



Clinical trial results:

Clinical trial to assess the efficacy of the fixed combination product Tepilta® in the treatment of radiation-induced oesophagitis compared to its active ingredients oxetacaine and antacids, and to placebo

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2009-014441-93 |
| Trial protocol | DE AT |
| Global end of trial date | 18 January 2017 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 16 December 2017 |
| First version publication date | 16 December 2017 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | X-03030-3277 |
|-----------------------|--------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Meda Pharma GmbH & Co. KG |
| Sponsor organisation address | Benzstr. 1, Bad Homburg, Germany, 61352 |
| Public contact | Group Leader Study Manager, Meda Pharma GmbH & Co. KG (A Mylan company), +49 6172-888-01, 42b@mylan.com |
| Scientific contact | Clinical Affairs Meda, Meda Pharma GmbH & Co. KG (A Mylan company), +49 06172-888-01, 42b@mylan.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 | 12 April 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 January 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 January 2017 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

Primary objective:

- To prove the combination effect of oxetacaine and antacids, i.e. to demonstrate superior efficacy of Tepilta® versus oxetacaine, antacids, and placebo.

Protection of trial subjects:

No specific additional measures to minimise pain and distress were required. The subjects could withdraw from treatment at any time and for any reason.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 05 April 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Austria: 4 |
| Country: Number of subjects enrolled | Germany: 36 |
| Worldwide total number of subjects | 40 |
| EEA total number of subjects | 40 |

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) | 25 |
| From 65 to 84 years | 15 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Relevant for inclusion: Score=0 NRS for oesophageal pain, RT or combined RCT of a solid tumour in head/neck/thorax region, min. length of 5cm of the oesophagus must be included in high-dose radiation field, duration of RT 5-8 weeks, radiation dosage, first radiation in the intended area. Other random and exclusion criteria.

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, Data analyst, Carer, Assessor |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Tepilta |

Arm description: -

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

Dosage and administration details:

Active dose: 10 ml suspension contain 20 mg oxetacaine, 582 mg aluminium hydroxide and 196 mg magnesium hydroxide. Study medication: Single dose: 1 sachet containing 10 ml of suspension. Minimum daily dose: 3 sachets or 30 ml of suspension. Maximum daily dose: 6 sachets or 60 ml of suspension. Dosing: Minimum: 1 sachet 5 to 10 minutes before breakfast, lunch, and dinner = 3 sachets. On demand: Up to 2 additional sachets on demand per day and up to 1 sachet per night = up to 3 sachets.

| | |
|------------------|------------|
| Arm title | Oxetacaine |
|------------------|------------|

Arm description: -

| | |
|--|---------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Oxetacaine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral suspension in sachet |
| Routes of administration | Oral use |

Dosage and administration details:

Active dose: 10 ml suspension contain 20 mg oxetacaine. Study medication: Single dose: 1 sachet containing 10 ml of suspension. Minimum daily dose: 3 sachets or 30 ml of suspension. Maximum daily dose: 6 sachets or 60 ml of suspension. Dosing: Minimum: 1 sachet 5 to 10 minutes before breakfast, lunch, and dinner = 3 sachets. On demand: Up to 2 additional sachets on demand per day and up to 1 sachet per night = up to 3 sachets.

| | |
|------------------|----------|
| Arm title | Antacids |
|------------------|----------|

Arm description: -

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|---------------------------|
| Investigational medicinal product name | Antacids |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral suspension in sachet |
| Routes of administration | Oral use |

Dosage and administration details:

Active dose: 10 ml suspension contain 582 mg aluminium hydroxide and 196 mg magnesium hydroxide. Study medication: Single dose: 1 sachet containing 10 ml of suspension. Minimum daily dose: 3 sachets or 30 ml of suspension. Maximum daily dose: 6 sachets or 60 ml of suspension. Dosing: Minimum: 1 sachet 5 to 10 minutes before breakfast, lunch, and dinner = 3 sachets. On demand: Up to 2 additional sachets on demand per day and up to 1 sachet per night = up to 3 sachets.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description: -

| | |
|--|---------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral suspension in sachet |
| Routes of administration | Oral use |

Dosage and administration details:

No active ingredient. Study medication: Single dose: 1 sachet containing 10 ml of suspension. Minimum daily dose: 3 sachets or 30 ml of suspension. Maximum daily dose: 6 sachets or 60 ml of suspension. Dosing: Minimum: 1 sachet 5 to 10 minutes before breakfast, lunch, and dinner = 3 sachets. On demand: Up to 2 additional sachets on demand per day and up to 1 sachet per night = up to 3 sachets.

| Number of subjects in period 1 | Tepilta | Oxetacaine | Antacids |
|---------------------------------------|---------|------------|----------|
| Started | 13 | 13 | 9 |
| Completed | 9 | 10 | 4 |
| Not completed | 4 | 3 | 5 |
| Adverse event, serious fatal | 1 | - | 1 |
| Consent withdrawn by subject | 1 | - | 4 |
| Adverse event, non-fatal | 2 | 2 | - |
| Protocol deviation | - | 1 | - |

| Number of subjects in period 1 | Placebo |
|---------------------------------------|---------|
| Started | 5 |
| Completed | 5 |
| Not completed | 0 |
| Adverse event, serious fatal | - |
| Consent withdrawn by subject | - |
| Adverse event, non-fatal | - |
| Protocol deviation | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------------------|
| Reporting group title | Overall study (overall period) |
|-----------------------|--------------------------------|

Reporting group description: -

| Reporting group values | Overall study (overall period) | Total | |
|---|-----------------------------------|-------|--|
| Number of subjects | 40 | 40 | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 25 | 25 | |
| From 65-84 years | 15 | 15 | |
| 85 years and over | 0 | 0 | |
| Gender categorical Units: Subjects | | | |
| Female | 12 | 12 | |
| Male | 28 | 28 | |

End points

End points reporting groups

| | |
|--------------------------------|------------|
| Reporting group title | Tepilta |
| Reporting group description: - | |
| Reporting group title | Oxetacaine |
| Reporting group description: - | |
| Reporting group title | Antacids |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

Primary: Time until first requirement of ASPO

| | |
|------------------------|---|
| End point title | Time until first requirement of ASPO ^[1] |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| Study duration. | |

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: Due to difficulties in recruiting suitable patients and low no. of patients reaching randomisation criteria, the study was stopped prematurely. Efficacy analyses were not performed since the no. of patients was too low to draw meaningful conclusions.

| End point values | Tepilta | Oxetacaine | Antacids | Placebo |
|-----------------------------|------------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | 0 ^[4] | 0 ^[5] |
| Units: days | | | | |
| number (not applicable) | | | | |

Notes:

[2] - cf. limitations and caveats: no efficacy analyses performed upon premature stop with low no. of pat.

[3] - cf. limitations and caveats: no efficacy analyses performed upon premature stop with low no. of pat.

[4] - cf. limitations and caveats: no efficacy analyses performed upon premature stop with low no. of pat.

[5] - cf. limitations and caveats: no efficacy analyses performed upon premature stop with low no. of pat.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events (TEAEs): Those AEs that occur in the time interval from first administration of study medication until 4 days after end of administration.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 13.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Tepilta |
|-----------------------|---------|

Reporting group description:

Safety analysis set (all patients having received at least one dose of the study medication will be included in the analysis of safety data).

| | |
|-----------------------|------------|
| Reporting group title | Oxetacaine |
|-----------------------|------------|

Reporting group description:

Safety analysis set (all patients having received at least one dose of the study medication will be included in the analysis of safety data).

| | |
|-----------------------|----------|
| Reporting group title | Antacids |
|-----------------------|----------|

Reporting group description:

Safety analysis set (all patients having received at least one dose of the study medication will be included in the analysis of safety data).

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events | Tepilta | Oxetacaine | Antacids |
|---|-----------------|-----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 13 (38.46%) | 2 / 12 (16.67%) | 2 / 9 (22.22%) |
| number of deaths (all causes) | 1 | 0 | 1 |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Skull fracture | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | 0 / 9 (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 |
| Vascular disorders | | | |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 0 / 9 (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 | | | |

| | | | |
|---|----------------|----------------|----------------|
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 0 / 9 (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 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 0 / 9 (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 |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | 0 / 9 (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 |
| Oesophageal stenosis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 1 / 9 (11.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 1 / 9 (11.11%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchopneumonia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 1 / 9 (11.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | 0 / 9 (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 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 0 / 9 (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 |

| Serious adverse events | Placebo | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Skull fracture | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Lymphoedema | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophageal stenosis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---------------|--|--|
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Tepilta | Oxetacaine | Antacids |
|---|------------------|------------------|----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 13 (92.31%) | 10 / 12 (83.33%) | 7 / 9 (77.78%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | 0 / 9 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General disorders and administration site conditions | | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 12 (8.33%) | 1 / 9 (11.11%) |
| occurrences (all) | 1 | 1 | 1 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 12 (8.33%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 12 (8.33%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 0 / 9 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pyrexia | | | |

| | | | |
|--|---------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dysphonia subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Cough subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 3 / 12 (25.00%) 3 | 1 / 9 (11.11%) 1 |
| Dyspnoea subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Hiccups subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 9 (0.00%) 0 |
| Psychiatric disorders | | | |
| Confusional state subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Depression subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Investigations | | | |
| C-reactive protein increased subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Body temperature increased subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Blood aluminium increased subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|--|----------------------|----------------------|---------------------|
| Radiation skin injury subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 4 / 12 (33.33%) 4 | 1 / 9 (11.11%) 1 |
| Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Headache subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 9 (0.00%) 0 |
| Syncope subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 9 (0.00%) 0 |
| Postictal state subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Vocal cord paresis subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all) | 2 / 13 (15.38%) 2 | 1 / 12 (8.33%) 1 | 2 / 9 (22.22%) 2 |
| Anaemia subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 9 (0.00%) 0 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 1 / 12 (8.33%) 1 | 1 / 9 (11.11%) 1 |
| Neutropenia subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 9 (0.00%) 0 |
| Ear and labyrinth disorders | | | |

| | | | |
|--|----------------------|----------------------|---------------------|
| Vertigo subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 9 (0.00%) 0 |
| Gastrointestinal disorders | | | |
| Nausea subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 1 | 3 / 9 (33.33%) 3 |
| Constipation subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 12 (0.00%) 0 | 2 / 9 (22.22%) 2 |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 2 / 12 (16.67%) 2 | 0 / 9 (0.00%) 0 |
| Dysphagia subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 12 (0.00%) 0 | 2 / 9 (22.22%) 2 |
| Odynophagia subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 1 / 12 (8.33%) 1 | 0 / 9 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis subjects affected / exposed occurrences (all) | 2 / 13 (15.38%) 2 | 1 / 12 (8.33%) 1 | 2 / 9 (22.22%) 2 |
| Erythema subjects affected / exposed occurrences (all) | 3 / 13 (23.08%) 3 | 1 / 12 (8.33%) 1 | 1 / 9 (11.11%) 1 |
| Eczema subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Skin hyperpigmentation subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Rash | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Skin lesion subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Back pain subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 12 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Bone pain subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Infections and infestations | | | |
| Pneumonia subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 9 (0.00%) 0 |
| Oral candidiasis subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Tracheitis subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 9 (11.11%) 1 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 12 (0.00%) 0 | 0 / 9 (0.00%) 0 |
| Hyponatraemia | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all) | 0 | 0 | 1 |

| Non-serious adverse events | Placebo | | |
|---|----------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 5 (80.00%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |
| General disorders and administration site conditions | | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dysphonia | | | |

| | | | |
|---|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Cough subjects affected / exposed occurrences (all) | 2 / 5 (40.00%) 2 | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Hiccups subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Psychiatric disorders Confusional state subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Depression subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Investigations C-reactive protein increased subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Body temperature increased subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Blood aluminium increased subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Injury, poisoning and procedural complications Radiation skin injury subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | | |
| Cardiac disorders | | | |

| | | | |
|--|---------------------|--|--|
| Sinus tachycardia subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Headache subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Syncope subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Postictal state subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Vocal cord paresis subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | | |
| Anaemia subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Neutropenia subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Gastrointestinal disorders | | | |

| | | | |
|--|----------------|--|--|
| Nausea | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 0 | | |
| Constipation | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | | |
| occurrences (all) | 2 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |
| Erythema | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eczema | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Skin lesion | | | |

| | | | |
|--|--------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | | |
| occurrences (all) | 1 | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tracheitis | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences (all) | 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 11 April 2012 | Substantial amendment to facilitate recruitment (change of inclusion and exclusion criteria; widening of screening period; additional administrative modifications). |
| 26 July 2013 | Substantial amendment to facilitate recruitment (removal of gastric inhibitors from list of prohibited prior and concomitant medication; additional administrative modifications). |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------------------|---|-----------------|
| 19 December 2012 | Temporary halt of the trial due to stability issues with parts of study medication batches. | 07 October 2013 |

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to difficulties in recruiting suitable patients and low no. of patients reaching randomisation criteria, the study was stopped prematurely. Efficacy analyses were not performed since the no. of patients was too low to draw meaningful conclusions.

Notes: