



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), $\geq 30\%$ 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

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|-----------------|--------|
| 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 | |
| Embolicism | | | |

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

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

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