point title	CA-125 Response Rate

End point description:

CA-125 response rate is the the percentage of participants with a confirmed CA-125 response, defined as ≥ 50% reduction in CA-125 level from baseline, confirmed by a repeat sample no less than 28 days after the criteria for CA-125 response were first met. CA-125 response was analyzed in participants in the ITT population with baseline CA-125 level ≥ 2 × ULN (evaluable for CA-125 response analysis set).

End point type	Secondary

End point timeframe:

From randomization to the primary analysis cut-off date of 21 October 2009; median time on follow-up was 46 weeks.

End point values	Trebananib 3 mg/kg + Paclitaxel	Trebananib 10 mg/kg + Paclitaxel	Placebo + Paclitaxel	Pooled Trebananib + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	38[16]	41[17]	40[18]	79[19]
Units: percentage of participants				
number (not applicable)	58	71	28	65

Notes:

[16] - Participants in the ITT population evaluable for CA-125 response

[17] - Participants in the ITT population evaluable for CA-125 response

[18] - Participants in the ITT population evaluable for CA-125 response

[19] - Participants in the ITT population evaluable for CA-125 response

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of CA-125 Response

End point title	Duration of CA-125 Response

End point description:

Duration of CA-125 response was calculated only for those participants with a confirmed CA-125 response at the time of the primary analysis as the time from the first CA-125 response (subsequently confirmed within no less than 4 weeks) to first observed disease progression per CA-125 or death due to any cause. Participants not meeting these criteria by the analysis data cutoff date were censored at their last evaluable CA-125 assessment date.
CA-125 progression is defined as CA-125 ≥ 2 x upper limit of normal (ULN) for participants with CA-125 < ULN at baseline, or CA-125 ≥ 2 x nadir value for participants with CA-125 ≥ ULN at baseline, confirmed with a second sample no less than 28 days after the criteria for progression were first met.
99999 indicates values that could not be estimated due to the low number of events.

End point type	Secondary

End point timeframe:

From randomization until the primary analysis data cut-off date of 21 October 2009; median time on follow-up was 46 weeks.

End point values	Trebananib 3 mg/kg + Paclitaxel	Trebananib 10 mg/kg + Paclitaxel	Placebo + Paclitaxel	Pooled Trebananib + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	22[20]	29[21]	11[22]	51[23]
Units: months				
median (confidence interval 80%)	11.1 (9.7 to 17.3)	18.6 (18.6 to 99999)	99999 (99999 to 99999)	17.3 (11.1 to 18.6)

Notes:

[20] - Participants evaluable for CA-125 response with a CA-125 response at the primary analysis

[21] - Participants evaluable for CA-125 response with a CA-125 response at the primary analysis

[22] - Participants evaluable for CA-125 response with a CA-125 response at the primary analysis

[23] - Participants evaluable for CA-125 response with a CA-125 response at the primary analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Percent Reduction in the Sum of Longest Diameters of Target Lesions

End point title	Maximum Percent Reduction in the Sum of Longest Diameters of Target Lesions

End point description:

Computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis was performed every 8 during the study.
Maximum percent reduction in the sum of the longest diameters of target lesions was calculated as the maximum change from baseline to the post-baseline nadir.

End point type	Secondary

End point timeframe:

Baseline and every 8 weeks thereafter, up to the data cut-off date of 09 December 2019; median time on follow-up was 89 weeks.

End point values	Trebananib 3 mg/kg + Paclitaxel	Trebananib 10 mg/kg + Paclitaxel	Placebo + Paclitaxel	Pooled Trebananib + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	37[24]	43[25]	45[26]	80[27]
Units: percent change				
arithmetic mean (confidence interval 80%)	-23.5 (-33.0 to -14.1)	-35.8 (-42.9 to -28.6)	-22.5 (-30.2 to -14.9)	-30.1 (-35.9 to -24.3)

Notes:

[24] - Participants with measurable disease at baseline and at least 1 postbaseline assessment

[25] - Participants with measurable disease at baseline and at least 1 postbaseline assessment

[26] - Participants with measurable disease at baseline and at least 1 postbaseline assessment

[27] - Participants with measurable disease at baseline and at least 1 postbaseline assessment

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Percent Reduction from Baseline in Blood CA-125 Levels

End point title	Maximum Percent Reduction from Baseline in Blood CA-125 Levels

End point description:

Maximum percent reduction in CA-125 level was calculated as the maximum change from baseline to post-baseline nadir.
Assays for CA-125 were performed every 8 weeks by both local and central laboratories.

End point type	Secondary

End point timeframe:

Baseline and every 8 weeks thereafter, up to the data cut-off date of 09 December 2019; median time on follow-up was 89 weeks.

End point values	Trebananib 3 mg/kg + Paclitaxel	Trebananib 10 mg/kg + Paclitaxel	Placebo + Paclitaxel	Pooled Trebananib + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	32[28]	39[29]	31[30]	71[31]
Units: percent change				
arithmetic mean (confidence interval 80%)	-59.8 (-70.0 to -48.8)	-73.2 (-80.3 to -66.0)	-2.1 (-31.2 to 27.1)	-67.2 (-73.5 to -60.8)

Notes:

[28] - Participants evaluable for CA-125 response with non-missing post-baseline CA-125 data

[29] - Participants evaluable for CA-125 response with non-missing post-baseline CA-125 data

[30] - Participants evaluable for CA-125 response with non-missing post-baseline CA-125 data

[31] - Participants evaluable for CA-125 response with non-missing post-baseline CA-125 data

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival was calculated using Kaplan-Meier methods as the time from the randomization date to the date of death from any cause. Participants who had not died by the analysis data cut-off date were censored at their last contact date.

End point type	Secondary

End point timeframe:

From randomization to the final analysis data cut-off date of 09 December 2019; median time on follow-up was 89 weeks.

End point values	Trebananib 3 mg/kg + Paclitaxel	Trebananib 10 mg/kg + Paclitaxel	Placebo + Paclitaxel	Pooled Trebananib + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	53	53	55	106
Units: months				
median (confidence interval 80%)	20.6 (18.4 to 28.5)	32.5 (22.3 to 34.9)	22.9 (16.4 to 27.9)	25.2 (20.7 to 30.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression

End point title	Time to Progression

End point description:

Time to progression (TTP) was calculated using Kaplan-Meier methods as the time from the randomization date to date of first observed disease progression per modified RECIST criteria, clinical progression, or CA-125 progression. Participants not meeting these criteria by the analysis data cut-off date were censored at their last evaluable disease assessment date.
Disease progression per modified RECIST criteria was defined as at least a 20% increase in the size of target lesions, any new lesions and/or unequivocal progression of non-target lesions.
CA-125 progression is defined as CA-125 ≥ 2 x ULN for participants with baseline CA-125 < ULN, or CA-125 ≥ 2 x nadir value for participants with baseline CA-125 ≥ ULN, confirmed with a second sample no less than 28 days after the criteria for progression were first met.

End point type	Secondary

End point timeframe:

From randomization until the primary analysis data cut-off date of 21 October 2009; median time on follow-up was 46 weeks.

End point values	Trebananib 3 mg/kg + Paclitaxel	Trebananib 10 mg/kg + Paclitaxel	Placebo + Paclitaxel	Pooled Trebananib + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	53	53	55	106
Units: months				
median (confidence interval 80%)	7.4 (5.3 to 8.0)	7.3 (6.4 to 7.8)	4.8 (3.4 to 6.7)	7.3 (6.0 to 7.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to response was calculated in participants in the ITT population with measurable disease at baseline who had an objective response at the primary analysis data cut-off date of 21 October 2009 as the time from the randomization date to first objective response (subsequently confirmed within no less than 4 weeks).

End point type	Secondary

End point timeframe:

From randomization until the primary analysis data cut-off date of 21 October 2009; median time on follow-up was 46 weeks.

End point values	Trebananib 3 mg/kg + Paclitaxel	Trebananib 10 mg/kg + Paclitaxel	Placebo + Paclitaxel	Pooled Trebananib + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	9[32]	17[33]	14[34]	26[35]
Units: weeks				
arithmetic mean (confidence interval 80%)	17.2 (14.1 to 20.2)	12.8 (10.8 to 14.9)	12.7 (10.9 to 14.5)	14.3 (12.6 to 16.0)

Notes:

[32] - Participants with measurable disease at baseline with an objective response at the primary analysis

[33] - Participants with measurable disease at baseline with an objective response at the primary analysis

[34] - Participants with measurable disease at baseline with an objective response at the primary analysis

[35] - Participants with measurable disease at baseline with an objective response at the primary analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Time to CA-125 Response

End point title	Time to CA-125 Response

End point description:

Time to CA-125 response was calculated in participants in the ITT population evaluable for CA-125 response who had a CA-125 response at the primary analysis data cut-off date of 21 October 2009 as the time from the randomization date to first CA-125 response (subsequently confirmed within no less than 4 weeks).

End point type	Secondary

End point timeframe:

From randomization until the primary analysis data cut-off date of 21 October 2009; median time on follow-up was 46 weeks.

End point values	Trebananib 3 mg/kg + Paclitaxel	Trebananib 10 mg/kg + Paclitaxel	Placebo + Paclitaxel	Pooled Trebananib + Paclitaxel
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	22[36]	29[37]	11[38]	51[39]
Units: weeks				
arithmetic mean (confidence interval 80%)	7.8 (6.4 to 9.3)	7.0 (6.1 to 7.9)	7.9 (6.0 to 9.8)	7.4 (6.6 to 8.1)

Notes:

[36] - Participants evaluable for CA-125 response who had a CA-125 response at the primary analysis

[37] - Participants evaluable for CA-125 response who had a CA-125 response at the primary analysis

[38] - Participants evaluable for CA-125 response who had a CA-125 response at the primary analysis

[39] - Participants evaluable for CA-125 response who had a CA-125 response at the primary analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Functional Assessment of Cancer Therapy – Ovarian Cancer (FACT-O) Ovarian Cancer-specific Subscale (OCS)

End point title	Change from Baseline in Functional Assessment of Cancer Therapy – Ovarian Cancer (FACT-O) Ovarian Cancer-specific Subscale (OCS)

End point description:

FACT-O evaluates health-related quality of life (QOL) and symptoms in women with ovarian cancer. It consists of a 27-item general cancer questionnaire (FACT-G) and a 12-item ovarian cancer-specific subscale (OCS). The OCS summary score was calculated from the following 11 items: swelling in stomach area, cramps in stomach area, weight loss, hair loss, bowel control, appetite, vomiting, ability to get around, liking the appearance of one's body, ability to feel like a woman, and interest in sex. Each item is scored from 0 to 4, such that a higher score indicates better QOL or less severe symptoms. The OCS summary score ranges from 0 to 44. A positive change from baseline indicates improvement. The overall change is the average across all the weeks analyzed in the model.
The linear mixed model included fixed effects for treatment, timepoint, baseline score and interaction of timepoint and treatment and a random intercept for patient.
99999: no participants with data at this time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 8, 16, 24, 32, 40, 48, and 56

End point values	Trebananib 3 mg/kg + Paclitaxel	Trebananib 10 mg/kg + Paclitaxel	Placebo + Paclitaxel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49[40]	46[41]	48[42]	
Units: units on a scale				
least squares mean (confidence interval 95%)				

Week 8 (n = 31, 36, 29)	-0.439 (-2.073 to 1.194)	-0.867 (-2.356 to 0.622)	-0.479 (-2.152 to 1.194)	
Week 16 (n = 23, 31, 19)	0.115 (-1.661 to 1.891)	-1.544 (-3.101 to 0.013)	-0.594 (-2.503 to 1.314)	
Week 24 (n = 20, 23, 15)	-0.682 (-2.525 to 1.161)	-1.803 (-3.488 to -0.118)	0.844 (-1.198 to 2.885)	
Week 32 (n = 8, 18, 9)	-1.035 (-3.484 to 1.414)	-0.660 (-2.470 to 1.150)	0.736 (-1.678 to 3.150)	
Week 40 (n = 8, 10, 5)	-1.133 (-3.597 to 1.330)	-1.462 (-3.645 to 0.721)	3.522 (0.551 to 6.492)	
Week 48 (n = 1, 3, 3)	-4.122 (-10.006 to 1.762)	0.795 (-2.742 to 4.332)	2.688 (-0.931 to 6.307)	
Week 56 (n = 0, 4, 3)	99999 (99999 to 99999)	0.672 (-2.452 to 3.797)	2.688 (-0.931 to 6.307)	
Overall (n = 34, 42, 34)	-1.216 (-3.002 to 0.569)	-0.696 (-2.170 to 0.779)	1.343 (-0.411 to 3.098)	

Notes:

[40] - Participants with at least 1 assessment prior to disease progression

[41] - Participants with at least 1 assessment prior to disease progression

[42] - Participants with at least 1 assessment prior to disease progression

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events

End point description:

The severity of each adverse event (AE) was graded according to the The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, or according to the following scale: 1 = mild 2 = moderate 3 = severe 4 = life-threatening 5 = fatal.
A serious adverse event (SAE) is defined as an adverse event that
• is fatal
• is life threatening
• requires in-patient hospitalization or prolongation of existing hospitalization
• results in persistent or significant disability/incapacity
• is a congenital anomaly/birth defect
• other significant medical hazard
The the relationship of each AE to study treatment was assessed by the investigator.

End point type	Secondary

End point timeframe:

From first dose of any study drug to 30 days after last dose; median treatment duration for trebananib and paclitaxel was 156 and 153 days in the Trebananib 3 mg/kg arm, 166 and 155 days in the Trebananib 10 mg/kg arm, and 98 days each in the Placebo arm.

End point values	Trebananib 3 mg/kg + Paclitaxel	Trebananib 10 mg/kg + Paclitaxel	Placebo + Paclitaxel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53[43]	52[44]	55[45]	
Units: participants				
Any adverse event	53	52	53	
Worst grade of 3	21	29	28	
Worst grade of 4	7	5	2	
Worst grade of 5	3	2	5	

Serious adverse event	17	15	18	
Leading to discontinuation from treatment or study	7	6	4	
Treatment-related AEs	51	51	49	

Notes:

[43] - All randomized participants who received at least 1 dose of trebananib/placebo or paclitaxel

[44] - All randomized participants who received at least 1 dose of trebananib/placebo or paclitaxel

[45] - All randomized participants who received at least 1 dose of trebananib/placebo or paclitaxel

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Developed Anti-trebananib Antibodies

End point title	Number of Participants who Developed Anti-trebananib Antibodies

End point description:

Samples were first tested in a validated electrochemiluminescent immunoassay to detect and confirm the presence of antibodies capable of binding to trebananib. Samples that were positive in the immunoassay were then further tested in a validated electrochemiluminescent receptor-binding assay to measure neutralizing or inhibitory effects of the antibodies in vitro.
Developing anti-trebananib antibodies is defined as participants with a negative or no immunoassay result at or before baseline and a positive immunoassay result at a post-baseline timepoint, out of participants with at least one post-baseline immunoassay result. If a sample was positive in both assays, a participant was defined as positive for neutralizing antibodies.

End point type	Secondary

End point timeframe:

Predose at weeks 1, 5, and 9, and every 16 weeks thereafter, up to 5 weeks after the last dose of trebananib. Median treatment duration for trebananib/placebo was 156 days, 166 days, and 98 days in each treatment group respectively.

End point values	Trebananib 3 mg/kg + Paclitaxel	Trebananib 10 mg/kg + Paclitaxel	Placebo + Paclitaxel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47[46]	48[47]	40[48]	
Units: participants				
Binding antibody positive	3	0	2	
Neutralizing antibody positive	0	0	0	

Notes:

[46] - Participants in the safety population with at least one post-baseline immunoassay result

[47] - Participants in the safety population with at least one post-baseline immunoassay result

[48] - Participants in the safety population with at least one post-baseline immunoassay result

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (Cmax) of Trebananib

End point title	Maximum Observed Concentration (Cmax) of Trebananib

End point description:

Serum trebananib concentrations were measured using an enzyme-linked immunosorbent assay (ELISA). The lower limit of quantification (LLOQ) of the serum assay was 20 ng/mL. Cmax is the observed concentration at the end of infusion.

End point type	Secondary

End point timeframe:

Weeks 1 and 5 at end of infusion

End point values	Trebananib 3 mg/kg + Paclitaxel	Trebananib 10 mg/kg + Paclitaxel	Placebo + Paclitaxel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39[49]	47[50]	40[51]	
Units: µg/mL				
arithmetic mean (standard deviation)				
Week 1 (n = 37, 43, 40)	73.5 (± 27.1)	252 (± 85.8)	0.00 (± 0.00)	
Week 5 (n = 39, 47, 39	80.6 (± 21.7)	269 (± 91.5)	0.00 (± 0.00)	

Notes:

[49] - Participants with evaluable concentration data at each time point

[50] - Participants with evaluable concentration data at each time point

[51] - Participants with evaluable concentration data at each time point

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Concentration (Cmin) of Trebananib

End point title	Minimum Observed Concentration (Cmin) of Trebananib

End point description:

Serum trebananib concentrations were measured using an enzyme-linked immunosorbent assay (ELISA). The lower limit of quantification (LLOQ) of the serum assay was 20 ng/mL. Cmin is the observed concentration predose.

End point type	Secondary

End point timeframe:

Predose at weeks 3, 5, 9, 17, and 25

End point values	Trebananib 3 mg/kg + Paclitaxel	Trebananib 10 mg/kg + Paclitaxel	Placebo + Paclitaxel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44[52]	46[53]	43[54]	
Units: µg/mL				
arithmetic mean (standard deviation)				
Week 3 (n = 44, 44, 43)	4.37 (± 2.55)	14.6 (± 6.79)	0.00 (± 0.00)	
Week 5 (n = 38, 46, 38)	7.13 (± 8.75)	19.2 (± 10.0)	0.00 (± 0.00)	
Week 9 (n = 34, 36, 29)	8.86 (± 12.2)	20.6 (± 11.2)	0.00 (± 0.00)	
Week 17 (n = 19, 31, 20)	7.34 (± 3.54)	26.8 (± 13.5)	0.00 (± 0.00)	
Week 25 (n = 15, 20, 8)	7.01 (± 3.46)	28.9 (± 13.0)	0.00 (± 0.00)	

Notes:

[52] - Participants with evaluable concentration data at each time point

[53] - Participants with evaluable concentration data at each time point

[54] - Participants with evaluable concentration data at each time point

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of any study drug to 30 days after last dose; median treatment duration for trebananib and paclitaxel was 156 and 153 days in the Trebananib 3 mg/kg arm, 166 and 155 days in the Trebananib 10 mg/kg arm, and 98 days each in the Placebo arm.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Trebananib 3 mg/kg + Paclitaxel

Reporting group description:

Participants received intravenous (IV) trebananib 3 mg/kg once a week (QW) and paclitaxel 80 mg/m² IV QW (3 weeks on and then 1 week off) until progression, unacceptable toxicity, or withdrawal of consent.

Reporting group title	Placebo + Paclitaxel

Reporting group description:

Participants received intravenous placebo to trebananib once a week and paclitaxel 80 mg/m² IV QW (3 weeks on and then 1 week off) until progression, unacceptable toxicity, or withdrawal of consent.

Reporting group title	Trebananib 10 mg/kg + Paclitaxel

Reporting group description:

Participants received intravenous trebananib 10 mg/kg once a week and paclitaxel 80 mg/m² IV QW (3 weeks on and then 1 week off) until progression, unacceptable toxicity, or withdrawal of consent.

Serious adverse events	Trebananib 3 mg/kg + Paclitaxel	Placebo + Paclitaxel	Trebananib 10 mg/kg + Paclitaxel
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 53 (32.08%)	18 / 55 (32.73%)	15 / 52 (28.85%)
number of deaths (all causes)	40	27	41
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian cancer			
subjects affected / exposed	0 / 53 (0.00%)	3 / 55 (5.45%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 3	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 53 (0.00%)	2 / 55 (3.64%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jugular vein thrombosis			

subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Fatigue			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 53 (1.89%)	1 / 55 (1.82%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	0 / 53 (0.00%)	2 / 55 (3.64%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 53 (0.00%)	0 / 55 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	2 / 53 (3.77%)	0 / 55 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 53 (3.77%)	2 / 55 (3.64%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 53 (0.00%)	0 / 55 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 53 (3.77%)	2 / 55 (3.64%)	2 / 52 (3.85%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 53 (0.00%)	0 / 55 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Investigations			

Platelet count decreased			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 53 (1.89%)	1 / 55 (1.82%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 55 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 53 (0.00%)	0 / 55 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 53 (1.89%)	1 / 55 (1.82%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Papilloedema			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	2 / 53 (3.77%)	0 / 55 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 53 (1.89%)	1 / 55 (1.82%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 53 (0.00%)	2 / 55 (3.64%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 53 (0.00%)	0 / 55 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			

subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faeces discoloured			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 53 (0.00%)	0 / 55 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 53 (0.00%)	0 / 55 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	4 / 53 (7.55%)	2 / 55 (3.64%)	2 / 52 (3.85%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 53 (3.77%)	1 / 55 (1.82%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	1 / 2	0 / 1	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Jaundice cholestatic			

subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 53 (0.00%)	0 / 55 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	1 / 53 (1.89%)	1 / 55 (1.82%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 53 (0.00%)	0 / 55 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 55 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			

subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Listeria sepsis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 55 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Peritonitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 53 (3.77%)	0 / 55 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	4 / 53 (7.55%)	2 / 55 (3.64%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	2 / 4	0 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	4 / 53 (7.55%)	0 / 55 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			

subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Trebananib 3 mg/kg + Paclitaxel	Placebo + Paclitaxel	Trebananib 10 mg/kg + Paclitaxel
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 53 (98.11%)	52 / 55 (94.55%)	52 / 52 (100.00%)
Vascular disorders			
Flushing			
subjects affected / exposed	5 / 53 (9.43%)	5 / 55 (9.09%)	7 / 52 (13.46%)
occurrences (all)	6	5	9
Hot flush			
subjects affected / exposed	5 / 53 (9.43%)	3 / 55 (5.45%)	5 / 52 (9.62%)
occurrences (all)	6	3	5
Hypertension			
subjects affected / exposed	3 / 53 (5.66%)	4 / 55 (7.27%)	5 / 52 (9.62%)
occurrences (all)	3	6	9
Lymphoedema			
subjects affected / exposed	3 / 53 (5.66%)	1 / 55 (1.82%)	2 / 52 (3.85%)
occurrences (all)	3	2	5
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 53 (5.66%)	5 / 55 (9.09%)	4 / 52 (7.69%)
occurrences (all)	3	5	5
Chest discomfort			
subjects affected / exposed	1 / 53 (1.89%)	1 / 55 (1.82%)	8 / 52 (15.38%)
occurrences (all)	1	1	10
Chest pain			
subjects affected / exposed	2 / 53 (3.77%)	4 / 55 (7.27%)	8 / 52 (15.38%)
occurrences (all)	2	5	9
Chills			
subjects affected / exposed	1 / 53 (1.89%)	1 / 55 (1.82%)	4 / 52 (7.69%)
occurrences (all)	1	1	4

Face oedema			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	5 / 52 (9.62%)
occurrences (all)	1	0	10
Fatigue			
subjects affected / exposed	36 / 53 (67.92%)	26 / 55 (47.27%)	34 / 52 (65.38%)
occurrences (all)	69	41	94
Generalised oedema			
subjects affected / exposed	3 / 53 (5.66%)	0 / 55 (0.00%)	1 / 52 (1.92%)
occurrences (all)	8	0	2
Influenza like illness			
subjects affected / exposed	1 / 53 (1.89%)	1 / 55 (1.82%)	3 / 52 (5.77%)
occurrences (all)	1	1	4
Localised oedema			
subjects affected / exposed	3 / 53 (5.66%)	1 / 55 (1.82%)	2 / 52 (3.85%)
occurrences (all)	4	1	2
Mucosal inflammation			
subjects affected / exposed	6 / 53 (11.32%)	4 / 55 (7.27%)	8 / 52 (15.38%)
occurrences (all)	7	6	11
Oedema			
subjects affected / exposed	3 / 53 (5.66%)	2 / 55 (3.64%)	3 / 52 (5.77%)
occurrences (all)	3	2	3
Oedema peripheral			
subjects affected / exposed	27 / 53 (50.94%)	15 / 55 (27.27%)	33 / 52 (63.46%)
occurrences (all)	59	30	87
Pain			
subjects affected / exposed	3 / 53 (5.66%)	4 / 55 (7.27%)	4 / 52 (7.69%)
occurrences (all)	4	6	4
Peripheral swelling			
subjects affected / exposed	4 / 53 (7.55%)	1 / 55 (1.82%)	8 / 52 (15.38%)
occurrences (all)	4	1	9
Pyrexia			
subjects affected / exposed	6 / 53 (11.32%)	2 / 55 (3.64%)	5 / 52 (9.62%)
occurrences (all)	6	2	6
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	17 / 53 (32.08%)	10 / 55 (18.18%)	18 / 52 (34.62%)
occurrences (all)	21	16	31
Dysphonia			
subjects affected / exposed	1 / 53 (1.89%)	3 / 55 (5.45%)	5 / 52 (9.62%)
occurrences (all)	1	4	5
Dyspnoea			
subjects affected / exposed	18 / 53 (33.96%)	11 / 55 (20.00%)	13 / 52 (25.00%)
occurrences (all)	23	11	17
Epistaxis			
subjects affected / exposed	8 / 53 (15.09%)	8 / 55 (14.55%)	10 / 52 (19.23%)
occurrences (all)	10	10	10
Nasal congestion			
subjects affected / exposed	4 / 53 (7.55%)	5 / 55 (9.09%)	3 / 52 (5.77%)
occurrences (all)	7	6	4
Oropharyngeal pain			
subjects affected / exposed	8 / 53 (15.09%)	8 / 55 (14.55%)	14 / 52 (26.92%)
occurrences (all)	10	9	22
Pleural effusion			
subjects affected / exposed	2 / 53 (3.77%)	0 / 55 (0.00%)	4 / 52 (7.69%)
occurrences (all)	2	0	5
Rhinorrhoea			
subjects affected / exposed	2 / 53 (3.77%)	4 / 55 (7.27%)	7 / 52 (13.46%)
occurrences (all)	2	4	7
Sinus congestion			
subjects affected / exposed	3 / 53 (5.66%)	0 / 55 (0.00%)	1 / 52 (1.92%)
occurrences (all)	3	0	1
Upper-airway cough syndrome			
subjects affected / exposed	2 / 53 (3.77%)	3 / 55 (5.45%)	2 / 52 (3.85%)
occurrences (all)	2	3	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 53 (7.55%)	6 / 55 (10.91%)	5 / 52 (9.62%)
occurrences (all)	4	7	6
Confusional state			

subjects affected / exposed	1 / 53 (1.89%)	1 / 55 (1.82%)	3 / 52 (5.77%)
occurrences (all)	1	1	3
Depression			
subjects affected / exposed	3 / 53 (5.66%)	1 / 55 (1.82%)	4 / 52 (7.69%)
occurrences (all)	3	1	4
Insomnia			
subjects affected / exposed	9 / 53 (16.98%)	5 / 55 (9.09%)	7 / 52 (13.46%)
occurrences (all)	9	5	9
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 53 (3.77%)	0 / 55 (0.00%)	3 / 52 (5.77%)
occurrences (all)	3	0	5
Blood albumin decreased			
subjects affected / exposed	1 / 53 (1.89%)	1 / 55 (1.82%)	3 / 52 (5.77%)
occurrences (all)	2	1	3
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 53 (0.00%)	0 / 55 (0.00%)	4 / 52 (7.69%)
occurrences (all)	0	0	9
Haemoglobin decreased			
subjects affected / exposed	4 / 53 (7.55%)	6 / 55 (10.91%)	4 / 52 (7.69%)
occurrences (all)	16	10	4
Weight decreased			
subjects affected / exposed	0 / 53 (0.00%)	3 / 55 (5.45%)	2 / 52 (3.85%)
occurrences (all)	0	3	2
Weight increased			
subjects affected / exposed	3 / 53 (5.66%)	1 / 55 (1.82%)	2 / 52 (3.85%)
occurrences (all)	5	1	3
White blood cell count decreased			
subjects affected / exposed	3 / 53 (5.66%)	2 / 55 (3.64%)	4 / 52 (7.69%)
occurrences (all)	8	7	10
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	3 / 52 (5.77%)
occurrences (all)	0	1	8
Fall			

subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	3 / 52 (5.77%)
occurrences (all)	0	1	3
Cardiac disorders			
Palpitations			
subjects affected / exposed	3 / 53 (5.66%)	1 / 55 (1.82%)	2 / 52 (3.85%)
occurrences (all)	3	1	5
Tachycardia			
subjects affected / exposed	1 / 53 (1.89%)	2 / 55 (3.64%)	3 / 52 (5.77%)
occurrences (all)	1	2	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 53 (11.32%)	10 / 55 (18.18%)	14 / 52 (26.92%)
occurrences (all)	9	17	22
Dysgeusia			
subjects affected / exposed	3 / 53 (5.66%)	3 / 55 (5.45%)	4 / 52 (7.69%)
occurrences (all)	3	3	5
Headache			
subjects affected / exposed	15 / 53 (28.30%)	8 / 55 (14.55%)	16 / 52 (30.77%)
occurrences (all)	16	11	27
Hypoaesthesia			
subjects affected / exposed	3 / 53 (5.66%)	4 / 55 (7.27%)	2 / 52 (3.85%)
occurrences (all)	7	5	3
Neuropathy peripheral			
subjects affected / exposed	15 / 53 (28.30%)	18 / 55 (32.73%)	20 / 52 (38.46%)
occurrences (all)	19	27	36
Paraesthesia			
subjects affected / exposed	4 / 53 (7.55%)	2 / 55 (3.64%)	3 / 52 (5.77%)
occurrences (all)	6	4	5
Peripheral sensory neuropathy			
subjects affected / exposed	5 / 53 (9.43%)	4 / 55 (7.27%)	3 / 52 (5.77%)
occurrences (all)	5	4	6
Restless legs syndrome			
subjects affected / exposed	4 / 53 (7.55%)	3 / 55 (5.45%)	1 / 52 (1.92%)
occurrences (all)	4	3	1
Taste disorder			

subjects affected / exposed	8 / 53 (15.09%)	4 / 55 (7.27%)	8 / 52 (15.38%)
occurrences (all)	10	4	9
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 53 (16.98%)	9 / 55 (16.36%)	5 / 52 (9.62%)
occurrences (all)	12	13	25
Leukopenia			
subjects affected / exposed	1 / 53 (1.89%)	2 / 55 (3.64%)	4 / 52 (7.69%)
occurrences (all)	1	11	4
Neutropenia			
subjects affected / exposed	9 / 53 (16.98%)	8 / 55 (14.55%)	8 / 52 (15.38%)
occurrences (all)	22	16	28
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 53 (0.00%)	2 / 55 (3.64%)	4 / 52 (7.69%)
occurrences (all)	0	2	4
Tinnitus			
subjects affected / exposed	2 / 53 (3.77%)	1 / 55 (1.82%)	3 / 52 (5.77%)
occurrences (all)	2	1	3
Eye disorders			
Lacrimation increased			
subjects affected / exposed	3 / 53 (5.66%)	0 / 55 (0.00%)	4 / 52 (7.69%)
occurrences (all)	4	0	6
Vision blurred			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	7 / 52 (13.46%)
occurrences (all)	0	2	11
Visual impairment			
subjects affected / exposed	1 / 53 (1.89%)	1 / 55 (1.82%)	3 / 52 (5.77%)
occurrences (all)	1	1	3
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	4 / 53 (7.55%)	1 / 55 (1.82%)	2 / 52 (3.85%)
occurrences (all)	4	1	2
Abdominal distension			
subjects affected / exposed	11 / 53 (20.75%)	7 / 55 (12.73%)	12 / 52 (23.08%)
occurrences (all)	13	7	20
Abdominal pain			

subjects affected / exposed	17 / 53 (32.08%)	20 / 55 (36.36%)	17 / 52 (32.69%)
occurrences (all)	26	22	42
Abdominal pain upper			
subjects affected / exposed	3 / 53 (5.66%)	3 / 55 (5.45%)	8 / 52 (15.38%)
occurrences (all)	3	3	12
Ascites			
subjects affected / exposed	5 / 53 (9.43%)	1 / 55 (1.82%)	6 / 52 (11.54%)
occurrences (all)	8	3	11
Constipation			
subjects affected / exposed	13 / 53 (24.53%)	16 / 55 (29.09%)	22 / 52 (42.31%)
occurrences (all)	14	19	32
Diarrhoea			
subjects affected / exposed	17 / 53 (32.08%)	16 / 55 (29.09%)	23 / 52 (44.23%)
occurrences (all)	29	30	65
Dry mouth			
subjects affected / exposed	2 / 53 (3.77%)	4 / 55 (7.27%)	6 / 52 (11.54%)
occurrences (all)	2	4	9
Dyspepsia			
subjects affected / exposed	6 / 53 (11.32%)	5 / 55 (9.09%)	13 / 52 (25.00%)
occurrences (all)	7	5	15
Flatulence			
subjects affected / exposed	5 / 53 (9.43%)	2 / 55 (3.64%)	2 / 52 (3.85%)
occurrences (all)	10	2	2
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 53 (9.43%)	1 / 55 (1.82%)	2 / 52 (3.85%)
occurrences (all)	5	1	3
Mouth ulceration			
subjects affected / exposed	3 / 53 (5.66%)	3 / 55 (5.45%)	6 / 52 (11.54%)
occurrences (all)	3	3	8
Nausea			
subjects affected / exposed	31 / 53 (58.49%)	18 / 55 (32.73%)	28 / 52 (53.85%)
occurrences (all)	51	26	84
Oral pain			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	3 / 52 (5.77%)
occurrences (all)	1	0	3
Rectal haemorrhage			

subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	3 / 52 (5.77%)
occurrences (all)	0	1	3
Stomatitis			
subjects affected / exposed	3 / 53 (5.66%)	2 / 55 (3.64%)	2 / 52 (3.85%)
occurrences (all)	3	2	2
Vomiting			
subjects affected / exposed	13 / 53 (24.53%)	9 / 55 (16.36%)	15 / 52 (28.85%)
occurrences (all)	19	13	39
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	21 / 53 (39.62%)	21 / 55 (38.18%)	26 / 52 (50.00%)
occurrences (all)	25	24	27
Dry skin			
subjects affected / exposed	1 / 53 (1.89%)	4 / 55 (7.27%)	6 / 52 (11.54%)
occurrences (all)	1	4	8
Erythema			
subjects affected / exposed	3 / 53 (5.66%)	2 / 55 (3.64%)	11 / 52 (21.15%)
occurrences (all)	6	2	13
Hyperhidrosis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 55 (1.82%)	5 / 52 (9.62%)
occurrences (all)	0	1	7
Nail discolouration			
subjects affected / exposed	2 / 53 (3.77%)	3 / 55 (5.45%)	3 / 52 (5.77%)
occurrences (all)	3	6	3
Nail disorder			
subjects affected / exposed	4 / 53 (7.55%)	2 / 55 (3.64%)	5 / 52 (9.62%)
occurrences (all)	5	2	5
Pruritus			
subjects affected / exposed	7 / 53 (13.21%)	6 / 55 (10.91%)	8 / 52 (15.38%)
occurrences (all)	12	6	8
Rash			
subjects affected / exposed	10 / 53 (18.87%)	5 / 55 (9.09%)	9 / 52 (17.31%)
occurrences (all)	16	9	11
Renal and urinary disorders			
Dysuria			

subjects affected / exposed	1 / 53 (1.89%)	4 / 55 (7.27%)	6 / 52 (11.54%)
occurrences (all)	1	4	17
Pollakiuria			
subjects affected / exposed	1 / 53 (1.89%)	2 / 55 (3.64%)	3 / 52 (5.77%)
occurrences (all)	1	2	13
Proteinuria			
subjects affected / exposed	3 / 53 (5.66%)	2 / 55 (3.64%)	4 / 52 (7.69%)
occurrences (all)	3	2	13
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 53 (16.98%)	9 / 55 (16.36%)	14 / 52 (26.92%)
occurrences (all)	9	10	25
Back pain			
subjects affected / exposed	13 / 53 (24.53%)	11 / 55 (20.00%)	13 / 52 (25.00%)
occurrences (all)	15	19	40
Flank pain			
subjects affected / exposed	1 / 53 (1.89%)	0 / 55 (0.00%)	4 / 52 (7.69%)
occurrences (all)	1	0	7
Muscle spasms			
subjects affected / exposed	1 / 53 (1.89%)	2 / 55 (3.64%)	4 / 52 (7.69%)
occurrences (all)	1	2	8
Muscular weakness			
subjects affected / exposed	1 / 53 (1.89%)	3 / 55 (5.45%)	5 / 52 (9.62%)
occurrences (all)	1	4	6
Musculoskeletal chest pain			
subjects affected / exposed	0 / 53 (0.00%)	5 / 55 (9.09%)	6 / 52 (11.54%)
occurrences (all)	0	5	8
Musculoskeletal pain			
subjects affected / exposed	3 / 53 (5.66%)	4 / 55 (7.27%)	7 / 52 (13.46%)
occurrences (all)	3	5	11
Myalgia			
subjects affected / exposed	3 / 53 (5.66%)	4 / 55 (7.27%)	12 / 52 (23.08%)
occurrences (all)	3	5	21
Neck pain			

subjects affected / exposed	2 / 53 (3.77%)	4 / 55 (7.27%)	3 / 52 (5.77%)
occurrences (all)	2	4	3
Pain in extremity			
subjects affected / exposed	15 / 53 (28.30%)	9 / 55 (16.36%)	15 / 52 (28.85%)
occurrences (all)	22	15	24
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 53 (5.66%)	0 / 55 (0.00%)	1 / 52 (1.92%)
occurrences (all)	3	0	1
Cellulitis			
subjects affected / exposed	2 / 53 (3.77%)	1 / 55 (1.82%)	4 / 52 (7.69%)
occurrences (all)	4	1	4
Herpes zoster			
subjects affected / exposed	0 / 53 (0.00%)	3 / 55 (5.45%)	5 / 52 (9.62%)
occurrences (all)	0	3	5
Nasopharyngitis			
subjects affected / exposed	3 / 53 (5.66%)	2 / 55 (3.64%)	4 / 52 (7.69%)
occurrences (all)	5	2	9
Rhinitis			
subjects affected / exposed	3 / 53 (5.66%)	3 / 55 (5.45%)	0 / 52 (0.00%)
occurrences (all)	4	3	0
Sinusitis			
subjects affected / exposed	3 / 53 (5.66%)	1 / 55 (1.82%)	4 / 52 (7.69%)
occurrences (all)	6	1	5
Upper respiratory tract infection			
subjects affected / exposed	4 / 53 (7.55%)	2 / 55 (3.64%)	7 / 52 (13.46%)
occurrences (all)	4	5	8
Urinary tract infection			
subjects affected / exposed	5 / 53 (9.43%)	7 / 55 (12.73%)	14 / 52 (26.92%)
occurrences (all)	6	24	42
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 53 (16.98%)	8 / 55 (14.55%)	10 / 52 (19.23%)
occurrences (all)	10	9	20
Hyperglycaemia			

subjects affected / exposed	1 / 53 (1.89%)	3 / 55 (5.45%)	5 / 52 (9.62%)
occurrences (all)	1	5	5
Hypoalbuminaemia			
subjects affected / exposed	0 / 53 (0.00%)	3 / 55 (5.45%)	0 / 52 (0.00%)
occurrences (all)	0	3	0
Hypocalcaemia			
subjects affected / exposed	4 / 53 (7.55%)	1 / 55 (1.82%)	0 / 52 (0.00%)
occurrences (all)	10	1	0
Hypokalaemia			
subjects affected / exposed	6 / 53 (11.32%)	4 / 55 (7.27%)	10 / 52 (19.23%)
occurrences (all)	10	6	20
Hypomagnesaemia			
subjects affected / exposed	6 / 53 (11.32%)	4 / 55 (7.27%)	3 / 52 (5.77%)
occurrences (all)	8	5	4
Hypophosphataemia			
subjects affected / exposed	1 / 53 (1.89%)	3 / 55 (5.45%)	1 / 52 (1.92%)
occurrences (all)	1	3	1
Increased appetite			
subjects affected / exposed	2 / 53 (3.77%)	1 / 55 (1.82%)	3 / 52 (5.77%)
occurrences (all)	2	1	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 July 2007	Amendment 1 made the following changes to the original protocol: • Updated the Informed Consent Form template, specifically the Risks and Discomforts section. • Revised the hypothesis statement to provide a more accurate estimate of the precision with which PFS hazard ratio was estimated. • Added Inclusion of female subjects with fallopian tube cancer. • Allowed subjects with clinical progression based upon Rustin criteria in addition to radiographic progression to enroll. • Clarified the secondary objective estimating the impact of AMG 386 on patient reported ovarian cancer specific symptoms. • Clarified that there is a 30 day washout period for any previous anticancer systemic therapies (60 days for bevacizumab). • Incorporated the following administrative changes: - Revised Appendix C: Pharmacy Guide to include additional preparation instructions. - Corrected the statement in the informed consent template background section that paclitaxel is approved in Australia to treat ovarian cancer.
21 July 2008	Amendment 2 made the following changes: • Clarified requirements for access to potentially unblinding information for DRT safety reviews and interim analyses • Updated AMG 386 background and additional rationale for the 2 dose regimens • Changed eligibility criteria for radiology and tumor measurements to 28 days prior to randomization • Excluded subjects at high risk for bowel perforation or with ongoing small bowel dysfunction • Allowed subjects with prior malignancies treated curatively without evidence of disease for ≥3 years or with adequately treated non-melanomatous skin cancer or cervical carcinoma in situ • Allowed aspirin and anti-platelet agents and concurrent use of low mw heparin or low dose warfarin • Clarified ULN or LLN to be based on institutional lab ranges • Clarified eligibility for PRO questionnaires; when and how these should be administered • Altered eligibility criteria for quantitative protein to ≤ 1000 mg / 24-hr urine sample • Added a threshold for serum albumin of ≥2.8 mg/dL • Removed requirement for triplicate post-dose ECGs; clarified that ECG reports must include HR, QRS, QT, QTc, RR, and PR intervals • Replaced cCa with raw calcium • Added specification for bicarbonate collection • Allowed a ±2-day window for AMG 386/placebo dosing • Allowed a ±7-day window for radiological assessments • Altered immunogenicity sample collection to coincide with PK time points, changed 45 days from last dose to the SFU visit; sample draws during LTFU for subjects positive for AMG 386 neutralizing antibodies at SFU • Clarified AMG 386 dose calculation in IVRS based on weight from previous visit • Added guidance regarding treatment delays due to treatment-related and non-treatment related toxicities • Added guidance regarding PK sampling site • Simplified the pharmacogenetic studies section • Clarified reporting of deaths and disease progression • Updated informed consent • Amended the number of sites; add India and Australia as participating countries

28 August 2008	Amendment 3 made the following changes: • Added an exclusion criterion regarding prior history of arterial or venous thrombosis to increase the likelihood that subjects at highest risk for thrombosis were excluded and for consistency across the AMG 386 Phase II program. • The Sample Informed Consent Form and Sample Pharmacogenetics Informed Consent Form were both removed as appendices to the protocol per new guidance. Both documents were provided as separate documents.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported