



Clinical trial results:

EVINEC: Safety and Tolerability of Everolimus as second-line treatment in poorly differentiated neuroendocrine carcinoma / neuroendocrine carcinoma G3 according to WHO 2010 and neuroendocrine tumor G3 - an investigator initiated Phase II study.

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2012-004550-28 |
| Trial protocol | DE |
| Global end of trial date | 04 May 2020 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 01 November 2022 |
| First version publication date | 01 November 2022 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | AIO-NET-0112 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|------------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02113800 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Novartis-Nr: : CRAD001KDE55T |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | AIO-Studien-gGmbH |
| Sponsor organisation address | Kuno-Fischer-Str. 8, Berlin, Germany, 14057 |
| Public contact | AIO-Studien-gGmbH, AIO-Studien-gGmbH, +49 30814534431, info@aio-studien-ggmbh.de |
| Scientific contact | AIO-Studien-gGmbH, AIO-Studien-gGmbH, +49 30814534431, info@aio-studien-ggmbh.de |

Notes:

Paediatric regulatory details

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|--|----|
| 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 | 07 September 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 04 May 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 May 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate tolerability and safety of everolimus in second-line treatment of poorly differentiated neuroendocrine carcinoma / neuroendocrine carcinoma G3 according to WHO 2010 and neuroendocrine tumors G3. Safety and tolerability of Everolimus can be inferred if type, frequency and seriousness of observed AEs is comparable to those determined in previous Everolimus trials in NET (Radiant-1,2 and 3).

Protection of trial subjects:

This study was planned, analyzed and conducted according to the study protocol and in accordance with the International Conference on Harmonization (ICH) 'Guideline for Good Clinical Practice E6(R1)', CPMP/ICH/135/95, based on the principles of the Declaration of Helsinki (1964) and its October 1996 amendment (Somerset West, South Africa). The study was duly conducted in compliance with the German Arzneimittelgesetz (AMG; German Drug Law), and the corresponding Directive 2001/20/EC. Subjects were fully informed regarding all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 01 March 2015 |
| 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 | Germany: 39 |
| Worldwide total number of subjects | 39 |
| EEA total number of subjects | 39 |

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) | 28 |
| From 65 to 84 years | 11 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

42 patients were screened for study participation, 39 of whom were found eligible.

Period 1

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

Arms

| | |
|--|--------------------|
| Arm title | Everolimus 10 mg/d |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Everolimus |
| Investigational medicinal product code | |
| Other name | Afinitor |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

A dose of 10 mg was to be administered orally once daily at the same time every day, consistently either with or without food, swallowed whole with a glass of water.

| | |
|--------------------------------|--------------------|
| Number of subjects in period 1 | Everolimus 10 mg/d |
| Started | 39 |
| Completed | 39 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Treatment |
|-----------------------|-----------|

Reporting group description: -

| Reporting group values | Treatment | Total | |
|---|-----------|-------|--|
| Number of subjects | 39 | 39 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 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) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous | | | |
| Units: years | | | |
| median | 57.0 | | |
| full range (min-max) | 33 to 77 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 16 | 16 | |
| Male | 23 | 23 | |

End points

End points reporting groups

| | |
|--------------------------------|--------------------|
| Reporting group title | Everolimus 10 mg/d |
| Reporting group description: - | |
| Subject analysis set title | Per protocol |
| Subject analysis set type | Per protocol |

Subject analysis set description:

Of 39 treated patients, 9 were excluded from the per protocol analysis set. Reasons were the retroactive histological tumor diagnosis as non-NEN by central pathology (3 patients), and major protocol violations (6 patients).

Primary: Overall survival

| | |
|-----------------|---------------------------------|
| End point title | Overall survival ^[1] |
|-----------------|---------------------------------|

End point description:

Primary objective of this study was limited to safety and tolerability. Hence, no primary efficacy endpoint was defined. One of the secondary endpoints, overall survival (OS), is given instead.

The median OS was 12.0 months for all NEN G3 patients together (95%-CI 7.0-23.9). A lower OS occurred in NEC G3 patients with 5.6 months (95%-CI 1.3-20.1) and for MANEC patients with 7.0 months (95%-CI 1.0-11.1) compared to NET G3 patients with 23.9 months (95%-CI 12.0-NC).

OS rate at 12 months in the PP Population was 49.0% (95%-CI 30.2%-65.4%). OS at 12 months was lowest in MANEC patients with 14.3% (95%-CI 0.7%-46.5%) and in NEC G3 patients with 30.0% (95%-CI 7.1%-57.8%) compared to NET G3 patients with 83.9% (95%-CI 49.4%-95.7%).

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Overall survival (OS) was defined as the time from the date of first treatment to the date of death. Patients for whom not date of death was recorded were censored at the date of last contact.

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: Since the study had no primary efficacy endpoint, OS is given for this data field instead. No in-depth statistical analysis was performed.

| End point values | Per protocol | | | |
|----------------------------------|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 30 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 12.0 (7.0 to 23.9) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

| | |
|-----------------|---------------------------|
| End point title | Progression-free survival |
|-----------------|---------------------------|

End point description:

The median progressive free survival (PFS) was 2.2 months for all NEN G3 patients together (95%-CI 1.8-4.8).

PFS was shorter in NEC G3 with a median of 1.8 months (95% CI 0.9-2.0) and in MANEC with 2.2 months (95% CI 0.7-4.1) as compared to NET G3 patients with 5.2 months (95% CI 1.6-7.3).

PFS rate at 6 months was lowest in MANEC patients with 14.3% (95%-CI 0.7%-46.5%) and NEC G3 patients with 20.0% (95%-CI 3.1%-47.5%) compared to NET G3 patients with 41.7% (95%-CI 15.2%-66.5%).

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Progression-Free Survival (PFS) was defined as the time from first treatment to PD or death. Patients who had no PD and did not die were censored at the time of the last tumor assessment. | |

| | | | | |
|----------------------------------|--------------------|--|--|--|
| End point values | Everolimus 10 mg/d | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 30 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 2.2 (1.8 to 4.8) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response, ORR and DCR

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|--|------------------------------------|
| End point title | Best overall response, ORR and DCR |
| End point description: | |
| Partial remission was observed for one patient, resulting in an Objective Response Rate (ORR) of 3.3%, [95%CI 0.6%-16.7%]. | |
| Disease control was documented for 14 NEN G3 patients, resulting in a disease control rate (DCR) of 46.7% [95%CI 30.2%-63.9%]. | |
| End point type | Secondary |
| End point timeframe: | |
| Best response among all available response assessments | |

| | | | | |
|-----------------------------|--------------------|--|--|--|
| End point values | Everolimus 10 mg/d | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 30 | | | |
| Units: CR, PR, SD and PD | | | | |
| Complete Remission (CR) | 0 | | | |
| Partial Remission (PR) | 1 | | | |
| Stable Disease (SD) | 13 | | | |
| Progressive Disease (PD) | 13 | | | |
| No assessment | 3 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Reporting of all adverse events started at the first treatment visit and ended on the EoT visit.

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|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 23 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|--------------------|
| Reporting group title | Everolimus 10 mg/d |
|-----------------------|--------------------|

Reporting group description: -

| Serious adverse events | Everolimus 10 mg/d | | |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 39 (12.82%) | | |
| number of deaths (all causes) | 29 | | |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Radiation pneumonitis | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 39 (2.56%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|----------------------------------|--|--|
| Cerebrovascular accident subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 39 (2.56%) 0 / 1 0 / 0 | | |
| General disorders and administration site conditions Pain subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 39 (2.56%) 1 / 1 0 / 0 | | |
| Gastrointestinal disorders Melaena subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 39 (2.56%) 0 / 3 0 / 0 | | |
| Infections and infestations Influenza subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 39 (2.56%) 0 / 1 0 / 0 | | |
| Respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 39 (2.56%) 1 / 1 0 / 0 | | |
| Sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 39 (2.56%) 0 / 1 0 / 0 | | |

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

| | | | |
|---|--------------------|--|--|
| Non-serious adverse events | Everolimus 10 mg/d | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 39 / 39 (100.00%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|--|--|--|--|
| Tumor pain subjects affected / exposed occurrences (all) | 4 / 39 (10.26%) 6 | | |
| Vascular disorders Lymphoedema subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | | |
| General disorders and administration site conditions Chills subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) General physical health deterioration subjects affected / exposed occurrences (all) Influenza like illness subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Swelling face subjects affected / exposed occurrences (all) | 5 / 39 (12.82%) 5 14 / 39 (35.90%) 16 5 / 39 (12.82%) 5 2 / 39 (5.13%) 4 5 / 39 (12.82%) 6 6 / 39 (15.38%) 7 6 / 39 (15.38%) 6 2 / 39 (5.13%) 2 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 3 / 39 (7.69%) 3 | | |

| | | | |
|--|----------------------|--|--|
| Dyspnoea subjects affected / exposed occurrences (all) | 4 / 39 (10.26%) 5 | | |
| Epistaxis subjects affected / exposed occurrences (all) | 8 / 39 (20.51%) 9 | | |
| Pneumonitis subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 3 | | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | | |
| Depression subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | | |
| Insomnia subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | | |
| C-reactive protein increased subjects affected / exposed occurrences (all) | 4 / 39 (10.26%) 4 | | |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | | |
| Platelet count decreased subjects affected / exposed occurrences (all) | 4 / 39 (10.26%) 7 | | |
| Weight decreased subjects affected / exposed occurrences (all) | 6 / 39 (15.38%) 8 | | |
| Cardiac disorders | | | |

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|--|----------------------|--|--|
| Angina pectoris subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | | |
| Atrial tachycardia subjects affected / exposed occurrences (all) | 1 / 39 (2.56%) 1 | | |
| Atrioventricular block subjects affected / exposed occurrences (all) | 1 / 39 (2.56%) 1 | | |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 3 | | |
| Dysgeusia subjects affected / exposed occurrences (all) | 3 / 39 (7.69%) 3 | | |
| Headache subjects affected / exposed occurrences (all) | 4 / 39 (10.26%) 4 | | |
| Paraesthesia subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | | |
| Taste disorder subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 3 / 39 (7.69%) 5 | | |
| Anaemia of malignant disease subjects affected / exposed occurrences (all) | 1 / 39 (2.56%) 1 | | |
| Increased tendency to bruise subjects affected / exposed occurrences (all) | 1 / 39 (2.56%) 1 | | |
| Lymphadenopathy | | | |

| | | | |
|---|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Lymphopenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Neutropenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Thrombocytopenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 39 (5.13%)</p> <p>2</p> <p>2 / 39 (5.13%)</p> <p>2</p> <p>1 / 39 (2.56%)</p> <p>1</p> <p>2 / 39 (5.13%)</p> <p>2</p> | | |
| <p>Ear and labyrinth disorders</p> <p>Tinnitus</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vertigo</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 39 (2.56%)</p> <p>1</p> <p>2 / 39 (5.13%)</p> <p>2</p> | | |
| <p>Eye disorders</p> <p>Eye swelling</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Visual impairment</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 39 (2.56%)</p> <p>1</p> <p>1 / 39 (2.56%)</p> <p>1</p> | | |
| <p>Gastrointestinal disorders</p> <p>Abdominal hernia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal mass</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain lower</p> | <p>1 / 39 (2.56%)</p> <p>1</p> <p>1 / 39 (2.56%)</p> <p>1</p> <p>9 / 39 (23.08%)</p> <p>11</p> | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 1 / 39 (2.56%) | | |
| occurrences (all) | 1 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 5 / 39 (12.82%) | | |
| occurrences (all) | 5 | | |
| Aphthous ulcer | | | |
| subjects affected / exposed | 5 / 39 (12.82%) | | |
| occurrences (all) | 5 | | |
| Constipation | | | |
| subjects affected / exposed | 6 / 39 (15.38%) | | |
| occurrences (all) | 10 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 11 / 39 (28.21%) | | |
| occurrences (all) | 14 | | |
| Dry mouth | | | |
| subjects affected / exposed | 5 / 39 (12.82%) | | |
| occurrences (all) | 5 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 5 / 39 (12.82%) | | |
| occurrences (all) | 6 | | |
| Nausea | | | |
| subjects affected / exposed | 14 / 39 (35.90%) | | |
| occurrences (all) | 14 | | |
| Stomatitis | | | |
| subjects affected / exposed | 16 / 39 (41.03%) | | |
| occurrences (all) | 20 | | |
| Toothache | | | |
| subjects affected / exposed | 3 / 39 (7.69%) | | |
| occurrences (all) | 3 | | |
| Vomiting | | | |
| subjects affected / exposed | 5 / 39 (12.82%) | | |
| occurrences (all) | 9 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 5 / 39 (12.82%) | | |
| occurrences (all) | 5 | | |

| | | | |
|---|----------------------|--|--|
| Dry skin subjects affected / exposed occurrences (all) | 3 / 39 (7.69%) 3 | | |
| Erythema subjects affected / exposed occurrences (all) | 3 / 39 (7.69%) 3 | | |
| Erythema multiforme subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | | |
| Night sweats subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | | |
| Pruritus subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | | |
| Rash subjects affected / exposed occurrences (all) | 7 / 39 (17.95%) 8 | | |
| Renal and urinary disorders Nocturia subjects affected / exposed occurrences (all) | 3 / 39 (7.69%) 3 | | |
| Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all) | 1 / 39 (2.56%) 1 | | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 3 / 39 (7.69%) 3 | | |
| Back pain subjects affected / exposed occurrences (all) | 7 / 39 (17.95%) 9 | | |
| Flank pain subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | | |

| | | | |
|---|-----------------------|--|--|
| Pain in extremity subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 3 | | |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 3 / 39 (7.69%) 3 | | |
| Uninary tract infection subjects affected / exposed occurrences (all) | 4 / 39 (10.26%) 4 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 9 / 39 (23.08%) 10 | | |
| Hypercalcaemia subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 3 / 39 (7.69%) 4 | | |
| Hypertriglyceridaemia subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | | |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 3 / 39 (7.69%) 3 | | |
| Iron deficiency subjects affected / exposed occurrences (all) | 3 / 39 (7.69%) 3 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|-------------------------------|
| 10 August 2015 | Addition of IMP package sizes |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported