Clinical trial results:
A multicenter, two stage, Phase II study, evaluating the efficacy of oral BEZ235 plus best supportive care (BSC) versus placebo plus BSC in the treatment of patients with advanced pancreatic neuroendocrine tumors (pNET) after failure of mTOR inhibitor therapy

Summary

EudraCT number	2012-000675-16
Trial protocol	AT GB NL DE IT BE ES
Global end of trial date	03 July 2015

Results information

Result version number	v1 (current)
This version publication date	16 June 2016
First version publication date	16 June 2016

Trial information

Trial identification

Sponsor protocol code	CBEZ235F2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01658436
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 Pharmaceuticals, 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	03 July 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the efficacy of BEZ235 in adult patients with advanced (unresectable or metastatic) pNET by means of Progression free survival (PFS) rate at 16 weeks according to local radiological assessment per modified response evaluation criteria in solid tumor (RECIST 1.1)).

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	21 November 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	Austria: 1
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	31
EEA total number of subjects	27

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	19
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a Phase II, two-stage, multicenter study, where Stage 1 was a singlearm,open label design and Stage 2 was planned to be a randomized, double-blind study.
However, at the end of Stage 1, the futility was met and hence the Stage 2 was not initiated.

Pre-assignment

Screening details:

Initially , the patients were started at BEZ235 400mg bid dose regimen. The preliminary safety & tolerability data fro first 3 patients treated at this dose showed all patients reported AEs leading to dose interruption. It was decided to decrease the dose of BEZ235 to 300mg bid dose regimen.

Period 1

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

Arms

Arm title	BEZ235 300 mg/400 mg bid

Arm description:

Oral BEZ235 300 mg bid was investigated in stage 1 of study

Arm type	Experimental
Investigational medicinal product name	BEZ235
Investigational medicinal product code	BEZ235
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

BEZ235 was provided in sachets of 50mg, 200mg, 300mg & 400mg for oral use.

Number of subjects in period 1	BEZ235 300 mg/400 mg bid
Started	31
Completed	0
Not completed	31
Adverse event, serious fatal	1
Physician decision	1
Adverse event, non-fatal	11
Study terminated by sponsor	1
Progressive disease	16
Subject/guardian decision	1

Baseline characteristics

Reporting groups	
Reporting group title	BEZ235 300 mg/400 mg bid
Reporting group description:	
Oral BEZ235 300 mg bid was investigated in stage 1 of study	

Reporting group values	BEZ235 300 mg/400 mg bid	Total	
Number of subjects	31	31	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	19	19	
From 65-84 years	12	12	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	60.1		
standard deviation	± 11.4	-	
Gender, Male/Female Units: Participants			
Female	18	18	
Male	13	13	

End points

End points reporting groups

Reporting group title	BEZ235 300 mg/400 mg bid
Reporting group description:	
Oral BEZ235 300 mg bid was investigated in stage 1 of study	

Primary: Stage 1 -Progression Free Survival (PFS) rate analysis at 16 weeks as per local radiology review

End point title	Stage 1 -Progression Free Survival (PFS) rate analysis at 16 weeks as per local radiology review[1]
End point description:	
PFS rate at 16 weeks was defined as a binary variable. Patients were considered as 'progression free' after 16 weeks if they had an overall lesion response of complete response (CR) partial response ('PR) or stable disease (SD)' and "progressed" if they had an overall lesion response of 'Progressive disease (PD) at the scan which occurred on day 105 after start of treatment, or later. Patients whose 16 weeks tumor assessment was unknown, missing or outside the window was not considered as 'progression free' and was considered a "failure" and counted only in the denominator for the estimation of the 16 week progression free rate. No statistical analysis was planned for this primary outcome.	
End point type	Primary
End point timeframe:	
16 weeks after the first BEZ235 administration.	

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 analysis was planned for this primary outcome.

End point values	BEZ235 300 mg/400 mg bid			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Percentage of participants				
number (confidence interval 95%)	51.6 (35.7 to 67.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 1 - Disease Control rate

End point title	Stage 1 - Disease Control rate
End point description:	
Disease control rate was defined as the proportion of patients with a best overall response of Complete Response, Partial response, or Stable disease, based on the investigator's assessment per RECIST version 1.1. Based on futility analysis conducted at the end of stage 1, stage 2 was not initiated.	
End point type	Secondary
End point timeframe:	
Baseline, every 8 weeks up to 31 months	

End point values	BEZ235 300 mg/400 mg bid			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Percentage of participants				
number (confidence interval 95%)	71 (54.8 to 83.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 1- Overall Response Rate (ORR)

End point title	Stage 1- Overall Response Rate (ORR)

End point description:

Overall Response rate was defined as the proportion of patients with a best overall response of complete response or partial response, based on investigator's assessment as per RECIST criteria version 1.1. Based on futility analysis conducted at the end of stage 1, stage 2 was not initiated.

End point type	Secondary

End point timeframe:

Baseline, every 8 weeks up to 31 months

End point values	BEZ235 300 mg/400 mg bid			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: Percentage of participants				
number (not applicable)				
Complete response	0			
Partial response	0			

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 L:ast 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	18.0

Reporting groups

Reporting group title	BEZ235 300 mg bid

Reporting group description:

BEZ235 300 mg bid

Reporting group title	BEZ235 400 mg bid

Reporting group description:

BEZ235 400 mg bid

Serious adverse events	BEZ235 300 mg bid	BEZ235 400 mg bid	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 20 (40.00%)	5 / 11 (45.45%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
CARDIAC ARREST			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
LEFT VENTRICULAR HYPERTROPHY			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYSTOLIC DYSFUNCTION			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
SPINAL CORD COMPRESSION			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (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			
PYREXIA			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (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 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLESTASIS			

subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC PAIN			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
SPINAL COLUMN STENOSIS			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ERYSIPELAS			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (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			
HYPONATRAEMIA			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (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	BEZ235 300 mg bid	BEZ235 400 mg bid	
Total subjects affected by non-serious adverse events subjects affected / exposed	20 / 20 (100.00%)	11 / 11 (100.00%)	
Vascular disorders			
FLUSHING			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
HOT FLUSH			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
HYPERTENSION			
subjects affected / exposed	3 / 20 (15.00%)	0 / 11 (0.00%)	
occurrences (all)	5	0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	4 / 20 (20.00%)	3 / 11 (27.27%)	
occurrences (all)	4	6	
FACE OEDEMA			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
FATIGUE			
subjects affected / exposed	7 / 20 (35.00%)	3 / 11 (27.27%)	
occurrences (all)	10	4	
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	1 / 20 (5.00%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
OEDEMA			

subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
OEDEMA PERIPHERAL			
subjects affected / exposed	4 / 20 (20.00%)	3 / 11 (27.27%)	
occurrences (all)	9	3	
PAIN			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
PYREXIA			
subjects affected / exposed	4 / 20 (20.00%)	1 / 11 (9.09%)	
occurrences (all)	8	1	
Immune system disorders			
HYPERSENSITIVITY			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
Reproductive system and breast disorders			
BENIGN PROSTATIC HYPERPLASIA			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
SCROTAL PAIN			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
VAGINAL DISCHARGE			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
VULVOVAGINAL DRYNESS			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
CATARRH			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
DYSPNOEA			
subjects affected / exposed	6 / 20 (30.00%)	1 / 11 (9.09%)	
occurrences (all)	7	1	
EPISTAXIS			

subjects affected / exposed	1 / 20 (5.00%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
HICCUPS			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
NASAL CONGESTION			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
OROPHARYNGEAL PAIN			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
RHINORRHOEA			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
SNEEZING			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
THROAT IRRITATION			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Psychiatric disorders			
AGITATION			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
DEPRESSED MOOD			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
DEPRESSION			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
HALLUCINATION			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
INSOMNIA			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	

Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	4	
BLOOD CHLORIDE DECREASED			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
BLOOD CREATININE INCREASED			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	3	
BLOOD IRON DECREASED			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
BLOOD LACTATE DEHYDROGENASE INCREASED			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
BLOOD POTASSIUM INCREASED			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
EJECTION FRACTION DECREASED			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	

ELECTROCARDIOGRAM QT PROLONGED			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	3 / 20 (15.00%)	2 / 11 (18.18%)	
occurrences (all)	3	2	
HEPATIC ENZYME INCREASED			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
LIVER FUNCTION TEST ABNORMAL			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
NEUTROPHIL COUNT INCREASED			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
PLATELET COUNT DECREASED			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
WEIGHT DECREASED			
subjects affected / exposed	2 / 20 (10.00%)	2 / 11 (18.18%)	
occurrences (all)	2	2	
WHITE BLOOD CELLS URINE			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
CONTRAST MEDIA REACTION			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
SPINAL COMPRESSION FRACTURE			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	

CARDIAC FAILURE			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
PALPITATIONS			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
DYSGEUSIA			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
HEADACHE			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
LETHARGY			
subjects affected / exposed	0 / 20 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	3	
LOSS OF CONSCIOUSNESS			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
MIGRAINE			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
PARAESTHESIA			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
TREMOR			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
LYMPHOPENIA			

subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
NEUTROPENIA			
subjects affected / exposed	0 / 20 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	4	
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
ABDOMINAL PAIN			
subjects affected / exposed	6 / 20 (30.00%)	2 / 11 (18.18%)	
occurrences (all)	8	2	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	2 / 20 (10.00%)	4 / 11 (36.36%)	
occurrences (all)	4	4	
ANAL FISSURE			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
ASCITES			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
CHEILITIS			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
CONSTIPATION			
subjects affected / exposed	4 / 20 (20.00%)	1 / 11 (9.09%)	
occurrences (all)	4	1	
DIARRHOEA			

subjects affected / exposed	16 / 20 (80.00%)	6 / 11 (54.55%)	
occurrences (all)	26	10	
DRY MOUTH			
subjects affected / exposed	2 / 20 (10.00%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
DYSPEPSIA			
subjects affected / exposed	2 / 20 (10.00%)	2 / 11 (18.18%)	
occurrences (all)	2	3	
GASTROINTESTINAL MOTILITY DISORDER			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
HAEMORRHOIDS			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
MELAENA			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
NAUSEA			
subjects affected / exposed	9 / 20 (45.00%)	6 / 11 (54.55%)	
occurrences (all)	16	9	
OESOPHAGITIS			
subjects affected / exposed	1 / 20 (5.00%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
PROCTALGIA			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
STOMATITIS			
subjects affected / exposed	6 / 20 (30.00%)	5 / 11 (45.45%)	
occurrences (all)	8	10	
TOOTH DISCOLOURATION			

subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
VOMITING			
subjects affected / exposed	6 / 20 (30.00%)	4 / 11 (36.36%)	
occurrences (all)	13	5	
Hepatobiliary disorders			
HEPATIC FUNCTION ABNORMAL			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
HEPATIC PAIN			
subjects affected / exposed	2 / 20 (10.00%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
HYPERTRANSAMINASAEMIA			
subjects affected / exposed	0 / 20 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
PORTAL VEIN THROMBOSIS			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
DRY SKIN			
subjects affected / exposed	3 / 20 (15.00%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
HAND DERMATITIS			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
HYPERHIDROSIS			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
NAIL DISORDER			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
NAIL TOXICITY			

subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
NIGHT SWEATS			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
PAIN OF SKIN			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
PHOTOSENSITIVITY REACTION			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
PRURITUS			
subjects affected / exposed	1 / 20 (5.00%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
RASH			
subjects affected / exposed	2 / 20 (10.00%)	3 / 11 (27.27%)	
occurrences (all)	2	3	
ROSACEA			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
SKIN FISSURES			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
DYSURIA			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
POLLAKIURIA			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			

ARTHRALGIA			
subjects affected / exposed	1 / 20 (5.00%)	3 / 11 (27.27%)	
occurrences (all)	1	3	
BACK PAIN			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
FLANK PAIN			
subjects affected / exposed	3 / 20 (15.00%)	0 / 11 (0.00%)	
occurrences (all)	5	0	
JOINT SWELLING			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
MUSCLE ATROPHY			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
MUSCLE SPASMS			
subjects affected / exposed	2 / 20 (10.00%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
MUSCULAR WEAKNESS			
subjects affected / exposed	1 / 20 (5.00%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	3 / 20 (15.00%)	1 / 11 (9.09%)	
occurrences (all)	4	1	
MYALGIA			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
NECK PAIN			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	

Infections and infestations			
BRONCHITIS			
subjects affected / exposed	2 / 20 (10.00%)	0 / 11 (0.00%)	
occurrences (all)	4	0	
CONJUNCTIVITIS			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
FOLLICULITIS			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
GASTROINTESTINAL INFECTION			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
GINGIVITIS			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
INFLUENZA			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
NASOPHARYNGITIS			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	2	0	
ORAL CANDIDIASIS			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
ORAL HERPES			
subjects affected / exposed	1 / 20 (5.00%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
PARONYCHIA			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
PHARYNGITIS			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
RHINITIS			

subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
SUBCUTANEOUS ABSCESS			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
VULVOVAGINAL CANDIDIASIS			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	6 / 20 (30.00%)	2 / 11 (18.18%)	
occurrences (all)	11	2	
HYPERCALCAEMIA			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
HYPERCHOLESTEROLAEMIA			
subjects affected / exposed	0 / 20 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
HYPERGLYCAEMIA			
subjects affected / exposed	7 / 20 (35.00%)	4 / 11 (36.36%)	
occurrences (all)	10	11	
HYPERKALAEMIA			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
HYPOGLYCAEMIA			
subjects affected / exposed	2 / 20 (10.00%)	1 / 11 (9.09%)	
occurrences (all)	4	2	
HYPONATRAEMIA			
subjects affected / exposed	1 / 20 (5.00%)	0 / 11 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 January 2013	The purpose of this amendment is to decrease the starting Dose of BEZ235 from 400 mg to 300 mg bid, clarify some of the eligibility criteria to better characterize the Study population, revise the management guidelines of stomatitis and rash, update one criterion for premature patient withdrawal and correct typographical errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported