



Clinical trial results:

Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, 18-Month Safety and Efficacy Study of Leuco-methylthioninium bis (hydromethanesulfonate) in Subjects with Mild Alzheimer's Disease Summary

EudraCT number	2012-002847-28
Trial protocol	DE BE GB NL ES FI IT HR
Global end of trial date	27 May 2016

Results information

Result version number	v1 (current)
This version publication date	10 April 2020
First version publication date	10 April 2020

Trial information

Trial identification

Sponsor protocol code	TRx-237-005
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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	04 February 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	27 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate clinical efficacy of leuco-methylthionium bis(hydromethanesulfonate) (LMTM; hereafter referred to by the international nonproprietary name hydromethylthionine mesylate) in mild 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 200 mg/day given for up to 78 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 tests (blood and urine), pulse co-oximetry, vital signs, electrocardiograms, physical and neurological examinations, brain Magnetic Resonance Imaging (MRI), assessment of suicidal ideation/self harm, and evaluation potential signs/symptoms of serotonin toxicity.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 October 2012
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	Netherlands: 2
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	United Kingdom: 88
Country: Number of subjects enrolled	Croatia: 25
Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	Finland: 28
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Italy: 29
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	United States: 524
Worldwide total number of subjects	795
EEA total number of subjects	253

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)	195
From 65 to 84 years	565
85 years and over	35

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1475 subjects provided informed consent, of whom 675 were considered to be screen failures. The most common reason for screen failure was not meeting CDR or MMSE total score requirements (11%). A total of 800 subjects were randomized; however, data for 5 subjects were excluded, thus 795 subjects were included in the ITT population.

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	Investigator, Monitor, Carer, Subject, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	LMTM 200 mg/day

Arm description:

Subjects were to be administered LMTM 100 mg tablets twice daily for 78 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 100 mg tablets were administered orally, in a twice daily regimen.

Arm title	LMTM 8 mg/day
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Arm description:

Subjects were to be administered LMTM 4 mg tablets twice daily for 78 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 200 mg/day	LMTM 8 mg/day
Started	399	396
Completed	221	305
Not completed	178	91
Adverse event, serious fatal	1	2
Noncompliance with Study Drug	8	3
Consent withdrawn by subject	57	25
Physician decision	2	2
Adverse event, non-fatal	62	23
Other	7	7
Consent withdrawn by caregiver	20	10
Lost to follow-up	7	4
Consent withdrawn by LAR	-	1
Lack of efficacy	8	8
Protocol deviation	6	6

Baseline characteristics

Reporting groups

Reporting group title	LMTM 200 mg/day
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Reporting group description:

Subjects were to be administered LMTM 100 mg tablets twice daily for 78 weeks.

Reporting group title	LMTM 8 mg/day
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Reporting group description:

Subjects were to be administered LMTM 4 mg tablets twice daily for 78 weeks.

Reporting group values	LMTM 200 mg/day	LMTM 8 mg/day	Total
Number of subjects	399	396	795
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	70.6 ± 8.9	70.5 ± 9.1	-
Gender categorical Units: Subjects			
Female	213	209	422
Male	186	187	373

End points

End points reporting groups

Reporting group title	LMTM 200 mg/day
Reporting group description:	
Subjects were to be administered LMTM 100 mg tablets twice daily for 78 weeks.	
Reporting group title	LMTM 8 mg/day
Reporting group description:	
Subjects were to be administered LMTM 4 mg tablets twice daily for 78 weeks.	

Primary: Change from Baseline to Week 78 in the Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-cog)

End point title	Change from Baseline to Week 78 in the Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-cog)
End point description:	
End point type	Primary
End point timeframe:	
78 weeks	

End point values	LMTM 200 mg/day	LMTM 8 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	299		
Units: none				
least squares mean (confidence interval 95%)	6.41 (5.31 to 7.50)	6.27 (5.31 to 7.24)		

Statistical analyses

Statistical analysis title	ADAS-cog Primary Analysis (ITT Population)
Comparison groups	LMTM 200 mg/day v LMTM 8 mg/day
Number of subjects included in analysis	515
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8584
Method	Mixed models analysis

Primary: Change from Baseline to Week 78 in the Alzheimer's Disease Cooperative Study - Activities of Daily living (ADCS-ADL)

End point title	Change from Baseline to Week 78 in the Alzheimer's Disease Cooperative Study - Activities of Daily living (ADCS-ADL)
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End point description:

End point type	Primary
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End point timeframe:

78 weeks

End point values	LMTM 200 mg/day	LMTM 8 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	216	298		
Units: none				
least squares mean (confidence interval 95%)	-8.92 (-10.35 to -7.49)	-8.18 (-9.43 to -6.92)		

Statistical analyses

Statistical analysis title	ADCS-ADL Primary Analysis (ITT Population)
Comparison groups	LMTM 200 mg/day v LMTM 8 mg/day
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4433
Method	Mixed models analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were to be recorded from the time of screening and continued throughout the study, including the follow-up safety visit (week 78).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	LMTM 200 mg/day
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Reporting group description:

Subjects were to be administered LMTM 100 mg tablets twice daily for 78 weeks.

Reporting group title	LMTM 8 mg/day
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Reporting group description:

Subjects were to be administered LMTM 4 mg tablets twice daily for 78 weeks.

Serious adverse events	LMTM 200 mg/day	LMTM 8 mg/day	
Total subjects affected by serious adverse events			
subjects affected / exposed	71 / 398 (17.84%)	76 / 396 (19.19%)	
number of deaths (all causes)	5	4	
number of deaths resulting from adverse events	5	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal papillary mucinous neoplasm			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			

subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	2 / 398 (0.50%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 398 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant hypertension			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subgaleal haematoma			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	3 / 398 (0.75%)	4 / 396 (1.01%)	
occurrences causally related to treatment / all	0 / 3	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Oedema peripheral			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perforated ulcer			
subjects affected / exposed	2 / 398 (0.50%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 398 (0.50%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Homicide			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	2 / 398 (0.50%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis chronic			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abnormal behaviour			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agitation			
subjects affected / exposed	2 / 398 (0.50%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	2 / 398 (0.50%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	2 / 398 (0.50%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delusion			
subjects affected / exposed	1 / 398 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			

subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	11 / 398 (2.76%)	12 / 396 (3.03%)	
occurrences causally related to treatment / all	0 / 16	2 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 398 (0.00%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	3 / 398 (0.75%)	6 / 396 (1.52%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 398 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			

subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 398 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 398 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	2 / 398 (0.50%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			

subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 398 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 398 (0.25%)	3 / 396 (0.76%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	2 / 398 (0.50%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	3 / 398 (0.75%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			

subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	2 / 398 (0.50%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dementia Alzheimer's type			
subjects affected / exposed	2 / 398 (0.50%)	3 / 396 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Metabolic encephalopathy			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Amyloid related imaging abnormalities			
subjects affected / exposed	1 / 398 (0.25%)	4 / 396 (1.01%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain stem haemorrhage			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			

subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoclonus			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serotonin syndrome			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	4 / 398 (1.01%)	5 / 396 (1.26%)	
occurrences causally related to treatment / all	1 / 4	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colonic stenosis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	2 / 398 (0.50%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			

subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis relapsing			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			

subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 398 (0.00%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 398 (0.00%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 398 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic fracture			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations Abdominal abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 398 (0.00%) 0 / 0 0 / 0	1 / 396 (0.25%) 1 / 1 0 / 0	
Babesiosis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 398 (0.25%) 0 / 1 0 / 0	0 / 396 (0.00%) 0 / 0 0 / 0	
Bronchitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 398 (0.25%) 0 / 1 0 / 0	0 / 396 (0.00%) 0 / 0 0 / 0	
Campylobacter gastroenteritis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 398 (0.00%) 0 / 0 0 / 0	1 / 396 (0.25%) 0 / 1 0 / 0	
Campylobacter infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 398 (0.00%) 0 / 0 0 / 0	1 / 396 (0.25%) 0 / 1 0 / 0	
Cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 398 (0.25%) 0 / 1 0 / 0	1 / 396 (0.25%) 0 / 1 0 / 0	
Cryptosporidiosis infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 398 (0.25%) 0 / 1 0 / 0	0 / 396 (0.00%) 0 / 0 0 / 0	
Cystitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 398 (0.25%) 0 / 1 0 / 0	0 / 396 (0.00%) 0 / 0 0 / 0	
Escherichia sepsis			

subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 398 (0.50%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	2 / 398 (0.50%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 398 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 398 (0.00%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 398 (0.25%)	5 / 396 (1.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 398 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food intolerance			
subjects affected / exposed	0 / 398 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 398 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 398 (0.25%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	LMTM 200 mg/day	LMTM 8 mg/day	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	342 / 398 (85.93%)	333 / 396 (84.09%)	
Investigations			
Blood folate decreased			
subjects affected / exposed	30 / 398 (7.54%)	18 / 396 (4.55%)	
occurrences (all)	32	20	
Injury, poisoning and procedural complications			

Fall subjects affected / exposed occurrences (all)	34 / 398 (8.54%) 46	44 / 396 (11.11%) 58	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	30 / 398 (7.54%) 35	27 / 396 (6.82%) 33	
Headache subjects affected / exposed occurrences (all)	27 / 398 (6.78%) 30	24 / 396 (6.06%) 24	
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	20 / 398 (5.03%) 22	12 / 396 (3.03%) 12	
Gastrointestinal disorders			
Nausea subjects affected / exposed occurrences (all)	41 / 398 (10.30%) 43	22 / 396 (5.56%) 27	
Diarrhoea subjects affected / exposed occurrences (all)	124 / 398 (31.16%) 187	66 / 396 (16.67%) 85	
Vomiting subjects affected / exposed occurrences (all)	28 / 398 (7.04%) 33	12 / 396 (3.03%) 13	
Psychiatric disorders			
Confusional state subjects affected / exposed occurrences (all)	20 / 398 (5.03%) 24	7 / 396 (1.77%) 11	
Anxiety subjects affected / exposed occurrences (all)	25 / 398 (6.28%) 28	28 / 396 (7.07%) 31	
Depression subjects affected / exposed occurrences (all)	17 / 398 (4.27%) 20	28 / 396 (7.07%) 31	
Agitation			

subjects affected / exposed occurrences (all)	24 / 398 (6.03%) 26	16 / 396 (4.04%) 19	
Renal and urinary disorders Urinary incontinence subjects affected / exposed occurrences (all)	24 / 398 (6.03%) 30	12 / 396 (3.03%) 15	
Dysuria subjects affected / exposed occurrences (all)	35 / 398 (8.79%) 40	3 / 396 (0.76%) 3	
Pollakiuria subjects affected / exposed occurrences (all)	28 / 398 (7.04%) 29	10 / 396 (2.53%) 11	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	22 / 398 (5.53%) 22	18 / 396 (4.55%) 19	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	20 / 398 (5.03%) 25	21 / 396 (5.30%) 21	
Urinary tract infection subjects affected / exposed occurrences (all)	47 / 398 (11.81%) 62	32 / 396 (8.08%) 44	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	23 / 398 (5.78%) 24	5 / 396 (1.26%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2013	In Protocol Version 2.1, revisions (relative to Protocol Version 1.0) included the following: study personnel information was corrected and/or updated; background information was updated to include new reproductive toxicity findings (the discussion of contraceptive measures was also updated accordingly); 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.
30 October 2013	In Protocol Version 3.0, revisions included modifications and/or clarifications to the overall protocol/background information; inclusion/exclusion criteria; study drug administration/packaging; efficacy, safety, and other assessments/procedures; statistical analysis; and administrative procedures. Target recruitment was modified to 700 subjects (350 per arm).
11 December 2013	In Protocol Version 4.0, revisions included clarifications and/or modifications to the inclusion and exclusion criteria, safety and other assessments or procedures, as well as other administrative revisions.
25 September 2015	In Protocol Version 7.0, revisions (relative to Protocol Version 4.0) 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, as well as other minor revisions to provide further clarification. Modifications to the procedures for quality assurance, clinical monitoring, and dose reduction were incorporated.

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.

None reported

Notes: