



## Clinical trial results:

### A Randomized Phase III, Double-Blind, Placebo-Controlled Multicenter Trial of Everolimus in Combination with Trastuzumab and Paclitaxel, as First Line Therapy in Women with HER2 Positive Locally Advanced or Metastatic Breast Cancer (BOLERO-1)

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.

#### Summary

EudraCT number	2008-006556-21
Trial protocol	DE GB FR IT IE BE GR
Global end of trial date	23 October 2017

#### Results information

Result version number	v2 (current)
This version publication date	28 December 2018
First version publication date	08 November 2018
Version creation reason	<ul style="list-style-type: none"><li>• Correction of full data set</li></ul> Changed Sponsor name to Novartis Pharma, AG from Novartis Pharmaceuticals

#### Trial information

##### Trial identification

Sponsor protocol code	CRAD001J2301
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00876395
WHO universal trial number (UTN)	-
Other trial identifiers	Acronym: BOLERO-1

Notes:

#### Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma, AG, +41 613241111, <a href="mailto:novartis.email@novartis.com">novartis.email@novartis.com</a>
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, +41 613241111, <a href="mailto:novartis.email@novartis.com">novartis.email@novartis.com</a>

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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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	23 October 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 October 2017
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The two primary objectives were to compare PFS between the combination treatment of everolimus, trastuzumab, paclitaxel, and the combination treatment of placebo, trastuzumab, paclitaxel in patients with HER2-overexpressing, unresectable, locally advanced or metastatic breast cancer (MBC) in the: Full population, and Hormone receptor (HR)-negative subpopulation

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 September 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 29
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Brazil: 35
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	China: 155
Country: Number of subjects enrolled	Colombia: 6
Country: Number of subjects enrolled	Egypt: 22
Country: Number of subjects enrolled	France: 43
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Hong Kong: 19

Country: Number of subjects enrolled	Ireland: 12
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Japan: 45
Country: Number of subjects enrolled	Korea, Republic of: 35
Country: Number of subjects enrolled	Lebanon: 2
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	Peru: 29
Country: Number of subjects enrolled	Russian Federation: 50
Country: Number of subjects enrolled	South Africa: 28
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Taiwan: 43
Country: Number of subjects enrolled	Turkey: 11
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	United States: 79
Country: Number of subjects enrolled	Venezuela, Bolivarian Republic of: 2
Worldwide total number of subjects	719
EEA total number of subjects	113

Notes:

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### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	595
From 65 to 84 years	122
85 years and over	2

## Subject disposition

### Recruitment

Recruitment details:

717 patients were planned to be randomized. A total of 719 patients were randomized between 10-Sep-2009 and 16-Dec-2012.

Not completed reasons = primary reasons for end of treatment

### Pre-assignment

Screening details:

717 patients were planned to be randomized. A total of 719 patients were randomized between 10-Sep-2009 and 16-Dec-2012.

Not completed reasons = primary reasons for end of treatment

### 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, Carer, Assessor

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Everolimus + Paclitaxel + Trastuzumab

Arm description:

Everolimus 10 mg daily in combination with paclitaxel 80mg/m2 weekly on days 1, 8, 15 and trastuzumab 2mg/kg weekly on days 1, 8, 15, 22

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Everolimus was administered in a continuous oral daily dosing of 10 mg (two 5-mg tablets).

Investigational medicinal product name	trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

trastuzumab 2 mg/kg weekly according to the Investigator country guidelines.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel 80 mg/m2 weekly according to the Investigator country guidelines.

<b>Arm title</b>	Placebo + Paclitaxel + Trastuzumab
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Arm description:

Placebo of everolimus 10 mg daily in combination with paclitaxel 80mg/m2 weekly on days 1, 8, 15 and trastuzumab 2mg/kg weekly on days 1, 8, 15, 22

Arm type	Placebo
Investigational medicinal product name	Everolimus Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Everolimus Placebo was administered in a continuous oral daily dosing of 10 mg (two 5-mg tablets).

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel 80 mg/m<sup>2</sup> weekly according to the Investigator country guidelines.

Investigational medicinal product name	trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

trastuzumab 2 mg/kg weekly according to the Investigator country guidelines.

Number of subjects in period 1	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab
Started	480	239
Untreated	8	1
Completed	0	0
Not completed	480	239
Adverse event, serious fatal	12	-
Consent withdrawn by subject	66	33
Disease progression	259	162
Adverse event, non-fatal	63	11
New cancer therapy	25	7
Administrative problems	39	23
Untreated	8	1
Lost to follow-up	2	-
Abnormal test procedure result(s)	1	-
Protocol deviation	5	2

## Baseline characteristics

### Reporting groups

Reporting group title	Everolimus + Paclitaxel + Trastuzumab
Reporting group description: Everolimus 10 mg daily in combination with paclitaxel 80mg/m2 weekly on days 1, 8, 15 and trastuzumab 2mg/kg weekly on days 1, 8, 15, 22	
Reporting group title	Placebo + Paclitaxel + Trastuzumab
Reporting group description: Placebo of everolimus 10 mg daily in combination with paclitaxel 80mg/m2 weekly on days 1, 8, 15 and trastuzumab 2mg/kg weekly on days 1, 8, 15, 22	

Reporting group values	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab	Total
Number of subjects	480	239	719
Age categorical Units: Subjects			
Adults (18-64 years)	399	196	595
From 65-84 years	79	43	122
85 years and over	2	0	2
Age Continuous Units: Years			
arithmetic mean	53.4	52.1	
standard deviation	± 11.46	± 11.63	-
Sex: Female, Male Units: Subjects			
Female	480	239	719
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Caucasian	214	97	311
Black	26	12	38
Asian	198	105	303
Native American	3	0	3
Other	39	25	64

## End points

### End points reporting groups

Reporting group title	Everolimus + Paclitaxel + Trastuzumab
Reporting group description: Everolimus 10 mg daily in combination with paclitaxel 80mg/m <sup>2</sup> weekly on days 1, 8, 15 and trastuzumab 2mg/kg weekly on days 1, 8, 15, 22	
Reporting group title	Placebo + Paclitaxel + Trastuzumab
Reporting group description: Placebo of everolimus 10 mg daily in combination with paclitaxel 80mg/m <sup>2</sup> weekly on days 1, 8, 15 and trastuzumab 2mg/kg weekly on days 1, 8, 15, 22	
Subject analysis set title	Everolimus 10 mg/day
Subject analysis set type	Sub-group analysis
Subject analysis set description: Everolimus 10 mg daily	
Subject analysis set title	Everolimus 5 mg/day
Subject analysis set type	Sub-group analysis
Subject analysis set description: Everolimus 5 mg daily	
Subject analysis set title	Everolimus
Subject analysis set type	Sub-group analysis
Subject analysis set description: Everolimus 10 mg/day	
Subject analysis set title	Everolimus Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Placebo of everolimus 10 mg daily	
Subject analysis set title	Everolimus + trastuzumab
Subject analysis set type	Sub-group analysis
Subject analysis set description: Everolimus plus trastuzumab	
Subject analysis set title	Everolimus Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Placebo of everolimus 10 mg daily	

### Primary: Progression-free Survival (PFS) per Investigators' assessment based on local radiology review - Full population

End point title	Progression-free Survival (PFS) per Investigators' assessment based on local radiology review - Full population
End point description: PFS is defined as the time from the date of randomization to the date of first documented tumor progression or death from any cause, whichever occurs first. This was assessed in the full patient population.	
End point type	Primary
End point timeframe: date of randomization to the date of first documented tumor progression or death from any cause, whichever occurs first, reported between day of first patient randomized up to about 56 months	

End point values	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	480	239		
Units: months				
median (confidence interval 95%)	14.95 (14.55 to 17.91)	14.49 (12.29 to 17.08)		

## Statistical analyses

Statistical analysis title	Drug vs. Pbo for PFS (FP)
Comparison groups	Everolimus + Paclitaxel + Trastuzumab v Placebo + Paclitaxel + Trastuzumab
Number of subjects included in analysis	719
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1166
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.08

## Primary: Progression-free Survival (PFS) per Investigators' assessment based on local radiology review - (hormone receptor (HR)-negative population

End point title	Progression-free Survival (PFS) per Investigators' assessment based on local radiology review - (hormone receptor (HR)-negative population
End point description:	
PFS is defined as the time from the date of randomization to the date of first documented tumor progression or death from any cause, whichever occurs first. This was assessed in the HR-negative patient population.	
End point type	Primary
End point timeframe:	
date of randomization to the date of first documented tumor progression or death from any cause, whichever occurs first, reported between day of first patient randomized up to about 56 months	



End point values	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	103		
Units: Months				
median (confidence interval 95%)	20.27 (14.95 to 24.08)	13.08 (10.05 to 16.56)		

## Statistical analyses

Statistical analysis title	Drug vs. Pbo for PFS (HR- pop.)
Comparison groups	Everolimus + Paclitaxel + Trastuzumab v Placebo + Paclitaxel + Trastuzumab
Number of subjects included in analysis	311
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0049
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	0.91

## Secondary: Overall Survival (OS) - Full Population

End point title	Overall Survival (OS) - Full Population
End point description:	OS is defined as the time from date of randomization to the date of death due to any cause. For patients with documented progression, survival follow up was performed either by telephone or clinic visit at least every 3 months. Additional survival updates were requested prior to interim or final analysis or prior to providing data to the health authorities. This was assessed in the full patient population.
End point type	Secondary
End point timeframe:	up to about 76 months

End point values	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	480	239		
Units: Months				
median (confidence interval 95%)	48.56 (40.94 to 58.94)	49.97 (40.84 to 999)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS) - HR-negative population

End point title	Overall Survival (OS) - HR-negative population
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End point description:

OS is defined as the time from date of randomization to the date of death due to any cause. For patients with documented progression, survival follow up was performed either by telephone or clinic visit at least every 3 months. Additional survival updates were requested prior to interim or final analysis or prior to providing data to the health authorities. This was assessed in the HR-negative patient population.

End point type	Secondary
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End point timeframe:

up to about 76 months

End point values	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	103		
Units: Months				
median (confidence interval 95%)	56.97 (44.09 to 999)	41.63 (34.83 to 999)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall response rate (ORR) - Full Population

End point title	Overall response rate (ORR) - Full Population
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End point description:

ORR is defined as the percentage of participants whose best overall response is either complete response (CR) or partial response (PR) according to RECIST. This was assessed in the full patient population. Complete response is achieved when all lesions evaluated at Baseline are absent at subsequent visit.

End point type	Secondary
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End point timeframe:

up to about 23 months

End point values	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	480	239		
Units: Percentage of participants				
number (confidence interval 95%)	67.1 (62.7 to 71.3)	69.0 (62.8 to 74.8)		

### Statistical analyses

Statistical analysis title	Drug vs. Pbo for ORR (FP)
Comparison groups	Everolimus + Paclitaxel + Trastuzumab v Placebo + Paclitaxel + Trastuzumab
Number of subjects included in analysis	719
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7276
Method	Exact Cochran-Mantel-Haenzel chi-square

### Secondary: Overall response rate (ORR) - HR-negative population

End point title	Overall response rate (ORR) - HR-negative population
End point description: ORR is defined as the percentage of participants whose best overall response is either complete response (CR) or partial response (PR) according to RECIST. This was assessed in a subset of patients with Hormone Receptor Negative disease. Complete response is achieved when all lesions evaluated at Baseline are absent at subsequent visit.	
End point type	Secondary
End point timeframe: up to about 23 months	

End point values	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	103		
Units: Percentage of participants				
number (confidence interval 95%)	73.1 (66.5 to 79.0)	70.9 (61.1 to 79.4)		

### Statistical analyses

Statistical analysis title	Drug vs. Pbo for ORR (HR- pop.)
Comparison groups	Everolimus + Paclitaxel + Trastuzumab v Placebo + Paclitaxel + Trastuzumab

Number of subjects included in analysis	311
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4085
Method	Exact Cochran-Mantel-Haenzel chi-square

### Secondary: Clinical benefit rate (CBR) equal to or greater than 24 weeks - Full Population

End point title	Clinical benefit rate (CBR) equal to or greater than 24 weeks - Full Population
End point description: CBR is defined as the percentage of participants whose best overall response is either complete response (CR), a partial response (PR) or stable disease (SD) lasting for at least 24 weeks, according to RECIST. This was assessed in the full patient population. Complete response is achieved when all lesions evaluated at Baseline are absent at subsequent visit.	
End point type	Secondary
End point timeframe: up to about 23 months	

End point values	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	480	239		
Units: Percentage of participants				
number (confidence interval 95%)	75.8 (71.7 to 79.6)	81.2 (75.6 to 85.9)		

### Statistical analyses

<b>Statistical analysis title</b>	Drug vs. Pbo for CBR (FP)
Comparison groups	Everolimus + Paclitaxel + Trastuzumab v Placebo + Paclitaxel + Trastuzumab
Number of subjects included in analysis	719
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9573
Method	Exact Cochran-Mantel-Haenzel chi-square

### Secondary: Clinical benefit rate (CBR) equal to or greater than 24 weeks - HR-negative Population

End point title	Clinical benefit rate (CBR) equal to or greater than 24 weeks - HR-negative Population
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End point description:

CBR is defined as the percentage of participants whose best overall response is either complete response (CR), a partial response (PR) or stable disease (SD) lasting for at least 24 weeks, according to RECIST. This was assessed in a subset of patients with Hormone Receptor Negative disease. Complete response is achieved when all lesions evaluated at Baseline are absent at subsequent visit.

End point type	Secondary
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End point timeframe:

up to about 23 months

End point values	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	103		
Units: Percentage of participants				
number (confidence interval 95%)	78.8 (72.7 to 84.2)	79.6 (70.5 to 86.9)		

## Statistical analyses

Statistical analysis title	Drug vs. Pbo for CBR (HR- pop.)
Comparison groups	Everolimus + Paclitaxel + Trastuzumab v Placebo + Paclitaxel + Trastuzumab
Number of subjects included in analysis	311
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6382
Method	Exact Cochran-Mantel-Haenzel chi-square

## Secondary: Time to overall response based on Investigator - Full Population

End point title	Time to overall response based on Investigator - Full Population
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End point description:

Time to overall response defined as the time between date of randomization until first documented response Complete response (CR) or partial response (PR) ), according to RECIST. This was assessed in the full patient population and in a subset of patients with Hormone Receptor Negative disease. Complete response is achieved when all lesions evaluated at Baseline are absent at subsequent visit.

End point type	Secondary
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End point timeframe:

up to about 23 months

End point values	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	480	239		
Units: months				
median (confidence interval 95%)	2.10 (2.00 to 3.58)	2.00 (1.94 to 2.27)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to overall response based on Investigator - HR-negative Population

End point title	Time to overall response based on Investigator - HR-negative Population
End point description: Time to overall response defined as the time between date of randomization until first documented response Complete response (CR) or partial response (PR) ), according to RECIST. This was assessed in the full patient population and in a subset of patients with Hormone Receptor Negative disease. Complete response is achieved when all lesions evaluated at Baseline are absent at subsequent visit.	
End point type	Secondary
End point timeframe: up to about 23 months	

End point values	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	103		
Units: months				
median (confidence interval 95%)	1.94 (1.87 to 2.00)	1.97 (1.87 to 3.58)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Response (OR) - Full Population

End point title	Overall Response (OR) - Full Population
End point description: OR applies only to patients whose best OR was CR or PR. Start date = date of first documented response (CR or PR) and end date = date of documented response (CR or PR) and end date = date of event defined as the first documented progression or death due to underlying cause. Complete response is achieved when all lesions evaluated at Baseline are absent at subsequent visit.	
End point type	Secondary

End point timeframe:  
up to about 23 months

End point values	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	480	239		
Units: Percentage of participants				
number (not applicable)				
Complete Response (CR)	5.6	5.9		
Partial Response (PR)	61.5	63.2		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Response (OR) - HR-negative Population

End point title	Overall Response (OR) - HR-negative Population
End point description: OR applies only to patients whose best OR was CR or PR. Start date = date of first documented response (CR or PR) and end date = date of documented response (CR or PR) and end date = date of event defined as the first documented progression or death due to underlying cause. This was assessed in the HR-negative patient population. Complete response is achieved when all lesions evaluated at Baseline are absent at subsequent visit.	
End point type	Secondary
End point timeframe: up to about 23 months	

End point values	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	103		
Units: Percentage of participants				
number (not applicable)				
Complete Response (CR)	7.7	2.9		
Partial Response (PR)	65.4	68.0		

### Statistical analyses

No statistical analyses for this end point

**Secondary: Everolimus blood level concentrations at steady states for everolimus**

End point title	Everolimus blood level concentrations at steady states for everolimus
End point description: Blood levels at steady states for everolimus 10 mg/day and 5 mg/day. Only valid samples are included. Cycle = 28 days	
End point type	Secondary
End point timeframe: predose, 2 hours post-dose at Cycle 2/Day 1, Cycle 2/Day 15, Cycle 2/ Day 22	

End point values	Everolimus 10 mg/day	Everolimus 5 mg/day		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	60 <sup>[1]</sup>	21 <sup>[2]</sup>		
Units: ng/mL				
arithmetic mean (standard deviation)				
Pre-dose (Cmin) @ C2D1	14.380 (± 10.0169)	7.959 (± 8.1546)		
2 hours post administration (C2h) @ C2D1	44.485 (± 22.1986)	23.449 (± 10.4112)		
Pre-dose (Cmin) @ C2D15	13.206 (± 9.9821)	5.473 (± 3.9690)		
2 hours post administration (C2h) @ C2D15	43.494 (± 21.5940)	20.329 (± 7.9518)		
Pre-dose (Cmin) @ C2D22	13.432 (± 13.2782)	7.494 (± 5.8503)		
2 hours post administration (C2h) @ C2D22	43.947 (± 28.0107)	22.192 (± 10.9277)		

Notes:

[1] - n for all categories for this arm = (54, 60, 44, 44, 44, 40, 48)

[2] - n for all categories for this arm = (14, 17, 17, 21, 17, 21)

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Paclitaxel plasma concentrations**

End point title	Paclitaxel plasma concentrations
End point description: Blood levels at steady states for everolimus/placebo	
End point type	Secondary
End point timeframe: Cycle 2/Day 15 (Pre-infusion and end of infusion)	



End point values	Everolimus	Everolimus Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91 <sup>[3]</sup>	43 <sup>[4]</sup>		
Units: ng/mL				
arithmetic mean (standard deviation)				
Pre-infusion (Cmin) @ C2D15	1.424 (± 5.8645)	0 (± 0)		
End of infusion (Cmax) @ C2D15	5159.338 (± 15473.636)	4296.697 (± 7431.0799)		

Notes:

[3] - n = (91, 65)

[4] - n = (43, 33)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Trastuzumab serum concentrations

End point title	Trastuzumab serum concentrations
End point description:	
Blood levels at steady states for everolimus/placebo	
End point type	Secondary
End point timeframe:	
Cycle 4/Day 1 (Pre-infusion and end of infusion)	

End point values	Everolimus + trastuzumab	Everolimus Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98 <sup>[5]</sup>	54 <sup>[6]</sup>		
Units: microgram/ml				
arithmetic mean (standard deviation)				
Pre-infusion (Cmin) @ C4D1	26.606 (± 9.6548)	29.180 (± 12.1252)		
End of infusion (Cmax) @ C4D1	64.296 (± 23.4635)	67.643 (± 20.8852)		

Notes:

[5] - n = (98, 83)

[6] - n = (54, 46)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to deterioration of Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score - Full Population

End point title	Time to deterioration of Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score - Full Population
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End point description:

Time to definitive deterioration of the ECOG PS by one category of the score from baseline will be performed. Baseline is the last available assessment on or before randomization date. A deterioration is considered definitive if no improvements in the ECOG PS status is observed at a subsequent time of measurement during the treatment period following the time point where the deterioration is observed.

End point type	Secondary
End point timeframe: up to about 56 months	

End point values	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	480	239		
Units: months				
median (confidence interval 95%)	39.20 (31.31 to 999)	99 (30.39 to 999)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to deterioration of Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score - HR-negative Population

End point title	Time to deterioration of Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score - HR-negative Population
End point description: Time to definitive deterioration of the ECOG PS by one category of the score from baseline will be performed. Baseline is the last available assessment on or before randomization date. A deterioration is considered definitive if no improvements in the ECOG PS status is observed at a subsequent time of measurement during the treatment period following the time point where the deterioration is observed.	
End point type	Secondary
End point timeframe: up to about 56 months	

End point values	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	103		
Units: months				
median (confidence interval 95%)	999 (25.56 to 999)	999 (26.91 to 999)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Patient First Treatment until 30 days after Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

### Reporting groups

Reporting group title	Everolimus + Paclitaxel + Trastuzumab
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Reporting group description:

Everolimus 10 mg daily in combination with paclitaxel 80mg/m2 weekly on days 1, 8, 15 and... more trastuzumab 2mg/kg weekly on days 1, 8, 15, 22

Reporting group title	Placebo + Paclitaxel + Trastuzumab
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Reporting group description:

Placebo of everolimus 10 mg daily in combination with paclitaxel 80mg/m2 weekly on days 1, 8, 15... more and trastuzumab 2mg/kg weekly on days 1, 8, 15, 22

Serious adverse events	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	173 / 472 (36.65%)	40 / 238 (16.81%)	
number of deaths (all causes)	23	2	
number of deaths resulting from adverse events	6	0	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	2 / 472 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calcinosis			
subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chest discomfort			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site related reaction			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 472 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated hernia			
subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			

subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	12 / 472 (2.54%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	5 / 13	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic shock			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast ulceration			
subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 472 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	12 / 472 (2.54%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	6 / 12	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Interstitial lung disease			
subjects affected / exposed	7 / 472 (1.48%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal inflammation			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	21 / 472 (4.45%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	20 / 21	0 / 0	
deaths causally related to treatment / all	2 / 3	0 / 0	
Pulmonary artery thrombosis			
subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 472 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Respiratory arrest			



subjects affected / exposed	2 / 472 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	3 / 472 (0.64%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	5 / 472 (1.06%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	3 / 472 (0.64%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conversion disorder			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			

Thrombosis in device			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 472 (0.64%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 472 (0.64%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium decreased			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	2 / 472 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Femur fracture			

subjects affected / exposed	2 / 472 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured ischium			
subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured sacrum			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			

subjects affected / exposed	1 / 472 (0.21%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle rupture			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 472 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			

subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 472 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 472 (0.21%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			

subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	2 / 472 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral artery embolism			
subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 472 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Depressed level of consciousness			

subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disturbance in attention			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	5 / 472 (1.06%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	3 / 472 (0.64%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersomnia			
subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			

subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 472 (0.42%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			



subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 472 (1.27%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	8 / 14	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	4 / 472 (0.85%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	3 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 472 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 472 (0.42%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	4 / 472 (0.85%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	2 / 472 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplopia			
subjects affected / exposed	2 / 472 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ocular surface disease			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Strabismus			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 472 (0.42%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colitis			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	5 / 472 (1.06%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	3 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 472 (0.21%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	2 / 472 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			

subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	2 / 472 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal perforation			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			

subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	2 / 472 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	10 / 472 (2.12%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	10 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 472 (0.42%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			

subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	3 / 472 (0.64%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ulcer			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 472 (0.85%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			

subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 472 (0.42%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercreatinaemia			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 472 (0.00%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Appendicitis			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 472 (0.21%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium colitis			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	5 / 472 (1.06%)	4 / 238 (1.68%)	
occurrences causally related to treatment / all	4 / 8	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	10 / 472 (2.12%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	4 / 10	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			



subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 472 (0.21%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection fungal			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection pseudomonal			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			
subjects affected / exposed	2 / 472 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	1 / 472 (0.21%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			

subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	3 / 472 (0.64%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	22 / 472 (4.66%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	11 / 22	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia klebsiella			
subjects affected / exposed	2 / 472 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			

subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculoma			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash pustular			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 472 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 472 (0.21%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	5 / 472 (1.06%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	1 / 6	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 0	
Skin infection			

subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdiaphragmatic abscess			
subjects affected / exposed	0 / 472 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	4 / 472 (0.85%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	2 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 472 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	7 / 472 (1.48%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	3 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Appetite disorder			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	3 / 472 (0.64%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	7 / 472 (1.48%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	3 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperglycaemia			
subjects affected / exposed	6 / 472 (1.27%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	3 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	3 / 472 (0.64%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	3 / 472 (0.64%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			

subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	1 / 472 (0.21%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Everolimus + Paclitaxel + Trastuzumab	Placebo + Paclitaxel + Trastuzumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	466 / 472 (98.73%)	236 / 238 (99.16%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	13 / 472 (2.75%)	12 / 238 (5.04%)	
occurrences (all)	14	12	
Hypertension			
subjects affected / exposed	74 / 472 (15.68%)	27 / 238 (11.34%)	
occurrences (all)	113	50	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	94 / 472 (19.92%)	41 / 238 (17.23%)	
occurrences (all)	176	65	
Fatigue			
subjects affected / exposed	168 / 472 (35.59%)	87 / 238 (36.55%)	
occurrences (all)	262	171	
Chills			
subjects affected / exposed	29 / 472 (6.14%)	6 / 238 (2.52%)	
occurrences (all)	37	7	

Oedema peripheral subjects affected / exposed occurrences (all)	156 / 472 (33.05%) 261	59 / 238 (24.79%) 82	
Peripheral swelling subjects affected / exposed occurrences (all)	30 / 472 (6.36%) 40	10 / 238 (4.20%) 15	
Pain subjects affected / exposed occurrences (all)	28 / 472 (5.93%) 37	12 / 238 (5.04%) 12	
Pyrexia subjects affected / exposed occurrences (all)	181 / 472 (38.35%) 367	63 / 238 (26.47%) 90	
Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all)	26 / 472 (5.51%) 32	12 / 238 (5.04%) 15	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	191 / 472 (40.47%) 341	80 / 238 (33.61%) 131	
Dysphonia subjects affected / exposed occurrences (all)	22 / 472 (4.66%) 28	14 / 238 (5.88%) 14	
Dyspnoea subjects affected / exposed occurrences (all)	110 / 472 (23.31%) 143	24 / 238 (10.08%) 35	
Epistaxis subjects affected / exposed occurrences (all)	156 / 472 (33.05%) 303	43 / 238 (18.07%) 74	
Pneumonitis subjects affected / exposed occurrences (all)	66 / 472 (13.98%) 73	11 / 238 (4.62%) 15	
Oropharyngeal pain subjects affected / exposed occurrences (all)	74 / 472 (15.68%) 103	31 / 238 (13.03%) 47	
Rhinorrhoea			

subjects affected / exposed	43 / 472 (9.11%)	18 / 238 (7.56%)	
occurrences (all)	52	19	
Productive cough			
subjects affected / exposed	25 / 472 (5.30%)	14 / 238 (5.88%)	
occurrences (all)	31	16	
Psychiatric disorders			
Depression			
subjects affected / exposed	23 / 472 (4.87%)	12 / 238 (5.04%)	
occurrences (all)	24	12	
Anxiety			
subjects affected / exposed	31 / 472 (6.57%)	12 / 238 (5.04%)	
occurrences (all)	33	12	
Insomnia			
subjects affected / exposed	78 / 472 (16.53%)	39 / 238 (16.39%)	
occurrences (all)	104	49	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	95 / 472 (20.13%)	45 / 238 (18.91%)	
occurrences (all)	195	107	
Aspartate aminotransferase increased			
subjects affected / exposed	72 / 472 (15.25%)	29 / 238 (12.18%)	
occurrences (all)	141	41	
Ejection fraction decreased			
subjects affected / exposed	35 / 472 (7.42%)	15 / 238 (6.30%)	
occurrences (all)	43	15	
Haemoglobin decreased			
subjects affected / exposed	41 / 472 (8.69%)	8 / 238 (3.36%)	
occurrences (all)	85	11	
Neutrophil count decreased			
subjects affected / exposed	44 / 472 (9.32%)	23 / 238 (9.66%)	
occurrences (all)	124	48	
Weight increased			
subjects affected / exposed	19 / 472 (4.03%)	26 / 238 (10.92%)	
occurrences (all)	26	29	
Weight decreased			



subjects affected / exposed	99 / 472 (20.97%)	13 / 238 (5.46%)	
occurrences (all)	111	14	
White blood cell count decreased			
subjects affected / exposed	34 / 472 (7.20%)	14 / 238 (5.88%)	
occurrences (all)	103	34	
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	32 / 472 (6.78%)	10 / 238 (4.20%)	
occurrences (all)	36	13	
Nervous system disorders			
Dizziness			
subjects affected / exposed	74 / 472 (15.68%)	37 / 238 (15.55%)	
occurrences (all)	120	85	
Headache			
subjects affected / exposed	130 / 472 (27.54%)	70 / 238 (29.41%)	
occurrences (all)	311	149	
Dysgeusia			
subjects affected / exposed	59 / 472 (12.50%)	24 / 238 (10.08%)	
occurrences (all)	78	28	
Hypoaesthesia			
subjects affected / exposed	61 / 472 (12.92%)	36 / 238 (15.13%)	
occurrences (all)	94	53	
Neuropathy peripheral			
subjects affected / exposed	136 / 472 (28.81%)	58 / 238 (24.37%)	
occurrences (all)	211	78	
Neurotoxicity			
subjects affected / exposed	40 / 472 (8.47%)	24 / 238 (10.08%)	
occurrences (all)	49	37	
Paraesthesia			
subjects affected / exposed	35 / 472 (7.42%)	25 / 238 (10.50%)	
occurrences (all)	46	37	
Peripheral sensory neuropathy			
subjects affected / exposed	61 / 472 (12.92%)	37 / 238 (15.55%)	
occurrences (all)	82	42	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	143 / 472 (30.30%)	38 / 238 (15.97%)	
occurrences (all)	231	77	
Leukopenia			
subjects affected / exposed	71 / 472 (15.04%)	24 / 238 (10.08%)	
occurrences (all)	404	128	
Neutropenia			
subjects affected / exposed	177 / 472 (37.50%)	59 / 238 (24.79%)	
occurrences (all)	540	248	
Thrombocytopenia			
subjects affected / exposed	46 / 472 (9.75%)	6 / 238 (2.52%)	
occurrences (all)	65	7	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	55 / 472 (11.65%)	26 / 238 (10.92%)	
occurrences (all)	77	51	
Abdominal pain			
subjects affected / exposed	71 / 472 (15.04%)	29 / 238 (12.18%)	
occurrences (all)	116	40	
Aphthous ulcer			
subjects affected / exposed	25 / 472 (5.30%)	4 / 238 (1.68%)	
occurrences (all)	38	9	
Constipation			
subjects affected / exposed	101 / 472 (21.40%)	51 / 238 (21.43%)	
occurrences (all)	179	81	
Diarrhoea			
subjects affected / exposed	267 / 472 (56.57%)	112 / 238 (47.06%)	
occurrences (all)	760	300	
Dyspepsia			
subjects affected / exposed	50 / 472 (10.59%)	26 / 238 (10.92%)	
occurrences (all)	74	44	
Mouth ulceration			
subjects affected / exposed	60 / 472 (12.71%)	14 / 238 (5.88%)	
occurrences (all)	160	36	
Haemorrhoids			

subjects affected / exposed	32 / 472 (6.78%)	7 / 238 (2.94%)	
occurrences (all)	34	7	
Stomatitis			
subjects affected / exposed	315 / 472 (66.74%)	77 / 238 (32.35%)	
occurrences (all)	898	148	
Nausea			
subjects affected / exposed	154 / 472 (32.63%)	83 / 238 (34.87%)	
occurrences (all)	297	213	
Toothache			
subjects affected / exposed	35 / 472 (7.42%)	21 / 238 (8.82%)	
occurrences (all)	51	34	
Vomiting			
subjects affected / exposed	122 / 472 (25.85%)	55 / 238 (23.11%)	
occurrences (all)	223	111	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	29 / 472 (6.14%)	4 / 238 (1.68%)	
occurrences (all)	60	8	
Alopecia			
subjects affected / exposed	221 / 472 (46.82%)	125 / 238 (52.52%)	
occurrences (all)	240	129	
Dry skin			
subjects affected / exposed	37 / 472 (7.84%)	20 / 238 (8.40%)	
occurrences (all)	42	26	
Erythema			
subjects affected / exposed	49 / 472 (10.38%)	16 / 238 (6.72%)	
occurrences (all)	83	24	
Nail disorder			
subjects affected / exposed	68 / 472 (14.41%)	27 / 238 (11.34%)	
occurrences (all)	84	35	
Pruritus			
subjects affected / exposed	64 / 472 (13.56%)	24 / 238 (10.08%)	
occurrences (all)	103	35	
Rash			
subjects affected / exposed	191 / 472 (40.47%)	49 / 238 (20.59%)	
occurrences (all)	394	92	

Renal and urinary disorders			
Dysuria			
subjects affected / exposed	40 / 472 (8.47%)	9 / 238 (3.78%)	
occurrences (all)	48	10	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	80 / 472 (16.95%)	41 / 238 (17.23%)	
occurrences (all)	174	60	
Back pain			
subjects affected / exposed	72 / 472 (15.25%)	42 / 238 (17.65%)	
occurrences (all)	97	58	
Bone pain			
subjects affected / exposed	30 / 472 (6.36%)	14 / 238 (5.88%)	
occurrences (all)	39	15	
Musculoskeletal pain			
subjects affected / exposed	37 / 472 (7.84%)	17 / 238 (7.14%)	
occurrences (all)	56	19	
Muscle spasms			
subjects affected / exposed	33 / 472 (6.99%)	9 / 238 (3.78%)	
occurrences (all)	55	11	
Myalgia			
subjects affected / exposed	78 / 472 (16.53%)	45 / 238 (18.91%)	
occurrences (all)	150	102	
Pain in extremity			
subjects affected / exposed	86 / 472 (18.22%)	39 / 238 (16.39%)	
occurrences (all)	131	53	
Infections and infestations			
Cellulitis			
subjects affected / exposed	28 / 472 (5.93%)	8 / 238 (3.36%)	
occurrences (all)	37	11	
Nasopharyngitis			
subjects affected / exposed	90 / 472 (19.07%)	47 / 238 (19.75%)	
occurrences (all)	214	134	
Influenza			
subjects affected / exposed	36 / 472 (7.63%)	24 / 238 (10.08%)	
occurrences (all)	62	36	

Paronychia			
subjects affected / exposed	26 / 472 (5.51%)	8 / 238 (3.36%)	
occurrences (all)	45	8	
Pharyngitis			
subjects affected / exposed	25 / 472 (5.30%)	5 / 238 (2.10%)	
occurrences (all)	29	5	
Pneumonia			
subjects affected / exposed	33 / 472 (6.99%)	10 / 238 (4.20%)	
occurrences (all)	37	11	
Upper respiratory tract infection			
subjects affected / exposed	67 / 472 (14.19%)	34 / 238 (14.29%)	
occurrences (all)	128	50	
Rhinitis			
subjects affected / exposed	30 / 472 (6.36%)	14 / 238 (5.88%)	
occurrences (all)	48	19	
Urinary tract infection			
subjects affected / exposed	56 / 472 (11.86%)	17 / 238 (7.14%)	
occurrences (all)	107	28	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	110 / 472 (23.31%)	36 / 238 (15.13%)	
occurrences (all)	170	69	
Hypercholesterolaemia			
subjects affected / exposed	88 / 472 (18.64%)	23 / 238 (9.66%)	
occurrences (all)	128	31	
Hyperglycaemia			
subjects affected / exposed	58 / 472 (12.29%)	13 / 238 (5.46%)	
occurrences (all)	88	27	
Hypertriglyceridaemia			
subjects affected / exposed	68 / 472 (14.41%)	17 / 238 (7.14%)	
occurrences (all)	130	32	
Hypocalcaemia			
subjects affected / exposed	24 / 472 (5.08%)	4 / 238 (1.68%)	
occurrences (all)	34	6	
Hypokalaemia			

subjects affected / exposed	68 / 472 (14.41%)	9 / 238 (3.78%)	
occurrences (all)	134	13	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2009	<p>In the original protocol, primary efficacy endpoint was based on independent central review of radiology data. In protocol amendment 1, the primary efficacy endpoint was changed to progression-free survival (PFS) assessed using local radiological assessment. The other changes introduced in amendment 1 were: Information on mTOR mechanism of action, safety &amp; PK was updated based on the latest published data &amp; updated everolimus Investigator Brochure Version 8. Management of hyperglycemia was updated as per the most recent everolimus Core Data Sheet Version 1.3, dated 22-Oct-2009. Guidance on the usage of CYP3A4 and/or P-glycoprotein (P-gp) inducers &amp; inhibitors was modified to be consistent with Internal Clinical Pharmacology Drug-Drug interaction memo, which was updated 02-Dec-2009; Inclusion criterion #8 was updated with clarification that in the metastatic setting the discontinuation of endocrine therapy before randomization should be due to disease progression. Exclusion criteria #16 was updated with notes explaining 3rd space fluid accumulation. - Guidelines regarding the management of hepatitis B virus and hepatitis C virus infections were added; Modification of neutropenia dose adjustment guidelines, allowing reintroduction at the same dose level if improvement occurs within 7 days; Exploratory PK analyses was added to explore exposure-response relationships between selected efficacy end points/safety parameters/biomarkers &amp; everolimus exposure (C<sub>min</sub> and C<sub>2h</sub>); Mandate for the IDMC to review PK data was removed. Therefore, ongoing PK data were not be submitted to the IDMC unless specifically requested; Everolimus was now to be administered after meals in clinical studies. This approach had been approved as the global strategy within the everolimus program to achieve consistency between clinical studies; Administrative and typographical revisions were made.</p>
31 December 2012	<p>This amendment, implemented prior to the planned interim analysis, replaced 514 with 420 events required for the final PFS analysis. It was noted that a higher percentage of patients than anticipated discontinued the study prior to a PFS event &amp; it was highly unlikely that originally targeted events required to perform the final analysis would be observed. Based on number &amp; timing of deaths observed, it was projected that the 434 OS events would not be reached prior to end of 2016. Due to longer time interval between the interim/final PFS analysis &amp; final OS analysis, an additional OS interim analysis was added, to be performed after observing approximately 329 (75% information fraction) deaths. As a result of adding an additional OS interim analysis &amp; to maintain the 80% power to detect HR of 0.75 as was originally planned, final number of OS events was revised to 438 from 434. Protocol Synopsis, primary &amp; key secondary efficacy analysis section including sample size &amp; statistical power sections were revised. List of pre-specified subgroups assessing consistency of the efficacy results was updated based on emerging data in the treatment of HER2 positive breast cancer patients &amp; also efficacy of everolimus in ER+ patients based on another study data. Additional safety updates: re-definition of hepatitis C reactivation &amp; AST/ALT dose adjustment guidelines were updated to be consistent with current safety recommendations with everolimus use; language emphasizing the risk of infection specifically pulmonary infection &amp; sepsis; language outlining reproductive toxicity &amp; use of everolimus with guidelines for contraceptive use &amp; pregnancy follow-up; a clarification was added to confirm SAE data was to be collected in the safety database, not clinical database for screen failure patients who signed the ICF. Other administrative changes were added, including updates on SSC membership, TRIO &amp; Novartis Project Teams, change of CIRG's name to TRIO &amp; editorial clarifications.</p>

26 March 2014	The primary purpose of this amendment was to add a second primary objective to evaluate PFS in the HR-negative subpopulation in addition to the full study population. Similarly OS and all other secondary objectives would be evaluated in HR-negative subpopulation in addition to the full study population. This amendment was supported by emerging pre-clinical and emerging scientific data from randomized Phase III studies of everolimus; and recent data from clinical studies using novel HER2 targeted therapies. The multiplicity arising from two tests performed to address two primary objectives was controlled via use of a weighted Hochberg procedure. Additional changes were: The protocol was updated with recent available clinical data from everolimus studies; data on HER2 targeted therapies in HR negative patients; and the number of patients with various malignancies exposed to everolimus; Sample size and statistical power; statistical hypothesis, model, and method of analysis; interim analysis for PFS and OS; and recording and processing of data were updated to address implications for the HR-negative subpopulation; Sections on schedule of assessments and disease-related events/outcomes were updated for consistency. Safety assessments were updated to clarify routine monitoring of vital signs; Administrative and typographical revisions were made.
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Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Of the 480 patients enrolled in the Everolimus arm, 8 were untreated and in the Placebo arm, of the 239 patients enrolled, 1 was untreated.

Notes: