



Clinical trial results:

A RANDOMISED, DOUBLE-BLIND, PARALLEL-GROUP, MULTICENTRE, PHASE II STUDY TO EVALUATE THE SAFETY AND PHARMACOLOGICAL ACTIVITY OF THE COMBINATION OF VANDETANIB (100 OR 300 MG/DAILY OR PLACEBO) WITH FULVESTRANT (LOADING DOSE), IN POSTMENOPAUSAL ADVANCED BREAST CANCER PATIENTS.

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2008-000579-12 |
| Trial protocol | IT |
| Global end of trial date | 28 September 2013 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 01 February 2017 |
| First version publication date | 05 August 2015 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | D4200L00009 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00752986 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Medical Dept AstraZeneca |
| Sponsor organisation address | Via Ludovico il Moro, 6/C, Basiglio, Italy, 20080 |
| Public contact | Constanza Oliveros, AstraZeneca Lab Italia, +39 02 98014269, constanza.oliveros@astrazeneca.com |
| Scientific contact | Constanza Oliveros, MD, AstraZeneca Lab Italia, +39 02 98011, ClinicalTrialTransparency@ASTRAZENECA.COM |

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 | 25 July 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 September 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess the event-free survival (EFS) defined as the time from randomisation to progression, death without progression, loss to follow up, whichever occurred first.

End-point Efficacy: event-free survival (EFS)

The secondary objectives of the study are to assess:

- Success rate at 6 months
- Objective tumor Response rates (complete response, CR and partial response, PR) according to RECIST criteria (Therasse P et al 2000)
- Time To Progression
- Progression Free Survival
- Overall Survival
- Safety and tolerability of vandetanib / Placebo in combination with fulvestrant

Efficacy- Safety main objective of Trial

Protection of trial subjects:

Pain relief medication

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 22 December 2008 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 6 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Italy: 41 |
| Worldwide total number of subjects | 41 |
| EEA total number of subjects | 41 |

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) | 23 |
| From 65 to 84 years | 18 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

the study was prematurely terminated with 41 enrolled patients and 39 randomized, out of the 135 scheduled by protocol.

A total of 8 serious adverse events have been reported in 6 patients overall. 2 patients had 2 SAEs
41 pts enrolled , 39 randomized. two patients never received the drug.

Pre-assignment

Screening details:

41 pts enrolled , 39 randomized. two patients never received the drug.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer, Data analyst |

Arms

| | |
|------------------------------|----------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Vandetanib at the dose of 100 mg |

Arm description:

vandetanib at the dose of 100 mg orally once-daily plus placebo to match vandetanib 300 mg orally once-daily plus fulvestrant LD (500 mg im. at day 1 and 250 mg at day 14, 28 and thereafter every 28th day +/- 3)

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Vandetanib |
| Investigational medicinal product code | Vandetanib |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

100mg

| | |
|------------------|----------------------------------|
| Arm title | Vandetanib at the dose of 300 mg |
|------------------|----------------------------------|

Arm description:

vandetanib at the dose of 300 mg orally once-daily plus placebo to match vandetanib 100 mg orally once-daily plus fulvestrant LD (500 mg im. at day 1 and 250 mg at day 14, 28 and thereafter every 28th day +/- 3)

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Vandetanib |
| Investigational medicinal product code | Vandetanib |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

300mg

| | |
|------------------|---|
| Arm title | Placebo to match vandetanib 100 mg and 300 mg |
|------------------|---|

Arm description:

placebo to match vandetanib 100 mg orally once-daily plus placebo to match vandetanib 300 mg orally once-daily plus fulvestrant LD (500 mg im. at day 1 and 250 mg at day 14, 28 and thereafter every 28th day +/- 3).

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|---------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | Placebo |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo to match vandetanib 100 mg and 300 mg

| Number of subjects in period 1 ^[1] | Vandetanib at the dose of 100 mg | Vandetanib at the dose of 300 mg | Placebo to match vandetanib 100 mg and 300 mg |
|--|-------------------------------------|-------------------------------------|---|
| | | | |
| Started | 16 | 12 | 11 |
| Completed | 11 | 11 | 9 |
| Not completed | 5 | 1 | 2 |
| Consent withdrawn by subject | 2 | 1 | 2 |
| Protocol deviation | 3 | - | - |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The total number of patients enrolled is equal to 41.

Only 39 patients received the treatment.

Baseline characteristics

Reporting groups

| | |
|--|---|
| Reporting group title | Vandetanib at the dose of 100 mg |
| Reporting group description: vandetanib at the dose of 100 mg orally once-daily plus placebo to match vandetanib 300 mg orally once-daily plus fulvestrant LD (500 mg im. at day 1 and 250 mg at day 14, 28 and thereafter every 28th day +/- 3) | |
| Reporting group title | Vandetanib at the dose of 300 mg |
| Reporting group description: vandetanib at the dose of 300 mg orally once-daily plus placebo to match vandetanib 100 mg orally once-daily plus fulvestrant LD (500 mg im. at day 1 and 250 mg at day 14, 28 and thereafter every 28th day +/- 3) | |
| Reporting group title | Placebo to match vandetanib 100 mg and 300 mg |
| Reporting group description: placebo to match vandetanib 100 mg orally once-daily plus placebo to match vandetanib 300 mg orally once-daily plus fulvestrant LD (500 mg im. at day 1 and 250 mg at day 14, 28 and thereafter every 28th day +/- 3). | |

| Reporting group values | Vandetanib at the dose of 100 mg | Vandetanib at the dose of 300 mg | Placebo to match vandetanib 100 mg and 300 mg |
|---|----------------------------------|----------------------------------|---|
| Number of subjects | 16 | 12 | 11 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 16 | 12 | 11 |
| Age Continuous Units: years arithmetic mean full range (min-max) | 63.6 44 to 78 | 59.8 48 to 79 | 59.6 43 to 74 |
| Gender, Male/Female | | | |
| Female | | | |
| Units: Participants | | | |
| Female | 16 | 12 | 11 |

| Reporting group values | Total | | |
|---|-------|--|--|
| Number of subjects | 39 | | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 39 | | |
| Age Continuous Units: years arithmetic mean full range (min-max) | - | | |
| Gender, Male/Female | | | |
| Female | | | |
| Units: Participants | | | |
| Female | 39 | | |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Vandetanib at the dose of 100 mg |
| Reporting group description: vandetanib at the dose of 100 mg orally once-daily plus placebo to match vandetanib 300 mg orally once-daily plus fulvestrant LD (500 mg im. at day 1 and 250 mg at day 14, 28 and thereafter every 28th day +/- 3) | |
| Reporting group title | Vandetanib at the dose of 300 mg |
| Reporting group description: vandetanib at the dose of 300 mg orally once-daily plus placebo to match vandetanib 100 mg orally once-daily plus fulvestrant LD (500 mg im. at day 1 and 250 mg at day 14, 28 and thereafter every 28th day +/- 3) | |
| Reporting group title | Placebo to match vandetanib 100 mg and 300 mg |
| Reporting group description: placebo to match vandetanib 100 mg orally once-daily plus placebo to match vandetanib 300 mg orally once-daily plus fulvestrant LD (500 mg im. at day 1 and 250 mg at day 14, 28 and thereafter every 28th day +/- 3). | |

Primary: Event Free Survival

| | |
|--|------------------------------------|
| End point title | Event Free Survival ^[1] |
| End point description: Success rate (patients without progression and still on treatment at 24 weeks) | |
| End point type | Primary |
| End point timeframe: Restaging (RECIST) is carried out at screening and every 3 months during the study until 1 year and than every 6 months until objective disease progression. | |
| Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical analysis of data was performed. | |

| End point values | Vandetanib at the dose of 100 mg | Vandetanib at the dose of 300 mg | Placebo to match vandetanib 100 mg and 300 mg | |
|-----------------------------|----------------------------------|----------------------------------|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | 0 ^[4] | |
| Units: participants | | | | |
| number (not applicable) | | | | |

Notes:

[2] - No statistical analysis was performed

[3] - No statistical analysis was performed

[4] - No statistical analysis was performed

Statistical analyses

No statistical analyses for this end point

Secondary: TTPI, PFS, CR+PR, disease control(CR+PR+SD),DOR

| | |
|-----------------|---|
| End point title | TTPI, PFS, CR+PR, disease control(CR+PR+SD),DOR |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Restaging (RECIST) is carried out at screening and every 3 months during the study until 1 year and than every 6 months until objective disease progression.

| End point values | Vandetanib at the dose of 100 mg | Vandetanib at the dose of 300 mg | Placebo to match vandetanib 100 mg and 300 mg | |
|-----------------------------|----------------------------------|----------------------------------|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[5] | 0 ^[6] | 0 ^[7] | |
| Units: participants | | | | |
| number (not applicable) | | | | |

Notes:

[5] - no statistical analysis was made

[6] - no statistical analysis was made

[7] - no statistical analysis was made

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

| | |
|-----------------|------------------|
| End point title | Overall survival |
|-----------------|------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Assessments for survival must be made at the 60 day follow-up visit and then every 3 months, unless the patient withdraws consent.

| End point values | Vandetanib at the dose of 100 mg | Vandetanib at the dose of 300 mg | Placebo to match vandetanib 100 mg and 300 mg | |
|-----------------------------|----------------------------------|----------------------------------|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[8] | 0 ^[9] | 0 ^[10] | |
| Units: participants | | | | |
| number (not applicable) | | | | |

Notes:

[8] - no statistical analysis was made

[9] - no statistical analysis was made

[10] - no statistical analysis was made

Statistical analyses

No statistical analyses for this end point

Secondary: AEs,lab,vital sign and ECG changes

| | |
|-----------------|------------------------------------|
| End point title | AEs,lab,vital sign and ECG changes |
|-----------------|------------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Continuous assessment of safety.

| End point values | Vandetanib at the dose of 100 mg | Vandetanib at the dose of 300 mg | Placebo to match vandetanib 100 mg and 300 mg | |
|-----------------------------|----------------------------------|----------------------------------|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[11] | 0 ^[12] | 0 ^[13] | |
| Units: participants | | | | |
| number (not applicable) | | | | |

Notes:

[11] - no statistical analysis was made

[12] - no statistical analysis was made

[13] - no statistical analysis was made

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:
ongoing basis as per law

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

| | |
|--------------------|---|
| Dictionary version | 0 |
|--------------------|---|

Reporting groups

| | |
|-----------------------|----------------------------------|
| Reporting group title | Vandetanib at the dose of 100 mg |
|-----------------------|----------------------------------|

Reporting group description:

vandetanib at the dose of 100 mg orally once-daily plus placebo to match vandetanib 300 mg orally once-daily plus fulvestrant LD (500 mg im. at day 1 and 250 mg at day 14, 28 and thereafter every 28th day +/- 3)

| | |
|-----------------------|---|
| Reporting group title | Placebo to match vandetanib 100 mg and 300 mg |
|-----------------------|---|

Reporting group description:

placebo to match vandetanib 100 mg orally once-daily plus placebo to match vandetanib 300 mg orally once-daily plus fulvestrant LD (500 mg im. at day 1 and 250 mg at day 14, 28 and thereafter every 28th day +/- 3).

| | |
|-----------------------|----------------------------------|
| Reporting group title | Vandetanib at the dose of 300 mg |
|-----------------------|----------------------------------|

Reporting group description:

vandetanib at the dose of 300 mg orally once-daily plus placebo to match vandetanib 100 mg orally once-daily plus fulvestrant LD (500 mg im. at day 1 and 250 mg at day 14, 28 and thereafter every 28th day +/- 3)

| Serious adverse events | Vandetanib at the dose of 100 mg | Placebo to match vandetanib 100 mg and 300 mg | Vandetanib at the dose of 300 mg |
|---|----------------------------------|---|----------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 16 (18.75%) | 1 / 11 (9.09%) | 2 / 12 (16.67%) |
| number of deaths (all causes) | 0 | 0 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| severe arthralgia | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |

| | | | |
|---|-----------------|----------------|----------------|
| gastroenteritis. | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| grade 3 diarrhoea | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| grade 3 erythema | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| diabetes complication | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Musculoskeletal and connective tissue disorders | | | |
| right iliac fracture | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | Vandetanib at the dose of 100 mg | Placebo to match vandetanib 100 mg and 300 mg | Vandetanib at the dose of 300 mg |
|---|----------------------------------|---|----------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 16 (75.00%) | 6 / 11 (54.55%) | 11 / 12 (91.67%) |
| General disorders and administration site conditions | | | |
| RECTAL BLEEDING | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| HEMORRHOIDS | | | |

| | | | |
|-----------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| TOOTH ACHE | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| NAUSEA | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 11 (0.00%) | 3 / 12 (25.00%) |
| occurrences (all) | 2 | 0 | 3 |
| VOMITING | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 2 |
| INSOMNIA | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 11 (0.00%) | 3 / 12 (25.00%) |
| occurrences (all) | 0 | 0 | 3 |
| HEADACHE | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 11 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 1 | 0 | 2 |
| ANOREXIA | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| ASTHENIA | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 11 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 2 | 0 | 2 |
| FEVER | | | |
| subjects affected / exposed | 2 / 16 (12.50%) | 0 / 11 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 2 | 0 | 2 |
| ONYCHOPATY | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| WEIGHT LOSS | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| LOSS OF APPETITE | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| SWEATING | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| ARTHRALGIA | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| FATIGUE | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| THORACIC PAIN | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| PAIN RIGHT THORAX | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| BRONCHITIS | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychiatric disorders | | | |
| ANXIETY | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| ANXIOUS-DEPRESSIVE SYNDROME | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Cardiac disorders | | | |
| HYPERTENSION | | | |
| subjects affected / exposed | 3 / 16 (18.75%) | 0 / 11 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 3 | 0 | 4 |
| TACHICARDY | | | |
| subjects affected / exposed | 0 / 16 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| FLUSHING | | | |
| subjects affected / exposed | 1 / 16 (6.25%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nervous system disorders | | | |

| | | | |
|---|---------------------|---------------------|----------------------|
| NEUROPATHY (ARMS) subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Blood and lymphatic system disorders | | | |
| AST ELEVATION subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 11 (9.09%) 1 | 0 / 12 (0.00%) 0 |
| ANAEMIA subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 3 | 1 / 11 (9.09%) 1 | 0 / 12 (0.00%) 0 |
| NEUTROPENIA subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 11 (9.09%) 1 | 0 / 12 (0.00%) 0 |
| LEUKOPENIA subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 11 (9.09%) 1 | 0 / 12 (0.00%) 0 |
| HYPERCALCEMIA subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 11 (9.09%) 1 | 0 / 12 (0.00%) 0 |
| HYPERTRANSAMINASEMIA subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 11 (9.09%) 1 | 2 / 12 (16.67%) 5 |
| PIASTRINOPENIA subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 12 (8.33%) 3 |
| TRANSAMINASE INCREASE subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| HYPERPOTASSEMIA subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Ear and labyrinth disorders | | | |
| DIZZINESS subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| VERTIGO | | | |

| | | | |
|---|----------------------|---------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Eye disorders LEFT EYE PAIN subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 11 (9.09%) 1 | 0 / 12 (0.00%) 0 |
| EYE ANGIOEDEMA subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Gastrointestinal disorders RIGHT HYPOCHONDRIC PAIN subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 11 (9.09%) 1 | 0 / 12 (0.00%) 0 |
| DIARRHEA subjects affected / exposed occurrences (all) | 3 / 16 (18.75%) 3 | 0 / 11 (0.00%) 0 | 7 / 12 (58.33%) 14 |
| Hepatobiliary disorders HEPATIC TOXICITY subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Skin and subcutaneous tissue disorders RASH subjects affected / exposed occurrences (all) | 3 / 16 (18.75%) 6 | 0 / 11 (0.00%) 0 | 6 / 12 (50.00%) 11 |
| HYPERPIGMENTATION subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| ERYTHEMA subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 | 2 / 12 (16.67%) 5 |
| SCALP ERITHEMA subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Renal and urinary disorders PROTEINURIA subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 11 (9.09%) 1 | 0 / 12 (0.00%) 0 |

| | | | |
|--|---------------------|---------------------|----------------------|
| CYSTITIS subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| HAEMORRHAGIC CYSTITIS subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders BONE PAIN subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 1 / 11 (9.09%) 1 | 3 / 12 (25.00%) 4 |
| JOINT PAIN subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| RIB FRACTURE subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| LUMBAR PAIN subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| MUSCOLOSKELETICAL PAIN subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Infections and infestations MUCOSITIS subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 12 (8.33%) 2 |
| STOMATITIS subjects affected / exposed occurrences (all) | 0 / 16 (0.00%) 0 | 0 / 11 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| UMBILICAL MYCOSES subjects affected / exposed occurrences (all) | 1 / 16 (6.25%) 2 | 0 / 11 (0.00%) 0 | 0 / 12 (0.00%) 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported