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

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

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

subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Muscoloskeletal chest pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Oral candidiasis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Tracheitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	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	0 / 5 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Hiccups			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Investigations			
C-reactive protein increased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Body temperature increased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Blood aluminium increased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Haemoglobin decreased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Cardiac disorders			

Sinus tachycardia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Syncope subjects affected / exposed occurrences (all) Postictal state subjects affected / exposed occurrences (all) Vocal cord paresis subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0		
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	 1 / 5 (20.00%) 1 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 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 occurrences (all)	1 / 5 (20.00%) 0			
Constipation subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2			
Diarrhoea subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0			
Dysphagia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0			
Odynophagia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0			
Vomiting subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0			
Skin and subcutaneous tissue disorders				
Dermatitis subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0			
Erythema subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0			
Eczema subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1			
Skin hyperpigmentation subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0			
Rash subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1			
Skin lesion				

subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	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		
Muscoloskeletal 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: