Clinical trial results:
A single blind, multicenter pilot study to investigate the safety and tolerability of a 14 day oral treatment with different doses of the chymase inhibitor BAY 1142524 in comparison to placebo in clinically stable patients with left-ventricular dysfunction after myocardial infarction

Summary

EudraCT number	2014-005297-12
Trial protocol	DE DK
Global end of trial date	04 March 2016

Results information

Result version number	v1 (current)
This version publication date	24 February 2017
First version publication date	24 February 2017

Trial information

Trial identification

Sponsor protocol code	BAY1142524/17055

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02452515
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368 Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	04 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this pilot study was to investigate the safety and tolerability after multiple oral doses of BAY1142524 administered twice daily (BID) (using 3 dose groups) or once daily (OD) (using a 4th dose group) as combinations of 5 and 50 milligram (mg) immediate release (IR) tablets for 14 days in 12 subjects with left-ventricular dysfunction after myocardial infarction (9 verum and 3 placebo) per dose group in a randomized, single blind, placebo-controlled, parallel group, multicenter design.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy:

All patients received evidence-based standard therapy for left ventricular dysfunction after myocardial infarction (MI). This therapy has to include at least an angiotensin-converting-enzyme (ACE) inhibitor or an angiotensin receptor blockers (ARB). Beta-blockers, diuretics, magnetic resonance angiograms (MRAs), antiplatelet therapy, statins, and aspirin are to be used if indicated. Treatment with stable doses of ACE inhibitors or ARBs using at least half of the recommended target dose (as defined in the European Society of Cardiology [ESC] guidelines)

Evidence for comparator: -

Actual start date of recruitment	08 July 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	Denmark: 15
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Italy: 12
Worldwide total number of subjects	49
EEA total number of subjects	49

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	27
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 9 active centers, enrolled subjects in 3 countries: Denmark, Germany and Italy between 08 July 2015 (first subject first visit) and 25 January 2016 (last subject last visit).

Pre-assignment

Screening details:

Overall, 65 subjects were enrolled and screened. Of these, 16 subjects failed screening. The remaining 49 subjects were randomized and assigned to treatment.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received placebo matched to BAY1142524 5 mg, 10 mg, 25 mg IR tablets orally BID and 50 mg IR tablets orally OD for 14 days in the respective arms.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo matched to BAY1142524 5 mg, 10 mg, 25 mg IR tablets orally BID and 50 mg IR tablets orally OD for 14 days.

Arm title	BAY1142524 5 mg BID

Arm description:

Subjects received 5 mg of BAY1142524 orally BID (given as 1 * 5 mg IR tablet in the morning and in the evening) for 14 days.

Arm type	Experimental
Investigational medicinal product name	BAY1142524
Investigational medicinal product code	BAY1142524
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 5 mg of BAY1142524 orally BID (given as 1 * 5 mg IR tablet in the morning and in the evening) for 14 days.

Arm title	BAY1142524 10 mg BID

Arm description:

Subjects received 10 mg of BAY1142524 orally BID (given as 2 * 5 mg IR tablets in the morning and in the evening) for 14 days.

Arm type	Experimental

Investigational medicinal product name	BAY1142524
Investigational medicinal product code	BAY1142524
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 10 mg of BAY1142524 orally BID (given as 2 * 5 mg IR tablets in the morning and in the evening) for 14 days.

Arm title	BAY1142524 25 mg BID

Arm description:

Subjects received 25 mg of BAY1142524 orally BID (given as 5 * 5 mg IR tablets in the morning and in the evening) for 14 days.

Arm type	Experimental
Investigational medicinal product name	BAY1142524
Investigational medicinal product code	BAY1142524
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 25 mg of BAY1142524 orally BID (given as 5 * 5 mg IR tablets in the morning and in the evening) for 14 days.

Arm title	BAY1142524 50 mg OD

Arm description:

Subjects received 50 mg of BAY1142524 orally OD (given as 1 * 50 mg IR tablet in the morning) for 14 days.

Arm type	Experimental
Investigational medicinal product name	BAY1142524
Investigational medicinal product code	BAY1142524
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 50 mg of BAY1142524 orally OD (given as 1 * 50 mg IR tablet in the morning) for 14 days.

Number of subjects in period 1	Placebo	BAY1142524 5 mg BID	BAY1142524 10 mg BID
Started	12	9	9
Completed	12	9	9
Not completed	0	0	0
Withdrawal by subject	-	-	-

Number of subjects in period 1	BAY1142524 25 mg BID	BAY1142524 50 mg OD
Started	10	9
Completed	9	9
Not completed	1	0
Withdrawal by subject	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to BAY1142524 5 mg, 10 mg, 25 mg IR tablets orally BID and 50 mg IR tablets orally OD for 14 days in the respective arms.	
Reporting group title	BAY1142524 5 mg BID
Reporting group description:	
Subjects received 5 mg of BAY1142524 orally BID (given as 1 * 5 mg IR tablet in the morning and in the evening) for 14 days.	
Reporting group title	BAY1142524 10 mg BID
Reporting group description:	
Subjects received 10 mg of BAY1142524 orally BID (given as 2 * 5 mg IR tablets in the morning and in the evening) for 14 days.	
Reporting group title	BAY1142524 25 mg BID
Reporting group description:	
Subjects received 25 mg of BAY1142524 orally BID (given as 5 * 5 mg IR tablets in the morning and in the evening) for 14 days.	
Reporting group title	BAY1142524 50 mg OD
Reporting group description:	
Subjects received 50 mg of BAY1142524 orally OD (given as 1 * 50 mg IR tablet in the morning) for 14 days.	

Reporting group values	Placebo	BAY1142524 5 mg BID	BAY1142524 10 mg BID
Number of subjects	12	9	9
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	62.5	61	64.8
standard deviation	± 9.7	± 7.9	± 7.7
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	12	9	9

Reporting group values	BAY1142524 25 mg BID	BAY1142524 50 mg OD	Total
Number of subjects	10	9	49
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	59.3	64.6	
standard deviation	± 8.3	± 7.1	-

Gender categorical Units: Subjects			
Female	0	2	2
Male	10	7	47

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to BAY1142524 5 mg, 10 mg, 25 mg IR tablets orally BID and 50 mg IR tablets orally OD for 14 days in the respective arms.	
Reporting group title	BAY1142524 5 mg BID
Reporting group description:	
Subjects received 5 mg of BAY1142524 orally BID (given as 1 * 5 mg IR tablet in the morning and in the evening) for 14 days.	
Reporting group title	BAY1142524 10 mg BID
Reporting group description:	
Subjects received 10 mg of BAY1142524 orally BID (given as 2 * 5 mg IR tablets in the morning and in the evening) for 14 days.	
Reporting group title	BAY1142524 25 mg BID
Reporting group description:	
Subjects received 25 mg of BAY1142524 orally BID (given as 5 * 5 mg IR tablets in the morning and in the evening) for 14 days.	
Reporting group title	BAY1142524 50 mg OD
Reporting group description:	
Subjects received 50 mg of BAY1142524 orally OD (given as 1 * 50 mg IR tablet in the morning) for 14 days.	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
SAF (N= 49) included all the subjects who received at least one dose of the study medication.	

Primary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs) by Severity

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs) by Severity[1]
End point description:	
An adverse event (AE) was any untoward medical occurrence in subject who received study drug without regard to possibility of causal relationship. A serious adverse event (SAE) was an AE resulting in any of following outcomes or deemed significant for any other reason: death; initial or prolonged in-patient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly and another medical important serious event as judged by investigator. AE/SAEs that started or worsened after study drug treatment were recorded as TEAE/TESAEs. Mild: an AE that usually transient and might have required only minimal treatment or therapeutic intervention. This did not interfere with usual activities of daily living. Moderate: an AE that usually alleviated with additional specific therapeutic intervention. This interfered with usual activities of daily living, causing discomfort but posed no significant or permanent risk of harm.	
End point type	Primary
End point timeframe:	
From the start of study treatment (Day 0) until end of follow-up (that is 7 to 9 days after last study drug administration on Day 13 and approximately 23 days after first study drug administration)	

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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Placebo	BAY1142524 5 mg BID	BAY1142524 10 mg BID	BAY1142524 25 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12[2]	9[3]	9[4]	10[5]
Units: subjects				
TEAEs	7	4	2	1
Mild TEAEs	5	2	2	1
Moderate TEAEs	2	2	0	0
TESAEs	0	0	0	0

Notes:

[2] - SAF

[3] - SAF

[4] - SAF

[5] - SAF

End point values	BAY1142524 50 mg OD			
Subject group type	Reporting group			
Number of subjects analysed	9[6]			
Units: subjects				
TEAEs	3			
Mild TEAEs	3			
Moderate TEAEs	0			
TESAEs	0			

Notes:

[6] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Potential Hemodynamic Effects (Blood Pressure, Pulse Rate)

End point title	Number of Subjects With Clinically Significant Potential Hemodynamic Effects (Blood Pressure, Pulse Rate)[7]

End point description:

The potential hemodynamic parameters included blood pressure and pulse rate. Blood pressure and pulse rate were measured by using semiautomatic devices after resting the subject in a supine position for at least 15 minutes.

End point type	Primary

End point timeframe:

Day 0 up to Day 20

Notes:

[7] - 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: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Placebo	BAY1142524 5 mg BID	BAY1142524 10 mg BID	BAY1142524 25 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12[8]	9[9]	9[10]	10[11]
Units: subjects				
Blood pressure	0	0	0	0
Pulse rate	0	0	0	0

Notes:

[8] - SAF

[9] - SAF

[10] - SAF

[11] - SAF

End point values	BAY1142524 50 mg OD			
Subject group type	Reporting group			
Number of subjects analysed	9[12]			
Units: subjects				
Blood pressure	0			
Pulse rate	0			

Notes:

[12] - SAF

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of treatment with study drug (day 0) until end of follow-up (i.e. 7 to 9 days after last study drug administration on day 13 and approximately 23 days after first study drug administration)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	BAY1142524 5 mg BID
Reporting group description:	
BAY1142524 5 mg BID	
Reporting group title	Placebo
Reporting group description:	
Placebo	
Reporting group title	BAY1142524 25 mg BID
Reporting group description:	
BAY1142524 25 mg BID	
Reporting group title	BAY1142524 50 mg OD
Reporting group description:	
BAY1142524 50 mg OD	
Reporting group title	BAY1142524 10 mg BID
Reporting group description:	
BAY1142524 10 mg BID	

Serious adverse events	BAY1142524 5 mg BID	Placebo	BAY1142524 25 mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 10 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	BAY1142524 50 mg OD	BAY1142524 10 mg BID	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	BAY1142524 5 mg BID	Placebo	BAY1142524 25 mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 9 (44.44%)	7 / 12 (58.33%)	1 / 10 (10.00%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Amylase increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Lipase increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Glutamate dehydrogenase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypotension			

subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Peripheral coldness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Restless legs syndrome			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Discomfort			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	1 / 9 (11.11%)	1 / 12 (8.33%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Feeling cold			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Ear discomfort			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Oscillopsia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Spinal osteoarthritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 12 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Vestibular neuronitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 12 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Anal abscess			

subjects affected / exposed	0 / 9 (0.00%)	1 / 12 (8.33%)	0 / 10 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	BAY1142524 50 mg OD	BAY1142524 10 mg BID	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)	2 / 9 (22.22%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Amylase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Lipase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Glutamate dehydrogenase increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Vascular disorders			

Hypotension			
subjects affected / exposed	2 / 9 (22.22%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Peripheral coldness			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	2	
Restless legs syndrome			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Discomfort			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Feeling cold			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Ear discomfort			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Oscillopsia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Epistaxis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Spinal osteoarthritis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	5	0	
Infections and infestations			

Vestibular neuronitis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	
Anal abscess subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 August 2015	This amendment included the following modifications: •Exclusion criterion was modified to reflect concomitantly prolonged corrected QT (QTc) interval values in subjects with complete bundle branch block and/or pacemaker, who were eligible for this study. •Additional exploratory metabolite measurements were to performed to investigate metabolite accumulation behaviour after multiple dosing. •An additional measurement for vital signs and electrocardiogram (ECG) on Day 13, pre-dose was added as it had been erroneously forgotten in the first version of the protocol. •Plasma choline esterase and bicarbonate assessment were eliminated from the list of parameters to be analyzed in the safety laboratory. •The paper velocity of the ECG devices to be used in this study was modified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Decimal places were automatically truncated if last decimal equals zero.

Notes: