Clinical trial results:
A Phase 1b/2 Trial of AMG 386 in Combination With Pemetrexed and Carboplatin as First Line Treatment of Metastatic Non-squamous Non-small Cell Lung Cancer

Summary

EudraCT number	2011-001111-31
Trial protocol	BE ES GR
Global end of trial date	18 November 2015

Results information

Result version number	v1 (current)
This version publication date	20 November 2016
First version publication date	20 November 2016

Trial information

Trial identification

Sponsor protocol code	20101128

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01666977
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	18 November 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 November 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the incidence of adverse events and clinical laboratory abnormalities defined as dose-limiting toxicity (DLT) in subjects with metastatic non-small cell lung cancer (NSCLC) treated with trebananib in combination with pemetrexed and carboplatin.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and US Food and Drug Administration (FDA) regulations/guidelines. All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.
The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 August 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	United States: 18
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	Spain: 3
Worldwide total number of subjects	37
EEA total number of subjects	3

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	19
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 18 centers in Australia, Canada, Spain, and the United States of America. The first participant enrolled on 23 August 2012 and the last participant enrolled on 25 October 2013.

Pre-assignment

Screening details:

Subjects were enrolled in 2 parts: In part 1, subjects were enrolled sequentially in 2 dose escalating treatment groups (trebananib 15 mg/mL or trebananib 30 mg//mL). After safety reviews, subjects were randomized in part 2 to receive placebo, trebananib 15 mg/mL or trebananib 30 mg//mL. Data are summarized together for both part 1 and part 2.

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

Blinding implementation details:

Part 1 was open label, 8 participants were enrolled. Part 2 was a double-blind and placebo-controlled study. Subjects were randomized in a 1:1:1 ratio to receive placebo, trebananib 15 mg/kg, or trebananib 30 mg/kg. A total of 29 participants were randomized in part 2

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo intravenously (IV) weekly (QW), pemetrexed 500 mg/m² IV every 3 weeks (Q3W), carboplatin IV Q3W, for up to 6 cycles. After completion of up to 6 cycles participants continued on maintenance therapy with placebo IV QW and pemetrexed, until disease progression, unacceptable toxicity, withdrawal of consent, or death.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered by intravenous infusion once every week

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

Dosage and administration details:

Administered by intravenous infusion every 3 weeks using the glomerular filtration rate (GFR) and Calvert formula to an AUC/time curve of 6 mg/mL*min

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	Alimta®
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered by intravenous infusion at 500 mg/m² every 3 weeks

Arm title	Trebananib 15 mg/kg

Arm description:

Participants received rebananib 15 mg/kg IV QW, pemetrexed 500 mg/m² IV Q3W, and carboplatin IV Q3W, for up to 6 cycles. After completion of up to 6 cycles participants continued on maintenance therapy with trebananib 15 mg/kg IV QW and pemetrexed, until disease progression, unacceptable toxicity, withdrawal of consent, or death.

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

Dosage and administration details:

Administered by intravenous infusion once every week

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	Alimta®
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered by intravenous infusion at 500 mg/m² every 3 weeks

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

Dosage and administration details:

Administered by intravenous infusion every 3 weeks using the glomerular filtration rate (GFR) and Calvert formula to an AUC/time curve of 6 mg/mL*min

Arm title	Trebananib 30 mg/kg

Arm description:

Participants received rebananib 30 mg/kg IV QW, pemetrexed 500 mg/m² IV Q3W, and carboplatin IV Q3W, for up to 6 cycles. After completion of up to 6 cycles participants continued on maintenance therapy with trebananib 30 mg/kg IV QW and pemetrexed, until disease progression, unacceptable toxicity, withdrawal of consent, or death.

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

Dosage and administration details:

Administered by intravenous infusion once every week

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	Alimta®
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details: Administered by intravenous infusion at 500 mg/m² every 3 weeks	
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	Paraplatin®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered by intravenous infusion every 3 weeks using the glomerular filtration rate (GFR) and Calvert formula to an AUC/time curve of 6 mg/mL*min

Number of subjects in period 1	Placebo	Trebananib 15 mg/kg	Trebananib 30 mg/kg
Started	10	15	12
Completed	3	3	2
Not completed	7	12	10
Consent withdrawn by subject	2	3	1
Death	1	3	4
Other	4	6	5

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo intravenously (IV) weekly (QW), pemetrexed 500 mg/m² IV every 3 weeks (Q3W), carboplatin IV Q3W, for up to 6 cycles. After completion of up to 6 cycles participants continued on maintenance therapy with placebo IV QW and pemetrexed, until disease progression, unacceptable toxicity, withdrawal of consent, or death.	
Reporting group title	Trebananib 15 mg/kg
Reporting group description:	
Participants received rebananib 15 mg/kg IV QW, pemetrexed 500 mg/m² IV Q3W, and carboplatin IV Q3W, for up to 6 cycles. After completion of up to 6 cycles participants continued on maintenance therapy with trebananib 15 mg/kg IV QW and pemetrexed, until disease progression, unacceptable toxicity, withdrawal of consent, or death.	
Reporting group title	Trebananib 30 mg/kg
Reporting group description:	
Participants received rebananib 30 mg/kg IV QW, pemetrexed 500 mg/m² IV Q3W, and carboplatin IV Q3W, for up to 6 cycles. After completion of up to 6 cycles participants continued on maintenance therapy with trebananib 30 mg/kg IV QW and pemetrexed, until disease progression, unacceptable toxicity, withdrawal of consent, or death.	

Reporting group values	Placebo	Trebananib 15 mg/kg	Trebananib 30 mg/kg
Number of subjects	10	15	12
Age Categorical Units: Subjects			
Adults (18-64 years)	4	8	7
From 65-84 years	6	7	5
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	68.5	62.1	65.2
standard deviation	± 7.6	± 10.9	± 9.8
Gender Categorical Units: Subjects			
Female	3	5	4
Male	7	10	8
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	0	0
Black or African American	0	2	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	7	13	11
Other	1	0	1
Ethnicity Units: Subjects			
Hispanic/Latino	1	0	1
Not Hispanic/Latino	9	15	11

Reporting group values	Total		
Number of subjects	37		
Age Categorical Units: Subjects			
Adults (18-64 years)	19		
From 65-84 years	18		
85 years and over	0		
Age Continuous Units: years arithmetic mean standard deviation	 -		
Gender Categorical Units: Subjects			
Female	12		
Male	25		
Race Units: Subjects			
American Indian or Alaska Native	0		
Asian	2		
Black or African American	2		
Native Hawaiian or Other Pacific Islander	0		
White	31		
Other	2		
Ethnicity Units: Subjects			
Hispanic/Latino	2		
Not Hispanic/Latino	35		

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo intravenously (IV) weekly (QW), pemetrexed 500 mg/m² IV every 3 weeks (Q3W), carboplatin IV Q3W, for up to 6 cycles. After completion of up to 6 cycles participants continued on maintenance therapy with placebo IV QW and pemetrexed, until disease progression, unacceptable toxicity, withdrawal of consent, or death.

Reporting group title	Trebananib 15 mg/kg

Reporting group description:

Participants received rebananib 15 mg/kg IV QW, pemetrexed 500 mg/m² IV Q3W, and carboplatin IV Q3W, for up to 6 cycles. After completion of up to 6 cycles participants continued on maintenance therapy with trebananib 15 mg/kg IV QW and pemetrexed, until disease progression, unacceptable toxicity, withdrawal of consent, or death.

Reporting group title	Trebananib 30 mg/kg

Reporting group description:

Participants received rebananib 30 mg/kg IV QW, pemetrexed 500 mg/m² IV Q3W, and carboplatin IV Q3W, for up to 6 cycles. After completion of up to 6 cycles participants continued on maintenance therapy with trebananib 30 mg/kg IV QW and pemetrexed, until disease progression, unacceptable toxicity, withdrawal of consent, or death.

Primary: Number of Participants with Dose-limiting Toxicities

End point title	Number of Participants with Dose-limiting Toxicities[1]

End point description:

A dose-limiting toxicity (DLT) was defined as any related, grade ≥ 3 hematologic or non-hematologic toxicity (according to Common Terminology Criteria for Adverse Events [CTCAE] version 3) with the exception of some modifications defined in the protocol.
The DLT analysis set includes part 1 subjects who had received ≥ 2 infusions of trebananib and 1 dose of both pemetrexed and carboplatin and followed for the first 21 days of treatment.

End point type	Primary

End point timeframe:

21 days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analyses were not performed.

End point values	Placebo	Trebananib 15 mg/kg	Trebananib 30 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[2]	3	4	
Units: participants		0	0	

Notes:

[2] - Only part 1 subjects were included in DLT analysis

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:

All adverse events (AEs) were graded for severity based on the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Trebananib-related adverse events are those events for which the investigator considered there to be a reasonable possibility that the event may have been caused by trebananib.

End point type	Secondary

End point timeframe:

From study day 1 through 30 days after the last dose of any study drug; median time on study was 32 weeks.

End point values	Placebo	Trebananib 15 mg/kg	Trebananib 30 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	15	12	
Units: participants				
Any adverse event (AE)	10	15	12	
Grade ≥ 3 adverse event	9	10	9	
Grade ≥ 4 adverse event	3	3	1	
Serious adverse events (SAE)	5	7	7	
Fatal adverse events	1	0	1	
AE leading to discontinuation of trebananib	1	5	4	
AE leading to discontinuation of all study drugs	1	2	2	
Trebananib-related adverse events	5	14	9	
Trebananib-related grade ≥ 3 adverse events	1	5	5	
Trebananib-related grade ≥ 4 adverse events	1	0	0	
Trebananib-related serious adverse events	1	4	3	
Trebananib-related fatal adverse events	0	0	0	
Related AE leading to trebananib discontinuation	1	5	3	
Related AE leading to discontinuation of all drugs	1	2	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with an Objective Response

End point title	Percentage of Participants with an Objective Response

End point description:

Participants underwent radiological assessment for tumor response including computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen and pelvis, and head/brain. Response was assessed by the investigator according to the response evaluation criteria in solid tumors (RECIST) guideline (version 1.1) with modifications. Objective response is defined as a complete response or partial response.
This analysis was performed in subjects in the safety analysis set with ≥ 1 unidimensionally measurable lesion per RECIST 1.1 with modifications.

End point type	Secondary

End point timeframe:

Radiological assessments were performed every 12 weeks until the end of treatment

End point values	Placebo	Trebananib 15 mg/kg	Trebananib 30 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	15	11	
Units: percentage of participants				
number (confidence interval 80%)	20 (5.5 to 45)	53.3 (34.2 to 71.8)	27.3 (10.5 to 51.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

PFS is defined as the time from the date of the first dosing of any study drug to the earlier of the dates of first disease progression per RECIST 1.1 with modifications or death from any cause. Subjects not meeting the criteria for disease progression by the analysis cutoff date were censored at their last evaluable radiographic assessment. Events of radiographic progression that occurred after initiation of subsequent anticancer therapy were not considered PFS events and were censored at the last evaluable radiographic tumor assessment before initiation of subsequent anticancer therapy. Deaths occurring after initiation of subsequent anticancer therapy were considered PFS events.
PFS was analyzed using Kaplan-Meier methods. "99999" indicates data that could not be estimated.

End point type	Secondary

End point timeframe:

From the first dose of any study drug until the end of study drug treatment

End point values	Placebo	Trebananib 15 mg/kg	Trebananib 30 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	15	12	
Units: months				
median (confidence interval 80%)	6.9 (1.7 to 99999)	7.2 (5.4 to 8.1)	5.4 (3.3 to 6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (Cmax) of Trebananib With and Without Pemetrexed and Carboplatin

End point title	Maximum Observed Serum Concentration (Cmax) of Trebananib With and Without Pemetrexed and Carboplatin[3]

End point description:

The Cmax of trebananib following weekly IV infusions was assessed at cycle 3 day 1 (administered with pemetrexed and carboplatin) and at cycle 2 day 15 (trebananib alone).

End point type	Secondary

End point timeframe:

Cycle 2, day 15 and cycle 3, day 1

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic analyses were only performed on participants enrolled in part 1 of the study.

End point values	Trebananib 15 mg/kg	Trebananib 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: µg/mL				
arithmetic mean (standard deviation)				
Trebananib Monotherapy (Cycle 2 Day 15)	289 (± 53.7)	603 (± 127)		
With Carboplatin + Pemetrexed (Cycle 3 Day1)	301 (± 40.6)	670 (± 123)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Serum Concentration (Tmax) of Trebananib Administered With and Without Pemetrexed and Carboplatin

End point title	Time to Maximum Serum Concentration (Tmax) of Trebananib Administered With and Without Pemetrexed and Carboplatin[4]

End point description:

Tmax of trebananib following weekly IV infusions was assessed at cycle 3 day 1 (administered with pemetrexed and carboplatin) and at cycle 2 day 15 (trebananib alone).

End point type	Secondary

End point timeframe:

Cycle 2 day 15 and cycle 3 day 1

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic analyses were only performed on participants enrolled in part 1 of the study.

End point values	Trebananib 15 mg/kg	Trebananib 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: hours				
median (full range (min-max))				
Trebananib Monotherapy (Cycle 2 Day 15)	0.583 (0.5 to 0.75)	0.625 (0.583 to 0.95)		

With Carboplatin + Pemetrexed (Cycle 3 Day1)	0.667 (0.667 to 0.833)	0.625 (0.55 to 0.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve from Start of Infusion to 168 Hours Post-dose (AUC0-168) of Trebananib

End point title	Area Under the Concentration-time Curve from Start of Infusion to 168 Hours Post-dose (AUC0-168) of Trebananib[5]

End point description:

The AUC0-168 of trebananib following weekly IV infusions was assessed at cycle 3 day 1 (administered with pemetrexed and carboplatin) and at cycle 2 day 15 (trebananib alone).

End point type	Secondary

End point timeframe:

Cycle 2 day 15 and cycle 3 day 1

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Pharmacokinetic analyses were only performed on participants enrolled in part 1 of the study.

End point values	Trebananib 15 mg/kg	Trebananib 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: hr*µg/mL				
arithmetic mean (standard deviation)				
Trebananib Monotherapy (Cycle 2 Day 15)	12300 (± 1110)	21800 (± 11400)		
With Carboplatin + Pemetrexed (Cycle 3 Day1)	10900 (± 3060)	21800 (± 11100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Concentration (Cmin) of Trebananib Administered With and Without Pemetrexed and Carboplatin

End point title	Minimum Observed Concentration (Cmin) of Trebananib Administered With and Without Pemetrexed and Carboplatin[6]

End point description:

The minimum observed concentration (trough concentration) of trebananib following weekly IV infusions was assessed at cycle 3 day 1 (administered with pemetrexed and carboplatin) and at cycle 2 day 15 (trebananib alone).

End point type	Secondary

End point timeframe:

Cycle 2 day 15 and cycle 3 day 1

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic analyses were only performed on participants enrolled in part 1 of the study.

End point values	Trebananib 15 mg/kg	Trebananib 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: µg/mL				
arithmetic mean (standard deviation)				
Trebananib Monotherapy (Cycle 2 Day 15)	24.7 (± 2.15)	58.1 (± 45.7)		
With Carboplatin + Pemetrexed (Cycle 3 Day1)	28.7 (± 19.4)	65.4 (± 85.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Pemetrexed Administered With and Without Trebananib

End point title	Maximum Observed Plasma Concentration (Cmax) of Pemetrexed Administered With and Without Trebananib[7]

End point description:

The Cmax of pemetrexed was assessed when administered without trebananib (cycle 1, day 1) and with trebananib (cycle 3 day 1).

End point type	Secondary

End point timeframe:

Cycle 1 day 1 and cycle 3 day 1

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic analyses were only performed on participants enrolled in part 1 of the study.

End point values	Trebananib 15 mg/kg	Trebananib 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4[8]		
Units: µg/mL				
arithmetic mean (standard deviation)				
Pemetrexed Without Trebananib (Cycle 1 Day 1)	137 (± 7.02)	114 (± 9.54)		
Pemetrexed With Trebananib (Cycle 3 Day 1)	104 (± 10.9)	92 (± 21.6)		

Notes:

[8] - N=3 for cycle 1 day 1

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Plasma Concentration (Tmax) of Pemetrexed Administered With and Without Trebananib

End point title	Time to Maximum Plasma Concentration (Tmax) of Pemetrexed Administered With and Without Trebananib[9]

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 day 1 and cycle 3 day 1

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic analyses were only performed on participants enrolled in part 1 of the study.

End point values	Trebananib 15 mg/kg	Trebananib 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4[10]		
Units: hours				
median (full range (min-max))				
Pemetrexed Without Trebananib (Cycle 1 Day 1)	0.2 (0.167 to 0.217)	0.25 (0.233 to 0.25)		
Pemetrexed With Trebananib (Cycle 3 Day 1)	0.25 (0.25 to 0.333)	0.308 (0.183 to 0.45)		

Notes:

[10] - N=3 for cycle 1 day 1

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the Concentration-time Curve from Time 0 to the Time of Last Quantifiable Concentration (AUClast) of Pemetrexed

End point title	Area under the Concentration-time Curve from Time 0 to the Time of Last Quantifiable Concentration (AUClast) of Pemetrexed[11]

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 day 1 and cycle 3 day 1

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic analyses were only performed on participants enrolled in part 1 of the study.

End point values	Trebananib 15 mg/kg	Trebananib 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4[12]		
Units: hr*µg/mL				
arithmetic mean (standard deviation)				
Pemetrexed Without Trebananib (Cycle 1 Day 1)	198 (± 84.1)	140 (± 12.7)		
Pemetrexed With Trebananib (Cycle 3 Day 1)	221 (± 87.8)	227 (± 223)		

Notes:

[12] - N=3 for cycle 1 day 1

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Concentration (Cmin) of Pemetrexed Administered With and Without Trebananib

End point title	Minimum Observed Concentration (Cmin) of Pemetrexed Administered With and Without Trebananib[13]

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 day 1 and cycle 3 day 1

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic analyses were only performed on participants enrolled in part 1 of the study.

End point values	Trebananib 15 mg/kg	Trebananib 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4[14]		
Units: µg/mL				
arithmetic mean (standard deviation)				
Pemetrexed Without Trebananib (Cycle 1 Day 1)	2.37 (± 2.45)	3.33 (± 0.702)		
Pemetrexed With Trebananib (Cycle 3 Day 1)	1.09 (± 1.51)	3.86 (± 2.16)		

Notes:

[14] - N=3 for cycle 1 day 1

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Total Platinum After Administration of Carboplatin With and Without Trebananib

End point title	Maximum Observed Plasma Concentration (Cmax) of Total Platinum After Administration of Carboplatin With and Without Trebananib[15]

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 day 1 and cycle 3 day 1

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic analyses were only performed on participants enrolled in part 1 of the study.

End point values	Trebananib 15 mg/kg	Trebananib 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[16]	4		
Units: µg/mL				
arithmetic mean (standard deviation)				
Carboplatin Without Trebananib (Cycle 1 Day 1)	23.1 (± 7.1)	20.1 (± 2.91)		
Carboplatin With Trebananib (Cycle 3 Day 1)	22.4 (± 5.76)	11.4 (± 1.55)		

Notes:

[16] - N=3 for cycle 3 day 1

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Plasma Concentration (Tmax) of Total Platinum After Administration of Carboplatin With and Without Trebananib

End point title	Time to Maximum Plasma Concentration (Tmax) of Total Platinum After Administration of Carboplatin With and Without Trebananib[17]

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 day 1 and cycle 3 day 1

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic analyses were only performed on participants enrolled in part 1 of the study.

End point values	Trebananib 15 mg/kg	Trebananib 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[18]	4		
Units: hours				
median (full range (min-max))				
Carboplatin Without Trebananib (Cycle 1 Day 1)	0.392 (0.25 to 0.833)	0.442 (0.333 to 0.833)		
Carboplatin With Trebananib (Cycle 3 Day 1)	0.5 (0.5 to 0.583)	0.517 (0.5 to 22.6)		

Notes:

[18] - N=3 for cycle 3 day 1

Statistical analyses

No statistical analyses for this end point

Secondary: AUC From Time 0 to the Time of Last Quantifiable Concentration (AUClast) of Total Platinum

End point title	AUC From Time 0 to the Time of Last Quantifiable Concentration (AUClast) of Total Platinum[19]

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 day 1 and cycle 3 day 1

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic analyses were only performed on participants enrolled in part 1 of the study.

End point values	Trebananib 15 mg/kg	Trebananib 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[20]	4		
Units: µg/mL				
arithmetic mean (standard deviation)				
Carboplatin Without Trebananib (Cycle 1 Day 1)	65.9 (± 45.8)	60.3 (± 19.2)		
Carboplatin With Trebananib (Cycle 3 Day 1)	93.9 (± 8.48)	66.2 (± 33.2)		

Notes:

[20] - N=3 for cycle 3 day 1

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Plasma Concentration (Cmin) of Total Platinum After Administration of Carboplatin With and Without Trebananib

End point title	Minimum Observed Plasma Concentration (Cmin) of Total Platinum After Administration of Carboplatin With and Without Trebananib[21]

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 day 1 and cycle 3 day 1

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic analyses were only performed on participants enrolled in part 1 of the study.

End point values	Trebananib 15 mg/kg	Trebananib 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[22]	4		
Units: hr*µg/mL				
arithmetic mean (standard deviation)				
Carboplatin Without Trebananib (Cycle 1 Day 1)	2.17 (± 0.505)	2.09 (± 0.64)		
Carboplatin With Trebananib (Cycle 3 Day 1)	1.13 (± 0.108)	1.18 (± 0.251)		

Notes:

[22] - N=3 for cycle 3 day 1

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Unbound Platinum After Administration of Carboplatin With and Without Trebananib

End point title	Maximum Observed Plasma Concentration (Cmax) of Unbound Platinum After Administration of Carboplatin With and Without Trebananib[23]

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 day 1 and cycle 3 day 1

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic analyses were only performed on participants enrolled in part 1 of the study.

End point values	Trebananib 15 mg/kg	Trebananib 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[24]	4		
Units: µg/mL				
arithmetic mean (standard deviation)				
Carboplatin Without Trebananib (Cycle 1 Day 1)	24.5 (± 8.44)	20.1 (± 3.28)		
Carboplatin With Trebananib (Cycle 3 Day 1)	23.6 (± 7.49)	12.4 (± 11.1)		

Notes:

[24] - N=3 for cycle 3 day 1

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Plasma Concentration (Tmax) of Unbound Platinum After Administration of Carboplatin With and Without Trebananib

End point title	Time to Maximum Plasma Concentration (Tmax) of Unbound Platinum After Administration of Carboplatin With and Without Trebananib[25]

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 day 1 and cycle 3 day 1

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic analyses were only performed on participants enrolled in part 1 of the study.

End point values	Trebananib 15 mg/kg	Trebananib 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[26]	4[27]		
Units: hours				
median (full range (min-max))				
Carboplatin Without Trebananib (Cycle 1 Day 1)	0.392 (0.25 to 0.833)	0.442 (0.333 to 0.833)		
Carboplatin With Trebananib (Cycle 3 Day 1)	0.5 (0.5 to 0.583)	0.5 (0.5 to 0.533)		

Notes:

[26] - N=3 for cycle 3 day 1

[27] - N=3 for cycle 3 day 1

Statistical analyses

No statistical analyses for this end point

Secondary: AUC from Time 0 to the Time of Last Quantifiable Concentration (AUClast) of Unbound Platinum

End point title	AUC from Time 0 to the Time of Last Quantifiable Concentration (AUClast) of Unbound Platinum[28]

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 day 1 and cycle 3 day 1

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic analyses were only performed on participants enrolled in part 1 of the study.

End point values	Trebananib 15 mg/kg	Trebananib 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[29]	4		
Units: hr*µg/mL				
arithmetic mean (standard deviation)				
Carboplatin Without Trebananib (Cycle 1 Day 1)	51.2 (± 16.6)	46.9 (± 4.51)		
Carboplatin With Trebananib (Cycle 3 Day 1)	50.2 (± 12.6)	24 (± 16.2)		

Notes:

[29] - N=3 for cycle 3 day 1

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Plasma Concentration (Cmin) of Unbound Platinum After Administration of Carboplatin With and Without Trebananib

End point title	Minimum Observed Plasma Concentration (Cmin) of Unbound Platinum After Administration of Carboplatin With and Without Trebananib[30]

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 day 1 and cycle 3 day 1

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Pharmacokinetic analyses were only performed on participants enrolled in part 1 of the study.

End point values	Trebananib 15 mg/kg	Trebananib 30 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[31]	4[32]		
Units: µg/mL				
arithmetic mean (standard deviation)				
Carboplatin Without Trebananib (Cycle 1 Day 1)	2.42 (± 1.28)	2.01 (± 0.835)		
Carboplatin With Trebananib (Cycle 3 Day 1)	3.19 (± 0.358)	2.93 (± 0.944)		

Notes:

[31] - N=3 for cycle 3 day 1

[32] - N=3 for cycle 3 day 1

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug until 30 days after last dose; median time on study was 32 weeks.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Induction Phase: Placebo
Reporting group description:	
Participants received placebo IV QW, pemetrexed 500 mg/m² IV Q3W, carboplatin IV Q3W, for up to 6 cycles in the induction phase.	
Reporting group title	Induction Phase: Trebananib 15 mg/kg
Reporting group description:	
Participants received rebananib 15 mg/kg IV QW, pemetrexed 500 mg/m² IV Q3W, and carboplatin IV Q3W, for up to 6 cycles in the induction phase.	
Reporting group title	Induction Phase: Trebananib 30 mg/kg
Reporting group description:	
Participants received rebananib 30 mg/kg IV QW, pemetrexed 500 mg/m² IV Q3W, and carboplatin IV Q3W, for up to 6 cycles in the induction phase.	
Reporting group title	Maintenance Phase: Placebo
Reporting group description:	
Participants continued on maintenance therapy with placebo IV QW and pemetrexed 500 mg/m² IV Q3W, until disease progression, unacceptable toxicity, withdrawal of consent, or death.	
Reporting group title	Maintenance Phase: Trebananib 15 mg/kg
Reporting group description:	
Participants continued on maintenance therapy with trebananib 15 mg/kg IV QW and pemetrexed 500 mg/m² IV Q3W, until disease progression, unacceptable toxicity, withdrawal of consent, or death.	
Reporting group title	Maintenance Phase: Trebananib 30 mg/kg
Reporting group description:	
Participants continued on maintenance therapy with trebananib 30 mg/kg IV QW and pemetrexed 500 mg/m² IV Q3W, until disease progression, unacceptable toxicity, withdrawal of consent, or death.	

Serious adverse events	Induction Phase: Placebo	Induction Phase: Trebananib 15 mg/kg	Induction Phase: Trebananib 30 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 10 (40.00%)	5 / 15 (33.33%)	7 / 12 (58.33%)
number of deaths (all causes)	2	3	5
number of deaths resulting from adverse events			
Investigations			
Platelet adhesiveness decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (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

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to spine			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (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
Atrial flutter			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (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
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (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
Loss of consciousness			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
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 / 10 (10.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (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 disorders and administration site conditions			
Localised oedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
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 / 10 (0.00%)	2 / 15 (13.33%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	2 / 12 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumothorax			

subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
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	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
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 haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (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
Skin and subcutaneous tissue disorders			
Dermatosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (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
Pneumonia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 15 (0.00%)	0 / 12 (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
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (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

Serious adverse events	Maintenance Phase: Placebo	Maintenance Phase: Trebananib 15 mg/kg	Maintenance Phase: Trebananib 30 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 2 (50.00%)	2 / 7 (28.57%)	1 / 5 (20.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Platelet adhesiveness decreased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to spine			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (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
Atrial fibrillation			

subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 7 (0.00%)	0 / 5 (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
Neutropenia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
Localised oedema			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatosis			

subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (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
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Induction Phase: Placebo	Induction Phase: Trebananib 15 mg/kg	Induction Phase: Trebananib 30 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	15 / 15 (100.00%)	12 / 12 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Diastolic hypertension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hot flush			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	1 / 10 (10.00%)	2 / 15 (13.33%)	1 / 12 (8.33%)
occurrences (all)	1	3	1
Hypotension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	2 / 12 (16.67%)
occurrences (all)	1	0	2
Peripheral coldness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Peripheral venous disease			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Phlebitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Thrombophlebitis superficial			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	1 / 10 (10.00%)	2 / 15 (13.33%)	1 / 12 (8.33%)
occurrences (all)	2	3	1
Chest pain			
subjects affected / exposed	1 / 10 (10.00%)	3 / 15 (20.00%)	1 / 12 (8.33%)
occurrences (all)	1	3	1
Fatigue			
subjects affected / exposed	7 / 10 (70.00%)	12 / 15 (80.00%)	9 / 12 (75.00%)
occurrences (all)	7	21	10
Generalised oedema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Localised oedema			
subjects affected / exposed	2 / 10 (20.00%)	7 / 15 (46.67%)	5 / 12 (41.67%)
occurrences (all)	2	16	11
Mucosal inflammation			
subjects affected / exposed	4 / 10 (40.00%)	2 / 15 (13.33%)	1 / 12 (8.33%)
occurrences (all)	4	2	2
Non-cardiac chest pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	3 / 15 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	3	1
Reproductive system and breast disorders			
Testicular pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	1 / 10 (10.00%)	5 / 15 (33.33%)	3 / 12 (25.00%)
occurrences (all)	1	5	4
Dyspnoea			
subjects affected / exposed	3 / 10 (30.00%)	4 / 15 (26.67%)	4 / 12 (33.33%)
occurrences (all)	3	5	5
Dyspnoea exertional			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Hypoxia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pleural effusion			
subjects affected / exposed	2 / 10 (20.00%)	2 / 15 (13.33%)	2 / 12 (16.67%)
occurrences (all)	2	2	2
Rhinitis allergic			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Rhinorrhoea			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Sinus disorder			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Wheezing			
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Anxiety			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Confusional state			

subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Delirium			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Depressed mood			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	1 / 10 (10.00%)	3 / 15 (20.00%)	0 / 12 (0.00%)
occurrences (all)	1	3	0
Insomnia			
subjects affected / exposed	1 / 10 (10.00%)	3 / 15 (20.00%)	2 / 12 (16.67%)
occurrences (all)	1	3	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	4 / 15 (26.67%)	0 / 12 (0.00%)
occurrences (all)	0	9	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	4
Investigation abnormal			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Neutrophil count abnormal			

subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Neutrophil count decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	3
Platelet count decreased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	1	2	2
Transaminases increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	1 / 10 (10.00%)	2 / 15 (13.33%)	3 / 12 (25.00%)
occurrences (all)	1	2	3
Weight increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	3
White blood cell count			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	3
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Infusion related reaction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Skin abrasion			

subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Atrial flutter			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Palpitations			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Sinus tachycardia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Dizziness			
subjects affected / exposed	3 / 10 (30.00%)	4 / 15 (26.67%)	4 / 12 (33.33%)
occurrences (all)	4	4	7
Dizziness postural			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dysgeusia			
subjects affected / exposed	0 / 10 (0.00%)	3 / 15 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	3	1
Headache			

subjects affected / exposed	1 / 10 (10.00%)	3 / 15 (20.00%)	0 / 12 (0.00%)
occurrences (all)	1	5	0
Hypoaesthesia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Lethargy			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Migraine			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Neuralgia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Neuropathy peripheral			
subjects affected / exposed	0 / 10 (0.00%)	3 / 15 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	3	1
Paraesthesia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Tremor			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 10 (40.00%)	4 / 15 (26.67%)	2 / 12 (16.67%)
occurrences (all)	5	6	5
Neutropenia			
subjects affected / exposed	3 / 10 (30.00%)	4 / 15 (26.67%)	2 / 12 (16.67%)
occurrences (all)	5	6	3

Platelet disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 10 (0.00%)	5 / 15 (33.33%)	4 / 12 (33.33%)
occurrences (all)	0	9	8
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Vertigo			
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Dry eye			
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Eye pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Lacrimation increased			
subjects affected / exposed	0 / 10 (0.00%)	3 / 15 (20.00%)	2 / 12 (16.67%)
occurrences (all)	0	3	2
Photophobia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	2 / 12 (16.67%)
occurrences (all)	0	2	2
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 10 (0.00%)	3 / 15 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Abdominal pain			

subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	2 / 12 (16.67%)
occurrences (all)	0	1	2
Ascites			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Colitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	4 / 10 (40.00%)	9 / 15 (60.00%)	2 / 12 (16.67%)
occurrences (all)	4	11	4
Diarrhoea			
subjects affected / exposed	2 / 10 (20.00%)	5 / 15 (33.33%)	3 / 12 (25.00%)
occurrences (all)	2	7	8
Dry mouth			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Dysphagia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 10 (10.00%)	3 / 15 (20.00%)	0 / 12 (0.00%)
occurrences (all)	1	3	0
Gingival bleeding			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hiatus hernia			

subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	2 / 10 (20.00%)	11 / 15 (73.33%)	8 / 12 (66.67%)
occurrences (all)	5	21	12
Retching			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	1 / 10 (10.00%)	3 / 15 (20.00%)	0 / 12 (0.00%)
occurrences (all)	1	3	0
Toothache			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	2 / 10 (20.00%)	7 / 15 (46.67%)	3 / 12 (25.00%)
occurrences (all)	3	14	5
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 10 (10.00%)	2 / 15 (13.33%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Dermatitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Night sweats			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Onychomadesis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pain of skin			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Purpura			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Rash			
subjects affected / exposed	2 / 10 (20.00%)	3 / 15 (20.00%)	2 / 12 (16.67%)
occurrences (all)	2	4	2
Skin mass			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dysuria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Haematuria			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Nephrolithiasis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nephropathy toxic			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pollakiuria			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Proteinuria			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Renal failure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Urinary retention			

subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Arthritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	3 / 15 (20.00%)	3 / 12 (25.00%)
occurrences (all)	0	3	3
Bone pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Flank pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Joint range of motion decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Limb discomfort			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Musculoskeletal chest pain			

subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pain in jaw			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Candida infection			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Cellulitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	2
Cystitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Eye infection bacterial			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hepatitis viral			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0

Herpes zoster			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	1 / 10 (10.00%)	2 / 15 (13.33%)	1 / 12 (8.33%)
occurrences (all)	1	3	1
Oral herpes			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Oral infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tooth abscess			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Wound infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0

Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Decreased appetite			
subjects affected / exposed	3 / 10 (30.00%)	5 / 15 (33.33%)	2 / 12 (16.67%)
occurrences (all)	3	5	6
Dehydration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Diabetes mellitus			
subjects affected / exposed	1 / 10 (10.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Food intolerance			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Gout			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypercalcaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hyperkalaemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hypocalcaemia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 15 (13.33%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Hypochloraemia			

subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypoglycaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	0 / 10 (0.00%)	3 / 15 (20.00%)	4 / 12 (33.33%)
occurrences (all)	0	4	11
Hypomagnesaemia			
subjects affected / exposed	2 / 10 (20.00%)	1 / 15 (6.67%)	2 / 12 (16.67%)
occurrences (all)	7	2	2
Hyponatraemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	1	4	0
Hypovolaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Increased appetite			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Iron deficiency			
subjects affected / exposed	0 / 10 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Non-serious adverse events	Maintenance Phase: Placebo	Maintenance Phase: Trebananib 15 mg/kg	Maintenance Phase: Trebananib 30 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	7 / 7 (100.00%)	5 / 5 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Diastolic hypertension			

subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hot flush			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypertension			
subjects affected / exposed	0 / 2 (0.00%)	2 / 7 (28.57%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Hypotension			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Peripheral coldness			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Peripheral venous disease			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	5	0
Phlebitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Thrombophlebitis superficial			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Chest pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 2 (50.00%)	3 / 7 (42.86%)	1 / 5 (20.00%)
occurrences (all)	1	6	2
Generalised oedema			

subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Influenza like illness			
subjects affected / exposed	1 / 2 (50.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Localised oedema			
subjects affected / exposed	2 / 2 (100.00%)	5 / 7 (71.43%)	3 / 5 (60.00%)
occurrences (all)	2	7	4
Mucosal inflammation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 2 (0.00%)	2 / 7 (28.57%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	1 / 2 (50.00%)	3 / 7 (42.86%)	0 / 5 (0.00%)
occurrences (all)	1	6	0
Reproductive system and breast disorders			
Testicular pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 2 (50.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Dyspnoea			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
Dyspnoea exertional			
subjects affected / exposed	1 / 2 (50.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hypoxia			

subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pleural effusion			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Rhinitis allergic			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Sinus disorder			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Wheezing			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Anxiety			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Delirium			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Depressed mood			
subjects affected / exposed	1 / 2 (50.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

Insomnia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Investigation abnormal			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Neutrophil count abnormal			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Transaminases increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Weight decreased			

subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
White blood cell count			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Infusion related reaction			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin abrasion			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Atrial flutter			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Palpitations			

subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Tachycardia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 2 (0.00%)	2 / 7 (28.57%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Dizziness postural			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 2 (0.00%)	2 / 7 (28.57%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Hypoaesthesia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Lethargy			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Migraine			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Neuralgia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Neuropathy peripheral			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 7 (28.57%)	2 / 5 (40.00%)
occurrences (all)	0	5	2
Neutropenia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Platelet disorder			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 7 (28.57%)	2 / 5 (40.00%)
occurrences (all)	0	2	2
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Eye disorders			

Diplopia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Eye pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Lacrimation increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Photophobia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	0 / 2 (0.00%)	2 / 7 (28.57%)	1 / 5 (20.00%)
occurrences (all)	0	3	1
Ascites			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Colitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	1 / 5 (20.00%)
occurrences (all)	0	2	1
Diarrhoea			

subjects affected / exposed	1 / 2 (50.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Dry mouth			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Flatulence			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Gingival bleeding			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hiatus hernia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 2 (50.00%)	2 / 7 (28.57%)	0 / 5 (0.00%)
occurrences (all)	2	2	0
Retching			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Stomatitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Toothache			

subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 2 (0.00%)	2 / 7 (28.57%)	1 / 5 (20.00%)
occurrences (all)	0	3	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Dermatitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Night sweats			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Onychomadesis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pain of skin			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Purpura			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin mass			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Dysuria			
subjects affected / exposed	1 / 2 (50.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Haematuria			
subjects affected / exposed	1 / 2 (50.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nephrolithiasis			
subjects affected / exposed	1 / 2 (50.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nephropathy toxic			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pollakiuria			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Proteinuria			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Renal failure			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Urinary retention			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Arthritis			

subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	1 / 2 (50.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Bone pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Flank pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Joint range of motion decreased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Limb discomfort			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Muscle spasms			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Pain in jaw			

subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Candida infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Cellulitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Eye infection bacterial			
subjects affected / exposed	1 / 2 (50.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hepatitis viral			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection			
subjects affected / exposed	1 / 2 (50.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Oral candidiasis			
subjects affected / exposed	0 / 2 (0.00%)	2 / 7 (28.57%)	0 / 5 (0.00%)
occurrences (all)	0	2	0

Oral herpes			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Oral infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 2 (0.00%)	2 / 7 (28.57%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Sinusitis			
subjects affected / exposed	1 / 2 (50.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Tooth abscess			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 2 (0.00%)	2 / 7 (28.57%)	1 / 5 (20.00%)
occurrences (all)	0	3	2
Wound infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Decreased appetite			
subjects affected / exposed	0 / 2 (0.00%)	4 / 7 (57.14%)	0 / 5 (0.00%)
occurrences (all)	0	8	0
Dehydration			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Diabetes mellitus			

subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Food intolerance			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gout			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypochloraemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypoglycaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	1 / 2 (50.00%)	1 / 7 (14.29%)	2 / 5 (40.00%)
occurrences (all)	2	3	2
Hypomagnesaemia			
subjects affected / exposed	1 / 2 (50.00%)	1 / 7 (14.29%)	0 / 5 (0.00%)
occurrences (all)	5	2	0
Hyponatraemia			

subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypovolaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Increased appetite			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Iron deficiency			
subjects affected / exposed	0 / 2 (0.00%)	0 / 7 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 December 2012	•Amgen documentation was amended regarding the process for determination of expectedness of clinical trial adverse events for the purpose of expedited reporting to regulatory agencies globally. •The change in timeline for serious adverse event reporting from Investigators to sponsors was updated to be within 24 hours. •The Pregnancy and Lactation Reporting section was updated per current Amgen protocol template. In line with this, a new lactation notification worksheet was added. •It was clarified that this study now reports serious adverse events through electronic serious adverse event report form. A sample electronic serious adverse event contingency report form has replaced the old version. •The exclusion criterion on subjects with known epidermal growth factor receptor mutation was clarified. •The Dose-limiting Toxicity analysis set definition was clarified. •Typographic and formatting errors were corrected.
26 November 2013	•The sponsor decided to close the study to further randomization/enrollment on 15 October 2013 because of the changing therapeutic landscape that limits the future utility of trebananib in this disease setting. •Total number of subjects in part 2 was decreased from 210 to 29. •All subjects randomized to part 2 were unblinded and placebo was discontinued. •Objectives, endpoints, and statistical analysis plan were updated. •Text was added on how to address and report serious adverse events occurring outside the protocol required reporting period. •Changes were made to the sample collection requirements, and other procedures such as electrocardiogram evaluation and imaging schedules. •Changes were made to the list of protocol-required or recommended drugs in the study. •Patient-related outcomes questionnaires were discontinued. •Administrative information was updated and typographical errors were corrected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported