# Clinical trial results:
# Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, 15-Month Trial of Leuco-methylthioninium bis(hydromethanesulfonate) in Subjects with Mild to Moderate Alzheimer's Disease

## Summary

| | |
|---|---|
| EudraCT number | 2012-002866-11 |
| Trial protocol | GB DE ES IT BG |
| Global end of trial date | 30 November 2015 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 08 February 2020 |
| First version publication date | 08 February 2020 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | TRx-237-015 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | TauRx Therapeutics Ltd |
| Sponsor organisation address | 395 King Street, Aberdeen, United Kingdom, |
| Public contact | Information Desk, TauRx Therapeutics Ltd, +44 1224 440905, info@taurx.com |
| Scientific contact | Information Desk, TauRx Therapeutics Ltd, +44 1224 440905, info@taurx.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 | 15 January 2020 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 30 November 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate clinical efficacy of at least one dose level of leuco-methylthioninium bis(hydromethanesulfonate) (LMTM; hereafter referred to by the international nonproprietary name hydromethylthionine mesylate) in mild to moderate Alzheimer's disease based on change from Baseline on Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog) and Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL), and to assess the safety and tolerability of LMTM 150 and 250 mg/day given for up to 65 weeks.

Protection of trial subjects:

The following measures were repeatedly assessed throughout the course of the study to monitor subject safety: adverse events, clinical laboratory testing (blood and urine), pulse co-oximetry, vital signs, electrocardiograms, physical and neurological examinations, assessment of suicidal ideation/self-harm, and evaluation for potential signs/symptoms of serotonin toxicity.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 02 January 2013 |
| 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 | Croatia: 25 |
| Country: Number of subjects enrolled | Korea, Republic of: 32 |
| Country: Number of subjects enrolled | Australia: 37 |
| Country: Number of subjects enrolled | Canada: 41 |
| Country: Number of subjects enrolled | Malaysia: 16 |
| Country: Number of subjects enrolled | Romania: 24 |
| Country: Number of subjects enrolled | Russian Federation: 68 |
| Country: Number of subjects enrolled | Singapore: 22 |
| Country: Number of subjects enrolled | Taiwan: 22 |
| Country: Number of subjects enrolled | United States: 257 |
| Country: Number of subjects enrolled | Spain: 36 |
| Country: Number of subjects enrolled | United Kingdom: 123 |
| Country: Number of subjects enrolled | Bulgaria: 6 |
| Country: Number of subjects enrolled | Germany: 16 |
| Country: Number of subjects enrolled | Italy: 51 |
| Country: Number of subjects enrolled | Poland: 115 |

| | |
|---|---|
| Worldwide total number of subjects | 891 |
| EEA total number of subjects | 396 |

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) | 213 |
| From 65 to 84 years | 641 |
| 85 years and over | 37 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 1740 subjects provided informed consent, of whom 849 subjects were considered to be screen failures. The most common reason for screen failure was presence of significant focal or vascular intracranial pathology (11%). Ultimately, 891 subjects were randomized (ITT).

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | LMTM 250 mg/day |

Arm description:

Subjects were to be administered LMTM 125 mg tablets twice daily for 65 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Hydromethylthionine mesylate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

LMTM 125 mg tablets were administered orally, in a twice daily regimen.

| | |
|---|---|
| **Arm title** | LMTM 150 mg/day |

Arm description:

Subjects were to be administered LMTM 75 mg tablets twice daily for 65 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Hydromethylthionine mesylate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

LMTM 75 mg tablets were administered orally, in a twice daily regimen.

| | |
|---|---|
| **Arm title** | LMTM 8 mg/day |

Arm description:

Subjects were to be administered LMTM 4 mg tablets twice daily for 65 weeks.

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

Dosage and administration details:

LMTM 4 mg tablets were administered orally, in a twice daily regimen to maintain the study blind.

| **Number of subjects in period 1** | LMTM 250 mg/day | LMTM 150 mg/day | LMTM 8 mg/day |
|---|---|---|---|
| Started | 266 | 268 | 357 |
| Completed | 162 | 183 | 268 |
| Not completed | 104 | 85 | 89 |
| Adverse event, serious fatal | 1 | 2 | - |
| Consent withdrawn by subject | 23 | 25 | 21 |
| Physician decision | 1 | 1 | 4 |
| Amyloid Related Imaging Abnormalities (ARIA) | 1 | 1 | - |
| Adverse event, non-fatal | 43 | 30 | 25 |
| Consent withdrawn by legal representative | - | - | 2 |
| Other | 3 | 4 | 10 |
| Consent withdrawn by caregiver | 16 | 12 | 17 |
| Non-compliance with study drug | 7 | 4 | 2 |
| Lost to follow-up | 4 | 4 | 2 |
| Lack of efficacy | 3 | 2 | 3 |
| Protocol deviation | 2 | - | 3 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | LMTM 250 mg/day |
| Reporting group description: | |
| Subjects were to be administered LMTM 125 mg tablets twice daily for 65 weeks. | |
| Reporting group title | LMTM 150 mg/day |
| Reporting group description: | |
| Subjects were to be administered LMTM 75 mg tablets twice daily for 65 weeks. | |
| Reporting group title | LMTM 8 mg/day |
| Reporting group description: | |
| Subjects were to be administered LMTM 4 mg tablets twice daily for 65 weeks. | |

| Reporting group values | LMTM 250 mg/day | LMTM 150 mg/day | LMTM 8 mg/day |
|---|---|---|---|
| Number of subjects | 266 | 268 | 357 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | <br><br>70.2<br>± 9.26 | <br><br>71.0<br>± 9.31 | <br><br>70.8<br>± 8.48 |
| Gender categorical<br>Units: Subjects | | | |
| Female<br>Male | 152<br>114 | 175<br>93 | 222<br>135 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 891 | | |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | <br><br><br>- | | |
| Gender categorical<br>Units: Subjects | | | |
| Female<br>Male | 549<br>342 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | LMTM 250 mg/day |
| Reporting group description: | |
| Subjects were to be administered LMTM 125 mg tablets twice daily for 65 weeks. | |
| Reporting group title | LMTM 150 mg/day |
| Reporting group description: | |
| Subjects were to be administered LMTM 75 mg tablets twice daily for 65 weeks. | |
| Reporting group title | LMTM 8 mg/day |
| Reporting group description: | |
| Subjects were to be administered LMTM 4 mg tablets twice daily for 65 weeks. | |

### Primary: Change from Baseline to Week 65 in the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog)

| | |
|---|---|
| End point title | Change from Baseline to Week 65 in the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog) |
| End point description: | |
| | |
| End point type | Primary |
| End point timeframe: | |
| 65 weeks | |

| End point values | LMTM 250 mg/day | LMTM 150 mg/day | LMTM 8 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 153 | 171 | 250 | |
| Units: none | | | | |
| least squares mean (confidence interval 95%) | 5.55 (4.27 to 6.83) | 5.97 (4.75 to 7.19) | 5.98 (4.98 to 6.99) | |

### Statistical analyses

| Statistical analysis title | ADAS-cog Primary Analysis (ITT Population) |
|---|---|
| Comparison groups | LMTM 8 mg/day v LMTM 250 mg/day |
| Number of subjects included in analysis | 403 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6022 |
| Method | Mixed models analysis |

| Statistical analysis title | ADAS-cog Primary Analysis (ITT Population) |
|---|---|

| | |
|---|---|
| Comparison groups | LMTM 8 mg/day v LMTM 150 mg/day |
| Number of subjects included in analysis | 421 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9834 |
| Method | Mixed models analysis |

## Primary: Change from Baseline to Week 65 in the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL)

| | |
|---|---|
| End point title | Change from Baseline to Week 65 in the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) |

End point description:

| | |
|---|---|
| End point type | Primary |

End point timeframe:

65 weeks

| **End point values** | LMTM 250 mg/day | LMTM 150 mg/day | LMTM 8 mg/day | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 152 | 172 | 251 | |
| Units: none | | | | |
| least squares mean (confidence interval 95%) | -8.27 (-10.06 to -6.47) | -8.86 (-10.55 to -7.17) | -7.93 (-9.32 to -6.53) | |

### Statistical analyses

| **Statistical analysis title** | ADCS-ADL Primary Analysis (ITT Population) |
|---|---|
| Comparison groups | LMTM 250 mg/day v LMTM 8 mg/day |
| Number of subjects included in analysis | 403 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7701 |
| Method | Mixed models analysis |

| **Statistical analysis title** | ADCS-ADL Primary Analysis (ITT Population) |
|---|---|
| Comparison groups | LMTM 8 mg/day v LMTM 150 mg/day |

| | |
|---|---|
| Number of subjects included in analysis | 423 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4074 |
| Method | Mixed models analysis |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were to be recorded from the time informed consent was signed and continued throughout the study, including the follow-up safety visit (Week 69).

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 16.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | LMTM 250 mg/day |
| Reporting group description: - | |
| Reporting group title | LMTM 150 mg/day |
| Reporting group description: - | |
| Reporting group title | LMTM 8 mg/day |

Reporting group description: -

| Serious adverse events | LMTM 250 mg/day | LMTM 150 mg/day | LMTM 8 mg/day |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 39 / 264 (14.77%) | 44 / 267 (16.48%) | 56 / 354 (15.82%) |
| number of deaths (all causes) | 3 | 3 | 3 |
| number of deaths resulting from adverse events | 3 | 3 | 3 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute lymphocytic leukaemia | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Bladder transitional cell carcinoma stage II | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchioloalveolar carcinoma | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Colon cancer | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 2 / 354 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal stromal tumour | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neoplasm malignant | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pancreatic carcinoma metastatic | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |

| | | | |
|---|---|---|---|
| Reproductive system and breast disorders | | | |
| Colpocele | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Haemothorax | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Abnormal behaviour | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aggression | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 2 / 354 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Agitation | | | |
| subjects affected / exposed | 2 / 264 (0.76%) | 1 / 267 (0.37%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 1 / 267 (0.37%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Delusional disorder, unspecified type | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Depression | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Suicidal ideation | | | |
| subjects affected / exposed | 8 / 264 (3.03%) | 7 / 267 (2.62%) | 11 / 354 (3.11%) |
| occurrences causally related to treatment / all | 0 / 9 | 1 / 7 | 2 / 13 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Suicide attempt | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Behavioural and psychiatric symptoms of dementia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clavicle fracture | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Concussion | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial bones fracture | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Fall | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Fibula fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Head injury | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic fracture | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Pneumothorax traumatic | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Pubis fracture | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 2 / 267 (0.75%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Skull fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Subdural haematoma | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 2 / 354 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 1 / 267 (0.37%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Cardiac arrest | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Nervous system disorders | | | |
| Amyloid related imaging abnormalities | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 4 / 267 (1.50%) | 3 / 354 (0.85%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 4 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebellar haematoma | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Cerebrovascular accident | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cognitive disorder | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Dementia Alzheimer's type | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 3 / 354 (0.85%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| Dizziness postural | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemic seizure | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Myoclonus | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parkinsonism | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Post polio syndrome | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Serotonin syndrome | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 2 / 264 (0.76%) | 1 / 267 (0.37%) | 2 / 354 (0.56%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Convulsion | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 5 / 354 (1.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 4 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 1 / 267 (0.37%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Enteritis | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric disorder | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Hepatobiliary disorders | | | |
| Biliary colic | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure chronic | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue | | | |

| | | | |
|---|---|---|---|
| disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Back pain | | | |
| subjects affected / exposed | 2 / 264 (0.76%) | 1 / 267 (0.37%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Costochondritis | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Myositis | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 2 / 354 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal column stenosis | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Abdominal abscess | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 1 / 267 (0.37%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis infective | | | |
| subjects affected / exposed | 1 / 264 (0.38%) | 0 / 267 (0.00%) | 0 / 354 (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 |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 0 / 267 (0.00%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 2 / 267 (0.75%) | 0 / 354 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 264 (0.76%) | 1 / 267 (0.37%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 0 / 354 (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 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 264 (0.00%) | 1 / 267 (0.37%) | 1 / 354 (0.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | LMTM 250 mg/day | LMTM 150 mg/day | LMTM 8 mg/day |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 228 / 264 (86.36%) | 221 / 267 (82.77%) | 291 / 354 (82.20%) |
| Investigations | | | |
| Blood folate decreased | | | |
| subjects affected / exposed | 19 / 264 (7.20%) | 18 / 267 (6.74%) | 21 / 354 (5.93%) |
| occurrences (all) | 22 | 20 | 23 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 11 / 264 (4.17%) | 17 / 267 (6.37%) | 30 / 354 (8.47%) |
| occurrences (all) | 13 | 20 | 39 |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Dizziness | | | |
| subjects affected / exposed | 8 / 264 (3.03%) | 22 / 267 (8.24%) | 21 / 354 (5.93%) |
| occurrences (all) | 12 | 26 | 28 |
| Headache | | | |
| subjects affected / exposed | 14 / 264 (5.30%) | 15 / 267 (5.62%) | 23 / 354 (6.50%) |
| occurrences (all) | 16 | 17 | 27 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 15 / 264 (5.68%) | 22 / 267 (8.24%) | 10 / 354 (2.82%) |
| occurrences (all) | 16 | 26 | 12 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 67 / 264 (25.38%) | 62 / 267 (23.22%) | 33 / 354 (9.32%) |
| occurrences (all) | 104 | 104 | 35 |
| Nausea | | | |
| subjects affected / exposed | 19 / 264 (7.20%) | 22 / 267 (8.24%) | 14 / 354 (3.95%) |
| occurrences (all) | 25 | 27 | 15 |
| Vomiting | | | |
| subjects affected / exposed | 18 / 264 (6.82%) | 24 / 267 (8.99%) | 2 / 354 (0.56%) |
| occurrences (all) | 28 | 29 | 2 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 11 / 264 (4.17%) | 14 / 267 (5.24%) | 12 / 354 (3.39%) |
| occurrences (all) | 13 | 14 | 13 |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 14 / 264 (5.30%) | 13 / 267 (4.87%) | 21 / 354 (5.93%) |
| occurrences (all) | 15 | 15 | 26 |
| Anxiety | | | |
| subjects affected / exposed | 7 / 264 (2.65%) | 3 / 267 (1.12%) | 19 / 354 (5.37%) |
| occurrences (all) | 7 | 5 | 20 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 27 / 264 (10.23%) | 7 / 267 (2.62%) | 3 / 354 (0.85%) |
| occurrences (all) | 31 | 8 | 3 |
| Pollakiuria | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 18 / 264 (6.82%) | 15 / 267 (5.62%) | 6 / 354 (1.69%) |
| occurrences (all) | 19 | 18 | 7 |
| Urinary incontinence | | | |
| subjects affected / exposed | 12 / 264 (4.55%) | 18 / 267 (6.74%) | 9 / 354 (2.54%) |
| occurrences (all) | 13 | 20 | 9 |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 25 / 264 (9.47%) | 28 / 267 (10.49%) | 28 / 354 (7.91%) |
| occurrences (all) | 31 | 42 | 34 |
| Metabolism and nutrition disorders | | | |
| Folate deficiency | | | |
| subjects affected / exposed | 15 / 264 (5.68%) | 10 / 267 (3.75%) | 11 / 354 (3.11%) |
| occurrences (all) | 17 | 14 | 12 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 19 February 2013 | In Protocol Version 2.0, study personnel information was corrected and/or updated; background information was modified to include new reproductive toxicity findings (the discussion of contraceptive measures was also updated accordingly) and clinical pharmacokinetic and safety data; inclusion and exclusion criteria were modified; and clarifications and/or modifications to efficacy, safety, and other assessments and procedural activities were incorporated. Additional administrative and/or editorial revisions were incorporated to eliminate discrepancies or provide clarification. |
| 25 October 2013 | In Protocol Version 3.0, the treatment duration was extended from 12 months to 15 months in order to allow for greater placebo decline; as a result, an additional post-baseline on-treatment visit and an additional telephone contact for assessment of safety were added and incorporated throughout the study protocol. Given that all subjects received some amount of LMTM, the Sponsor did not plan to routinely unblind treatment allocation for suspected, unexpected serious adverse reactions (SUSARs) for expedited reporting; guidance for Sponsor reporting of SUSARs to regulatory authorities was revised accordingly. Revisions also included modifications or clarifications to background information; inclusion and exclusion criteria; study drug administration and packaging; efficacy, safety, and other assessments/procedures; statistical analyses; and administrative procedures. Additional editorial revisions were incorporated to eliminate discrepancies or provide clarification. |
| 14 September 2015 | In Protocol Version 6.0, modifications (relative to Protocol Version 3.0) included updates to administrative and background information, clarifications to exclusion criteria, modifications to study objectives and efficacy/statistical analyses, safety and exploratory assessments and/or procedures (including for quality assurance and clinical monitoring), as well as other minor revisions to provide further clarification. It should be noted that the protocol was amended in the interim to modify the procedure for dose reduction and to no longer require magnetic resonance imaging (MRI) monitoring for evaluation of amyloid-related imaging abnormalities; however, as these interim amendments were not distributed for implementation at the clinical sites and were superseded by Protocol Version 6.0, the dose reduction procedures and MRI monitoring were maintained. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported