Clinical trial results:
Randomized phase II study of BEZ235 or everolimus in advanced pancreatic neuroendocrine tumors.

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	2012-000769-19
Trial protocol	ES GB IT FR NL PL
Global end of trial date	17 September 2014

Results information

Result version number	v1 (current)
This version publication date	07 July 2018
First version publication date	07 July 2018

Trial information

Trial identification

Sponsor protocol code	CBEZ235Z2401

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01628913
WHO universal trial number (UTN)	-

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,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	19 August 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 September 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the treatment effect of BEZ235 relative to everolimus on progression free survival (PFS) in patients with advanced pNET who have not been previously treated with an mTOR inhibitor.

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	26 October 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	France: 8
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	United States: 11
Worldwide total number of subjects	62
EEA total number of subjects	49

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)	45
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients were assigned to one of the following 2 treatment arms in a ratio of 1:1: BEZ235 (investigational arm) or everolimus (control arm)

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	BEZ235

Arm description:

Patients received BEZ235 400 mg bid p.o. (by mouth, twice daily)

Arm type	Experimental
Investigational medicinal product name	BEZ235
Investigational medicinal product code	BEZ235
Other name	
Pharmaceutical forms	Granules in sachet
Routes of administration	Oral use

Dosage and administration details:

Patients received BEZ235 400 mg bid p.o. (by mouth, twice daily)

Arm title	Everolimus

Arm description:

Patients received Everolimus 10 mg qd p.o. (by mouth, daily)

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

Dosage and administration details:

Patients received Everolimus 10 mg qd p.o. (by mouth, daily)

Number of subjects in period 1	BEZ235	Everolimus
Started	31	31
Completed	0	0
Not completed	31	31
Adverse event, serious fatal	1	-
Consent withdrawn by subject	1	-

Physician decision	1	3
study terminated by Sponsor	4	9
Adverse event, non-fatal	12	5
Disease Progression	11	14
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	BEZ235
Reporting group description:	
Patients received BEZ235 400 mg bid p.o. (by mouth, twice daily)	
Reporting group title	Everolimus
Reporting group description:	
Patients received Everolimus 10 mg qd p.o. (by mouth, daily)	

Reporting group values	BEZ235	Everolimus	Total
Number of subjects	31	31	62
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	25	20	45
From 65-84 years	6	11	17
85 years and over	0	0	0
Age Continuous | Units: Years			
arithmetic mean	56.3	57.8	
standard deviation	± 12.43	± 11.85	-
Gender, Male/Female Units: participants			
Female	14	16	30
Male	17	15	32

End points

End points reporting groups

Reporting group title	BEZ235
Reporting group description:	
Patients received BEZ235 400 mg bid p.o. (by mouth, twice daily)	
Reporting group title	Everolimus
Reporting group description:	
Patients received Everolimus 10 mg qd p.o. (by mouth, daily)	

Primary: Progression free survival (PFS)

End point title	Progression free survival (PFS)[1]

End point description:

PFS is defined as the time from the date of randomization until the date of the first radiologically documented disease progression or death due to any cause. PFS is based on local investigator assessment. Patients will be followed up for the duration of the study and for an expected average of every 12 weeks after randomization. Progression is defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0), as a 20% increase in the sum of the longest diameter of all target lesions, or unequivocal progression of non-target lesions, or the appearance of new lesions. In the data table, 99999.9 represents “not applicable” data and used as place holder to avoid system error because EudraCT system is not accepting "NA" for not available/not applicable data.

End point type	Primary

End point timeframe:

up to approx. 18 months

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: No statistical Analyses have been specified as the trial was terminated based on an interim analysis.

End point values	BEZ235	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	31		
Units: Months				
median (confidence interval 95%)	8.2 (5.3 to 999.99)	10.8 (8.1 to 999.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

End point title	Objective response rate

End point description:

Proportion of patients with a best overall response during the study of complete response (CR) or partial response (PR), based on the investigator assessment. 2. Per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0) for all target and non-target lesions, as well as new lesions as assessed by CT or MRI: Complete Response (CR), Disappearance of all target and non-target lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of all target lesions; Overall Response (OR) = CR + PR.

End point type	Secondary

End point timeframe:

up to approx. 18 months

End point values	BEZ235	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Patients				

Notes:

[2] - Trial was terminated based on an interim analysis.

[3] - Trial was terminated based on an interim analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Time from randomization to the date of death due to any cause

End point type	Secondary

End point timeframe:

up to approx. 30 months

End point values	BEZ235	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: Participants				

Notes:

[4] - Trial was terminated based on an interim analysis.

[5] - Trial was terminated based on an interim analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to treatment failure (TTF)

End point title	Time to treatment failure (TTF)

End point description:

Time from randomization to the date of the first of the following events:death due to any cause or progressive disease, treatment discontinuation due to toxicity or treatment discontinuation due to patient preference

End point type	Secondary

End point timeframe:

up to approx. 18 months

End point values	BEZ235	Everolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: Time				

Notes:

[6] - Trial was terminated based on an interim analysis.

[7] - Trial was terminated based on an interim analysis.

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 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

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Everolimus

Reporting group description:

Patients received Everolimus 10 mg qd p.o. (by mouth, daily)

Reporting group title	BEZ235

Reporting group description:

Patients received BEZ235 400 mg bid p.o. (by mouth, twice daily)

Serious adverse events	Everolimus	BEZ235	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 31 (29.03%)	11 / 31 (35.48%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma stage III			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			

subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery aneurysm			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 31 (3.23%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			

subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 31 (0.00%)	3 / 31 (9.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephritis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Adrenal insufficiency			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cushing's syndrome			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Escherichia sepsis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (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	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Hypercalcaemia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Everolimus	BEZ235	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 31 (96.77%)	31 / 31 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 31 (6.45%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
General disorders and administration site conditions			
Face oedema			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	3	0	
Asthenia			
subjects affected / exposed	13 / 31 (41.94%)	13 / 31 (41.94%)	
occurrences (all)	28	24	
Non-cardiac chest pain			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Mucosal inflammation			
subjects affected / exposed	3 / 31 (9.68%)	1 / 31 (3.23%)	
occurrences (all)	3	1	

Influenza like illness			
subjects affected / exposed	2 / 31 (6.45%)	3 / 31 (9.68%)	
occurrences (all)	2	3	
Oedema peripheral			
subjects affected / exposed	11 / 31 (35.48%)	6 / 31 (19.35%)	
occurrences (all)	13	7	
Fatigue			
subjects affected / exposed	10 / 31 (32.26%)	7 / 31 (22.58%)	
occurrences (all)	12	11	
Pyrexia			
subjects affected / exposed	4 / 31 (12.90%)	9 / 31 (29.03%)	
occurrences (all)	6	11	
Xerosis			
subjects affected / exposed	3 / 31 (9.68%)	0 / 31 (0.00%)	
occurrences (all)	4	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 31 (25.81%)	3 / 31 (9.68%)	
occurrences (all)	12	4	
Dyspnoea			
subjects affected / exposed	5 / 31 (16.13%)	1 / 31 (3.23%)	
occurrences (all)	8	1	
Epistaxis			
subjects affected / exposed	5 / 31 (16.13%)	4 / 31 (12.90%)	
occurrences (all)	5	4	
Nasal inflammation			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	3	
Pneumonitis			
subjects affected / exposed	4 / 31 (12.90%)	0 / 31 (0.00%)	
occurrences (all)	4	0	
Productive cough			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			

Depression			
subjects affected / exposed	2 / 31 (6.45%)	3 / 31 (9.68%)	
occurrences (all)	2	3	
Insomnia			
subjects affected / exposed	3 / 31 (9.68%)	1 / 31 (3.23%)	
occurrences (all)	3	1	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 31 (6.45%)	4 / 31 (12.90%)	
occurrences (all)	2	7	
Alanine aminotransferase increased			
subjects affected / exposed	3 / 31 (9.68%)	5 / 31 (16.13%)	
occurrences (all)	3	6	
Blood cholesterol increased			
subjects affected / exposed	4 / 31 (12.90%)	1 / 31 (3.23%)	
occurrences (all)	4	1	
Blood creatinine increased			
subjects affected / exposed	2 / 31 (6.45%)	6 / 31 (19.35%)	
occurrences (all)	2	8	
Cardiac murmur			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 31 (0.00%)	3 / 31 (9.68%)	
occurrences (all)	0	3	
Pancreatic enzymes decreased			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Weight decreased			
subjects affected / exposed	6 / 31 (19.35%)	4 / 31 (12.90%)	
occurrences (all)	6	5	
Platelet count decreased			
subjects affected / exposed	7 / 31 (22.58%)	0 / 31 (0.00%)	
occurrences (all)	9	0	
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 31 (3.23%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Dysgeusia			
subjects affected / exposed	3 / 31 (9.68%)	5 / 31 (16.13%)	
occurrences (all)	3	5	
Tremor			
subjects affected / exposed	1 / 31 (3.23%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Lethargy			
subjects affected / exposed	1 / 31 (3.23%)	2 / 31 (6.45%)	
occurrences (all)	1	3	
Headache			
subjects affected / exposed	7 / 31 (22.58%)	6 / 31 (19.35%)	
occurrences (all)	13	6	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 31 (35.48%)	8 / 31 (25.81%)	
occurrences (all)	14	15	
Leukocytosis			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Neutropenia			
subjects affected / exposed	2 / 31 (6.45%)	2 / 31 (6.45%)	
occurrences (all)	8	2	
Thrombocytopenia			
subjects affected / exposed	4 / 31 (12.90%)	2 / 31 (6.45%)	
occurrences (all)	5	2	
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	3 / 31 (9.68%)	1 / 31 (3.23%)	
occurrences (all)	4	1	
Cheilitis			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Abdominal pain upper			
subjects affected / exposed	5 / 31 (16.13%)	5 / 31 (16.13%)	
occurrences (all)	8	8	
Abdominal pain			
subjects affected / exposed	8 / 31 (25.81%)	12 / 31 (38.71%)	
occurrences (all)	11	16	
Constipation			
subjects affected / exposed	5 / 31 (16.13%)	4 / 31 (12.90%)	
occurrences (all)	8	4	
Diarrhoea			
subjects affected / exposed	17 / 31 (54.84%)	28 / 31 (90.32%)	
occurrences (all)	36	64	
Dry mouth			
subjects affected / exposed	4 / 31 (12.90%)	0 / 31 (0.00%)	
occurrences (all)	4	0	
Dyspepsia			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Dysphagia			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Flatulence			
subjects affected / exposed	2 / 31 (6.45%)	4 / 31 (12.90%)	
occurrences (all)	2	4	
Haemorrhoids			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Mouth ulceration			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	4	0	

Nausea			
subjects affected / exposed	10 / 31 (32.26%)	17 / 31 (54.84%)	
occurrences (all)	15	28	
Oesophagitis			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Proctitis			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Proctalgia			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Rectal haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	3	
Stomatitis			
subjects affected / exposed	20 / 31 (64.52%)	23 / 31 (74.19%)	
occurrences (all)	35	34	
Vomiting			
subjects affected / exposed	7 / 31 (22.58%)	14 / 31 (45.16%)	
occurrences (all)	16	20	
Toothache			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 31 (3.23%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Acne			
subjects affected / exposed	2 / 31 (6.45%)	1 / 31 (3.23%)	
occurrences (all)	2	1	
Dry skin			
subjects affected / exposed	8 / 31 (25.81%)	0 / 31 (0.00%)	
occurrences (all)	10	0	
Eczema			

subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	5	0	
Erythema			
subjects affected / exposed	4 / 31 (12.90%)	2 / 31 (6.45%)	
occurrences (all)	5	2	
Onychoclasis			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Pruritus			
subjects affected / exposed	2 / 31 (6.45%)	6 / 31 (19.35%)	
occurrences (all)	5	7	
Rash			
subjects affected / exposed	13 / 31 (41.94%)	11 / 31 (35.48%)	
occurrences (all)	16	17	
Skin exfoliation			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Rash maculo-papular			
subjects affected / exposed	2 / 31 (6.45%)	1 / 31 (3.23%)	
occurrences (all)	3	1	
Rash pruritic			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	3	
Skin lesion			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 31 (3.23%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Proteinuria			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	4 / 31 (12.90%)	3 / 31 (9.68%)	
occurrences (all)	5	3	
Back pain			
subjects affected / exposed	2 / 31 (6.45%)	4 / 31 (12.90%)	
occurrences (all)	2	4	
Musculoskeletal pain			
subjects affected / exposed	1 / 31 (3.23%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Myalgia			
subjects affected / exposed	1 / 31 (3.23%)	3 / 31 (9.68%)	
occurrences (all)	1	3	
Pain in extremity			
subjects affected / exposed	3 / 31 (9.68%)	3 / 31 (9.68%)	
occurrences (all)	3	5	
Pain in jaw			
subjects affected / exposed	2 / 31 (6.45%)	1 / 31 (3.23%)	
occurrences (all)	2	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 31 (16.13%)	2 / 31 (6.45%)	
occurrences (all)	5	2	
Conjunctivitis			
subjects affected / exposed	2 / 31 (6.45%)	1 / 31 (3.23%)	
occurrences (all)	3	1	
Oral herpes			
subjects affected / exposed	2 / 31 (6.45%)	0 / 31 (0.00%)	
occurrences (all)	3	0	
Tooth infection			
subjects affected / exposed	4 / 31 (12.90%)	0 / 31 (0.00%)	
occurrences (all)	4	0	
Upper respiratory tract infection			
subjects affected / exposed	3 / 31 (9.68%)	3 / 31 (9.68%)	
occurrences (all)	3	3	
Urinary tract infection			

subjects affected / exposed	0 / 31 (0.00%)	3 / 31 (9.68%)	
occurrences (all)	0	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	13 / 31 (41.94%)	9 / 31 (29.03%)	
occurrences (all)	16	11	
Hypercholesterolaemia			
subjects affected / exposed	4 / 31 (12.90%)	0 / 31 (0.00%)	
occurrences (all)	6	0	
Hyperglycaemia			
subjects affected / exposed	11 / 31 (35.48%)	9 / 31 (29.03%)	
occurrences (all)	12	10	
Hyponatraemia			
subjects affected / exposed	1 / 31 (3.23%)	2 / 31 (6.45%)	
occurrences (all)	1	2	
Hypokalaemia			
subjects affected / exposed	2 / 31 (6.45%)	1 / 31 (3.23%)	
occurrences (all)	3	1	
Hypertriglyceridaemia			
subjects affected / exposed	5 / 31 (16.13%)	0 / 31 (0.00%)	
occurrences (all)	5	0	
Hypophosphataemia			
subjects affected / exposed	2 / 31 (6.45%)	1 / 31 (3.23%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 February 2014	Number of patients was revised to reflect the total number of patients enrolled at the time of the halt of enrollment, and updated the time point for the main (safety and efficacy) analysis to be performed. Following an unplanned, preliminary assessment of the first randomized patients further enrollment into the study was terminated on 20-Sep-2013 with a last patient randomized on 29-Oct-2013. They were followed per protocol for approximately 6 months after the last patient started the study treatment and that the new cut-off date for the final (safety and efficacy) analysis was performed approximately 6 months after the last patient had started study treatment. The statistical considerations section was updated as the initially planned efficacy criteria would not be met. Laboratory evaluation and cardiac assessments were updated to reflect that not all tests were collected post approximately 6 months after the last patient had started study treatment.

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.

Trial terminated based on the results of a pre-planned interim analysis of the primary OM (which demonstrated BEX235 not having improved PFS (progression free survival) vs everolimus). The secondary OM analyses were not conducted.

Notes: