Clinical trial results:
A dose-finding phase Ib study followed by an open-label, randomized phase II study of BEZ235 plus paclitaxel in patients with HER2 negative, inoperable locally advanced or metastatic breast cancer

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	2011-002400-32
Trial protocol	FR ES
Global end of trial date	19 May 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	CBEZ235B2101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01495247
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Novartis Pharmaceuticals AG, Novartis Pharmaceuticals 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 May 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 May 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This was a Phase Ib/II study and each phase had a prmary objective:

Phase Ib: To determine the MTD and/or RP2D of oral twice daily (bid) BEZ235 in combinationwith weekly (qw) paclitaxel in patients with in HER2 negative metastatic or inoperable, locally advanced breast cancer.

Phase II: To estimate the treatment effect of BEZ235/ paclitaxel combination therapy versus paclitaxel alone in HER2-patients with first line metastatic or inoperable locally advanced breast cancer.

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. The MTD was defined as the highest dose of BEZ235 and paclitaxel not causing pre-defined, medically unacceptable, dose-limiting toxicity in more than 35% of patients treated during the first cycle of treatment. The starting BEZ235 dose and paclitaxel dose in the current study met the overdose control requirements. It was recommended that patients use drugs that do not cause QT prolongation. Some anti-emetics were prohibited due to interaction with CYP3A. Patients were instructed to treat diarrhea at its earliest occurrence. Appropriate anti-emetic treatment was recommended, including prophylaxis. Proactive approach to managing skin reactions was encouraged. Patients were informed about the possibility of developing mouth ulcers/ oral mucositis and educated about good oral hygiene. Patients were also instructed about potential effect on glucuse homeostasis and this was monitored.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 January 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	Spain: 8
Country: Number of subjects enrolled	France: 10
Worldwide total number of subjects	18
EEA total number of subjects	18

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)	16
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Fifteen to 30 patients were planned for Phase Ib; 18 patients were enrolled and analyzed. Based on DLT, the study did not meet the Phase Ib primary objective to establish MTD/RP2D of BEZ235 with paclitaxel and was terminated. The Phase II part of the study was not conducted.

Period 1

Period 1 title	Phase 1b-Treatment and Evaluation Phases (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	BEZ235 100 mg bid + P80

Arm description:

As 200 mg bid did not meet overdose criteria, patients in this arm were treated with BEZ235 100 mg bid plus paclitaxel. BEZ235 was administered orally as a continuous daily dose of 100 mg bid and a fiixed dose of paclitaxel (80 mg/m2 qw per 28 day cycle).

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

Dosage and administration details:

BEZ235 was administered orally on a continuous bid dosing schedule. Patients were dosed on a flat scale of mg/day and the dose of the drug was not adjusted to body weight or body surface area.

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

Dosage and administration details:

Paclitaxel was administered at a weekly dose of 80 mg/m2 as a one-hour IV infusion after standard premedication. In each 28 day cycle, one week without paclitaxel administration was permitted if judged clinically appropriate by the Investigator.

Arm title	BEZ235 200 mg bid + P80

Arm description:

This was the first cohort treated. Patients were treated with BEZ235 200 mg bid plus paclitaxel. BEZ235 was administered orally as a continuous daily dose of 200 mg bid and a fiixed dose of paclitaxel (80 mg/m2 qw per 28 day cycle).

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

Dosage and administration details:

BEZ235 was administered orally on a continuous bid dosing schedule. Patients were dosed on a flat scale of mg/day and the dose of the drug was not adjusted to body weight or body surface area.

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

Dosage and administration details:

Paclitaxel was administered at a weekly dose of 80 mg/m2 as a one-hour IV infusion after standard premedication. In each 28 day cycle, one week without paclitaxel administration was permitted if judged clinically appropriate by the Investigator.

Number of subjects in period 1	BEZ235 100 mg bid + P80	BEZ235 200 mg bid + P80
Started	5	13
Completed	0	0
Not completed	5	13
Physician decision	-	1
Adverse event	2	3
Progressive disease	3	8
Subject/guardian decision	-	1

Baseline characteristics

Reporting groups	
Reporting group title	BEZ235 100 mg bid + P80
Reporting group description:	
As 200 mg bid did not meet overdose criteria, patients in this arm were treated with BEZ235 100 mg bid plus paclitaxel. BEZ235 was administered orally as a continuous daily dose of 100 mg bid and a fiixed dose of paclitaxel (80 mg/m2 qw per 28 day cycle).	
Reporting group title	BEZ235 200 mg bid + P80
Reporting group description:	
This was the first cohort treated. Patients were treated with BEZ235 200 mg bid plus paclitaxel. BEZ235 was administered orally as a continuous daily dose of 200 mg bid and a fiixed dose of paclitaxel (80 mg/m2 qw per 28 day cycle).	

Reporting group values	BEZ235 100 mg bid + P80	BEZ235 200 mg bid + P80	Total
Number of subjects	5	13	18
Age categorical			
Included full analysis set.			
Units: Subjects			
<65 years	5	11	16
≥ 65 years	0	2	2
Age continuous			
Included full analysis set.			
Units: years			
arithmetic mean	43	53.1	
standard deviation	± 8.03	± 11.77	-
Gender categorical			
The study only included patients that were female ≥ 18 years of age on the day of consenting to the study. Included full analysis set.			
Units: Subjects			
Female	5	13	18
Race			
Included full analysis set.			
Units: Subjects			
Caucasian	5	13	18
ECOG performance status			
ECOG=Eastern Cooperative Oncology Group. Included full analysis set.			
Units: Subjects			
ECOG 0	1	3	4
ECOG 1	4	10	14

End points

End points reporting groups

Reporting group title	BEZ235 100 mg bid + P80

Reporting group description:

As 200 mg bid did not meet overdose criteria, patients in this arm were treated with BEZ235 100 mg bid plus paclitaxel. BEZ235 was administered orally as a continuous daily dose of 100 mg bid and a fiixed dose of paclitaxel (80 mg/m2 qw per 28 day cycle).

Reporting group title	BEZ235 200 mg bid + P80

Reporting group description:

This was the first cohort treated. Patients were treated with BEZ235 200 mg bid plus paclitaxel. BEZ235 was administered orally as a continuous daily dose of 200 mg bid and a fiixed dose of paclitaxel (80 mg/m2 qw per 28 day cycle).

Primary: Summary of posterior distribution of DLT rates at end of study

End point title	Summary of posterior distribution of DLT rates at end of

End point description:

Based on the observed DLTs, the tested dose level (BEZ235 200 mg bid) did not meet the overdose control criterion as per the BLRM with a posterior probability of excessive toxicityof 39.3% (interval of interest [0.35, 1]). As the BLRM did not allow further enrollment at the BEZ235 200 mg bid + P80 dose level, five additional patients were enrolled and given reduced dose of BEZ235 100 mg bid in combination with weekly paclitaxel (80 mg/kg). This was performed on the dose-determining set.

End point type	Primary

End point timeframe:

First 28 days of treatment (first dose up to and including Cycle 1, Day 28)

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: An adaptive 5-parameter Bayesian logistic regression model guided by the escalation with overdose control principle guided the dose-escalation and determined the MTD/RP2D. The BLRM was fitted on the Cycle 1 DLT data accumulated throughout the dose-escalation phase to model the dose-toxicity relationship of paclitaxel and BEZ235. Therefore, only summary statistics as presented were provided for this endpoint.

End point values	BEZ235 100 mg bid + P80	BEZ235 200 mg bid + P80		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[2]	5[3]		
Units: Probability				
number (not applicable)				
Probability Pr(DLT) in interval 0.35-1	0.084	0.137		

Notes:

[2] - Posterior probability that that Pr(DLT) is in interval. Dose determining set.

[3] - Posterior probability that that Pr(DLT) is in interval. Dose determining set.

Statistical analyses

No statistical analyses for this end point

Primary: Dose limiting toxicities during the first 28 days of treatment by primary system organ class, preferred term

End point title	Dose limiting toxicities during the first 28 days of treatment by primary system organ class, preferred term[4]

End point description:

A DLT is defined as any treatment-related toxicities occurring up to and including Cycle 1 Day 28, and which are unrelated to disease, disease progression, intercurrent illness, and concomitant medications.

End point type	Primary

End point timeframe:

first 28 days of treatment

Notes:

[4] - 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: Only summary statistics as presented were provided for this primary endpoint.

End point values	BEZ235 100 mg bid + P80	BEZ235 200 mg bid + P80		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[5]	5[6]		
Units: Patients				
Blood and lymphatic system-neutropenia	1	2		
Gastrointestinal disorders-stomatitis	0	3		
Gastrointestinal disorders-nausea	0	2		
Gastrointestinal disorders-vomiting	0	1		

Notes:

[5] - Dose-determining set

[6] - Dose-determining set

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response as per Investigator, by dose level

End point title	Best overall response as per Investigator, by dose level

End point description:

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment depended on the achievement of both measurement and confirmation criteria. The primary analysis of the best overall response was based on the sequence of investigator/central blinded review/calculated (investigator)/calculated (central) overall lesion responses.

End point type	Secondary

End point timeframe:

from the start of the treatment until disease progression/recurrence

End point values	BEZ235 100 mg bid + P80	BEZ235 200 mg bid + P80		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[7]	13[8]		
Units: Patients				
Partial response (PR)	1	2		
Non-CR/Non-PD	0	2		
Stable disease (SD)	4	2		
Progressive disease (PD)	0	4		
Unknown (UNK)	0	3		

Notes:

[7] - Full analysis set

[8] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response and clinical benefit rate as per Investigator, by dose level

End point title	Overall response and clinical benefit rate as per Investigator, by dose level

End point description:

The Overall response rate is defined as (ORR:CR+PR). The clinical benefit rate is defined as (CBR: CR+PR+SD+Non-CR/Non- PD >24 weeks). The 95% CI for the frequency distribution of each variable were computed using Clopper-Pearson method if there were sufficient data.

End point type	Secondary

End point timeframe:

For ORR: best overall response during the study. For CBR, best overall response wit a duration of 24 weeks or longer.

End point values	BEZ235 100 mg bid + P80	BEZ235 200 mg bid + P80		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[9]	13[10]		
Units: Percentage				
number (confidence interval 95%)				
Overall response rate(ORR:CR+PR), n=1,2	20 (0.5 to 71.6)	15.4 (1.9 to 45.4)		
Clinical benefit rate (CBR), n=3, 3	60 (14.7 to 94.7)	23.1 (5 to 53.8)		

Notes:

[9] - Full analysis set.

[10] - Full analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Mean plasma concentrations of BEZ235, by dose level

End point title	Mean plasma concentrations of BEZ235, by dose level

End point description:

For BEZ235 pharmacokinetic characteristics (PK) in Phase Ib, the pre-dose PK sample were collected prior to the paclitaxel pre-medication/prior to any study treatment on the PK collection day and post-dose samples were to be taken 4-6 hours after the morning BEZ235. All analyses were based on plasma concentrations. The PK analysis set was used for these analyses. Only PK blood sample with date and time and for which the last prior dose dates and times were adequately recorded were included in the population PK analyses. EMA directed use of 999999 as the EU results system will not accept "not estimable".

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and 8, and Day 1 of Cycles 2, 3, 5, 7, 9, 11, 13, and 15

End point values	BEZ235 100 mg bid + P80	BEZ235 200 mg bid + P80		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[11]	13[12]		
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (0 hrs) n=5, 11	0 (± 0)	0 (± 0)		
Cycle 1 Day 1 (4-6 hrs) n=5,12	30.92 (± 13.325)	80.47 (± 55.264)		
Cycle 1 Day 8 (0 hrs) n=5, 11	57.68 (± 63.494)	509.66 (± 695.589)		
Cycle 1 Day 8 (4-6 hrs) n=5,11	111.5 (± 68.765)	575.1 (± 627.337)		
Cycle 2 Day 1 (0 hrs) n=4, 10	43.65 (± 41.018)	285.34 (± 425.588)		
Cycle 2 Day 1 (4-6 hrs) n=5,10	74.12 (± 72.792)	369.14 (± 357.038)		
Cycle 3 Day 1 (0 hrs) n=4,7	4.61 (± 6.279)	372.86 (± 407.032)		
Cycle 3 Day 1 (4-6 hrs) n=4,7	99.35 (± 138.914)	283.77 (± 233.317)		
Cycle 5 Day 1 (0 hrs) n=4,3	5.38 (± 3.72)	143.23 (± 192.136)		
Cycle 5 Day 1 (4-6 hrs) n=4,3	39.7 (± 50.241)	236.67 (± 30.072)		
Cycle 7 Day 1 (0 hrs) n=2,1	2.04 (± 2.885)	0 (± 999999)		
Cycle 9 Day 1 (0 hrs) n=1,2	0 (± 999999)	559.1 (± 736.664)		
Cycle 11 Day 1 (0 hrs) n=0,3	999999 (± 999999)	848.05 (± 1148.271)		
Cycle 13 Day 1 (0 hrs) n=0,1	999999 (± 999999)	17.2 (± 999999)		
Cycle 15 Day 1 (0 hrs) n=0,1	999999 (± 999999)	20.2 (± 999999)		

Notes:

[11] - Pharmacokinetic analysis set.

[12] - Pharmacokinetic analysis set.

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric mean of BEZ235 plasma concentration, by dose level

End point title	Geometric mean of BEZ235 plasma concentration, by dose level

End point description:

For BEZ235 pharmacokinetic characteristics (PK) in Phase Ib, the pre-dose PK sample were collected prior to the paclitaxel pre-medication/prior to any study treatment on the PK collection day and post-dose samples were to be taken 4-6 hours after the morning BEZ235. All analyses were based on plasma concentrations. The PK analysis set was used for these analyses. Only PK blood sample with date and time and for which the last prior dose dates and times were adequately recorded were included in the population PK analyses. EMA directed use of 999999 as the EU results system will not accept "not estimable".

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and 8, and Day 1 of Cycles 2, 3, 5, 7, 9, 11, 13, and 15

End point values	BEZ235 100 mg bid + P80	BEZ235 200 mg bid + P80		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[13]	13[14]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 (0 hrs) n=5, 11	999999 (± 999999)	999999 (± 999999)		
Cycle 1 Day 1 (4-6 hrs) n=5,12	28.1 (± 56.05)	59.09 (± 116.87)		
Cycle 1 Day 8 (0 hrs) n=5, 11	37.71 (± 132.52)	168.87 (± 933.52)		
Cycle 1 Day 8 (4-6 hrs) n=5,11	94.24 (± 73.96)	326.68 (± 167.45)		
Cycle 2 Day 1 (0 hrs) n=4, 10	49.15 (± 89.67)	153.22 (± 337.99)		
Cycle 2 Day 1 (4-6 hrs) n=5,10	51.5 (± 117.44)	228.3 (± 149.34)		
Cycle 3 Day 1 (0 hrs) n=4,7	8.25 (± 75.97)	211.73 (± 187.23)		
Cycle 3 Day 1 (4-6 hrs) n=4,7	47.2 (± 243.96)	221.59 (± 86.04)		
Cycle 5 Day 1 (0 hrs) n=4,3	7.1 (± 16.54)	63.88 (± 374.49)		
Cycle 5 Day 1 (4-6 hrs) n=4,3	24.28 (± 141.06)	235.44 (± 12.4)		
Cycle 7 Day 1 (0 hrs) n=2,1	4.08 (± 999999)	999999 (± 999999)		
Cycle 9 Day 1 (0 hrs) n=1,2	999999 (± 999999)	203.12 (± 1628.36)		
Cycle 11 Day 1 (0 hrs) n=0,3	999999 (± 999999)	244.8 (± 3900.16)		
Cycle 13 Day 1 (0 hrs) n=0,1	999999 (± 999999)	17.2 (± 999999)		
Cycle 15 Day 1 (0 hrs) n=0,1	999999 (± 999999)	20.2 (± 999999)		

Notes:

[13] - Pharmacokinetic analysis set

[14] - Pharmacokinetic analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Coefficient of variation of mean of BEZ235 plasma concentration, by dose level

End point title	Coefficient of variation of mean of BEZ235 plasma concentration, by dose level

End point description:

For BEZ235 pharmacokinetic characteristics (PK) in Phase Ib, the pre-dose PK sample were collected prior to the paclitaxel pre-medication/prior to any study treatment on the PK collection day and post-

dose samples were to be taken 4-6 hours after the morning BEZ235. All analyses were based on plasma concentrations. The PK analysis set was used for these analyses. Only PK blood sample with date and time and for which the last prior dose dates and times were adequately recorded were included in the population PK analyses. Samples taken from patients who vomited within 4 hours of BEZ235 dosing will be excluded from the analysis

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 and 8, and Day 1 of Cycles 2, 3, 5, 7, 9, 11, 13, and 15

End point values	BEZ235 100 mg bid + P80	BEZ235 200 mg bid + P80		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[15]	13[16]		
Units: CV% of mean (ng/mL)				
number (not applicable)				
Cycle 1 Day 1 (0 hrs) n=5, 11	999999	999999		
Cycle 1 Day 1 (4-6 hrs) n=5,12	43.1	68.68		
Cycle 1 Day 8 (0 hrs) n=5, 11	110.08	136.48		
Cycle 1 Day 8 (4-6 hrs) n=5,11	61.67	109.08		
Cycle 2 Day 1 (0 hrs) n=4, 10	93.97	149.15		
Cycle 2 Day 1 (4-6 hrs) n=5,10	98.21	96.72		
Cycle 3 Day 1 (0 hrs) n=4,7	136.35	109.17		
Cycle 3 Day 1 (4-6 hrs) n=4,7	139.82	82.22		
Cycle 5 Day 1 (0 hrs) n=4,3	69.18	134.14		
Cycle 5 Day 1 (4-6 hrs) n=4,3	126.55	12.71		
Cycle 7 Day 1 (0 hrs) n=2,1	141.42	999999		
Cycle 9 Day 1 (0 hrs) n=1,2	999999	131.76		
Cycle 11 Day 1 (0 hrs) n=0,3	999999	135.4		
Cycle 13 Day 1 (0 hrs) n=0,1	999999	999999		
Cycle 15 Day 1 (0 hrs) n=0,1	999999	999999		

Notes:

[15] - Pharmacokinetic analysis set

[16] - Pharmacokinetic analysis set

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 are reported in this record from 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	BEZ235 100 bid + P80
Reporting group description:	
BEZ235 100 bid + P80	
Reporting group title	BEZ235 200 bid + P80
Reporting group description:	
BEZ235 200 bid + P80	

Serious adverse events	BEZ235 100 bid + P80	BEZ235 200 bid + P80	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)	5 / 13 (38.46%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
FEBRILE NEUTROPENIA			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			

subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (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 UPPER			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STOMATITIS			
subjects affected / exposed	0 / 5 (0.00%)	3 / 13 (23.08%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
HYPOKALAEMIA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	BEZ235 100 bid + P80	BEZ235 200 bid + P80	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	13 / 13 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

METASTASES TO SKIN			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Vascular disorders			
FLUSHING			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
HAEMATOMA			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
HOT FLUSH			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
LYMPHOEDEMA			
subjects affected / exposed	1 / 5 (20.00%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	5 / 5 (100.00%)	9 / 13 (69.23%)	
occurrences (all)	8	14	
FATIGUE			
subjects affected / exposed	0 / 5 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	3	
INDURATION			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
LOCALISED OEDEMA			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
PAIN			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
OEDEMA PERIPHERAL			
subjects affected / exposed	1 / 5 (20.00%)	2 / 13 (15.38%)	
occurrences (all)	2	3	
PYREXIA			

subjects affected / exposed	2 / 5 (40.00%)	2 / 13 (15.38%)	
occurrences (all)	3	3	
Immune system disorders			
DRUG HYPERSENSITIVITY			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
SEASONAL ALLERGY			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
VAGINAL INFLAMMATION			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			
DYSPHONIA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
COUGH			
subjects affected / exposed	1 / 5 (20.00%)	3 / 13 (23.08%)	
occurrences (all)	1	4	
DYSPNOEA			
subjects affected / exposed	0 / 5 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
DYSPNOEA EXERTIONAL			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
EPISTAXIS			
subjects affected / exposed	1 / 5 (20.00%)	7 / 13 (53.85%)	
occurrences (all)	1	7	
LARYNGEAL DISCOMFORT			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
NASAL CONGESTION			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
RHINITIS ALLERGIC			

subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
PRODUCTIVE COUGH			
subjects affected / exposed	1 / 5 (20.00%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
RHINORRHOEA			
subjects affected / exposed	0 / 5 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
TRACHEAL PAIN			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Psychiatric disorders			
FOOD AVERSION			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
ANXIETY			
subjects affected / exposed	1 / 5 (20.00%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
INSOMNIA			
subjects affected / exposed	2 / 5 (40.00%)	1 / 13 (7.69%)	
occurrences (all)	2	1	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 5 (20.00%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 5 (20.00%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
BLOOD ALKALINE PHOSPHATASE			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
BLOOD CREATININE INCREASED			

subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
BLOOD PHOSPHORUS INCREASED			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	3 / 5 (60.00%)	1 / 13 (7.69%)	
occurrences (all)	5	2	
GLYCOSYLATED HAEMOGLOBIN INCREASED			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
TRANSAMINASES INCREASED			
subjects affected / exposed	1 / 5 (20.00%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
WEIGHT DECREASED			
subjects affected / exposed	0 / 5 (0.00%)	4 / 13 (30.77%)	
occurrences (all)	0	4	
Cardiac disorders			
PALPITATIONS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
SUPRAVENTRICULAR EXTRASYSTOLES			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
HEADACHE			
subjects affected / exposed	1 / 5 (20.00%)	2 / 13 (15.38%)	
occurrences (all)	2	2	
DYSGEUSIA			
subjects affected / exposed	1 / 5 (20.00%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
HYPERAESTHESIA			

subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
HYPOREFLEXIA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
HYPOAESTHESIA			
subjects affected / exposed	3 / 5 (60.00%)	0 / 13 (0.00%)	
occurrences (all)	9	0	
NEUROTOXICITY			
subjects affected / exposed	1 / 5 (20.00%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
PARAESTHESIA			
subjects affected / exposed	1 / 5 (20.00%)	4 / 13 (30.77%)	
occurrences (all)	1	7	
PRESYNCOPE			
subjects affected / exposed	1 / 5 (20.00%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
TREMOR			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	2 / 5 (40.00%)	5 / 13 (38.46%)	
occurrences (all)	7	7	
LYMPHOPENIA			
subjects affected / exposed	1 / 5 (20.00%)	1 / 13 (7.69%)	
occurrences (all)	3	1	
NEUTROPENIA			
subjects affected / exposed	3 / 5 (60.00%)	10 / 13 (76.92%)	
occurrences (all)	18	21	
Ear and labyrinth disorders			
TINNITUS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
EAR PAIN			

subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Eye disorders			
EYELID OEDEMA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
MACULAR OEDEMA			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
VISUAL ACUITY REDUCED			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
VITREOUS HAEMORRHAGE			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
CHEILITIS			
subjects affected / exposed	0 / 5 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
ABDOMINAL PAIN			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	2 / 5 (40.00%)	4 / 13 (30.77%)	
occurrences (all)	3	4	
DYSPEPSIA			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
DIARRHOEA			
subjects affected / exposed	3 / 5 (60.00%)	10 / 13 (76.92%)	
occurrences (all)	9	49	
CONSTIPATION			
subjects affected / exposed	2 / 5 (40.00%)	4 / 13 (30.77%)	
occurrences (all)	2	5	
GINGIVAL INFLAMMATION			

subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	0 / 5 (0.00%)	4 / 13 (30.77%)	
occurrences (all)	0	7	
GINGIVAL BLEEDING			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
ODYNOPHAGIA			
subjects affected / exposed	1 / 5 (20.00%)	2 / 13 (15.38%)	
occurrences (all)	2	2	
NAUSEA			
subjects affected / exposed	5 / 5 (100.00%)	11 / 13 (84.62%)	
occurrences (all)	11	19	
HAEMORRHOIDS			
subjects affected / exposed	1 / 5 (20.00%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
REFLUX GASTRITIS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
STOMATITIS			
subjects affected / exposed	2 / 5 (40.00%)	10 / 13 (76.92%)	
occurrences (all)	8	21	
RECTAL HAEMORRHAGE			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
VOMITING			
subjects affected / exposed	3 / 5 (60.00%)	7 / 13 (53.85%)	
occurrences (all)	20	10	
TONGUE ULCERATION			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
CHOLESTASIS			

subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
HEPATOCELLULAR INJURY			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	0 / 5 (0.00%)	4 / 13 (30.77%)	
occurrences (all)	0	4	
DERMATITIS ACNEIFORM			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
DRY SKIN			
subjects affected / exposed	0 / 5 (0.00%)	6 / 13 (46.15%)	
occurrences (all)	0	7	
DERMATITIS CONTACT			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
ECZEMA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
ERYTHEMA			
subjects affected / exposed	1 / 5 (20.00%)	1 / 13 (7.69%)	
occurrences (all)	2	1	
ERYTHEMA MULTIFORME			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
NAIL DISORDER			
subjects affected / exposed	0 / 5 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
NAIL DYSTROPHY			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
ONYCHOLYSIS			
subjects affected / exposed	2 / 5 (40.00%)	3 / 13 (23.08%)	
occurrences (all)	3	6	

ONYCHOMADESIS			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
PHOTOSENSITIVITY REACTION			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
PRURIGO			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
PRURITUS			
subjects affected / exposed	1 / 5 (20.00%)	3 / 13 (23.08%)	
occurrences (all)	1	4	
RASH			
subjects affected / exposed	2 / 5 (40.00%)	4 / 13 (30.77%)	
occurrences (all)	6	9	
RASH ERYTHEMATOUS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
SKIN HYPOPIGMENTATION			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Renal and urinary disorders			
URINARY TRACT PAIN			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
DYSURIA			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	3 / 5 (60.00%)	3 / 13 (23.08%)	
occurrences (all)	7	4	
BACK PAIN			
subjects affected / exposed	1 / 5 (20.00%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
JOINT SWELLING			

subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
MUSCLE SPASMS			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
MYALGIA			
subjects affected / exposed	3 / 5 (60.00%)	4 / 13 (30.77%)	
occurrences (all)	7	5	
NECK PAIN			
subjects affected / exposed	1 / 5 (20.00%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
OSTEONECROSIS OF JAW			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
PAIN IN JAW			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Infections and infestations			
ANAL FUNGAL INFECTION			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
BRONCHITIS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
CONJUNCTIVITIS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
GASTROINTESTINAL INFECTION			
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
FOLLICULITIS			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	

GINGIVITIS				
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)		
occurrences (all)	1	0		
HERPES SIMPLEX				
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)		
occurrences (all)	0	1		
HORDEOLUM				
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)		
occurrences (all)	0	1		
NAIL INFECTION				
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)		
occurrences (all)	1	0		
NASOPHARYNGITIS				
subjects affected / exposed	1 / 5 (20.00%)	2 / 13 (15.38%)		
occurrences (all)	1	3		
ORAL CANDIDIASIS				
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)		
occurrences (all)	0	1		
ORAL HERPES				
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)		
occurrences (all)	2	0		
PHARYNGITIS				
subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)		
occurrences (all)	1	0		
RHINITIS				
subjects affected / exposed	0 / 5 (0.00%)	3 / 13 (23.08%)		
occurrences (all)	0	3		
UPPER RESPIRATORY TRACT INFECTION				
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)		
occurrences (all)	0	1		
URINARY TRACT INFECTION				
subjects affected / exposed	1 / 5 (20.00%)	1 / 13 (7.69%)		
occurrences (all)	1	1		
VULVOVAGINAL MYCOTIC INFECTION				

subjects affected / exposed	1 / 5 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	4 / 5 (80.00%)	7 / 13 (53.85%)	
occurrences (all)	5	8	
DEHYDRATION			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
HYPERCHOLESTEROLAEMIA			
subjects affected / exposed	2 / 5 (40.00%)	2 / 13 (15.38%)	
occurrences (all)	2	2	
HYPERPHOSPHATAEMIA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 5 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
HYPOALBUMINAEMIA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
HYPOKALAEMIA			
subjects affected / exposed	0 / 5 (0.00%)	3 / 13 (23.08%)	
occurrences (all)	0	5	
HYPONATRAEMIA			
subjects affected / exposed	1 / 5 (20.00%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
HYPOPHOSPHATAEMIA			
subjects affected / exposed	0 / 5 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 August 2012	The main purpose of this amendment was to introduce a new dose strength of BEZ235 (50 mg sachet) and permit exploration of dose levels below 200 mg bid in future cohorts in combination with paclitaxel. Based on the clinical findings in the first 2 cohorts, the Bayesian logistic regression model (BLRM) did not allow continuation at a dose level of BEZ235 (200 mg BID) or any other of the higher planned BEZ235 doses in the original protocol. It did support the clinical recommendation to test lower dose level of BEZ235 (e.g. 100 mg bid). Two additional time points for PMBC collection will be added at trough concentrations during cycles 1 and 2 to study the effects of BEZ235 on PI3K signaling in surrogate tissue. In additional optional pre-post treatment tumor biopsies for patients in phase Ib (orginally planned only phase II) was included in order to gather data on pathway inhibition at lower dose of BEZ235BID in tumor tissue.The clinical experience section was updated based on new information. Updated data on managing stomatitis and pneumonitis was added.

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.

The study did not meet the Phase Ib primary objective to establish MTD. Therefore, Novartis terminated the study during Phase Ib and Phase II was not conducted.

Notes: