# 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<br>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<br>subjects affected / exposed<br>occurrences (all) | 0 / 9 (0.00%)<br>0 | 0 / 9 (0.00%)<br>0 | |
| Anal abscess<br>subjects affected / exposed<br>occurrences (all) | 0 / 9 (0.00%)<br>0 | 0 / 9 (0.00%)<br>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:<br>•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.<br>•Additional exploratory metabolite measurements were to performed to investigate metabolite accumulation behaviour after multiple dosing.<br>•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.<br>•Plasma choline esterase and bicarbonate assessment were eliminated from the list of parameters to be analyzed in the safety laboratory.<br>•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: