



## 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
<b>Arm title</b>	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.

<b>Arm title</b>	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.

<b>Arm title</b>	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.

<b>Number of subjects in period 1</b>	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			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	70.2	71.0	70.8
standard deviation	± 9.26	± 9.31	± 8.48
Gender categorical			
Units: Subjects			
Female	152	175	222
Male	114	93	135

Reporting group values	Total		
Number of subjects	891		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	549		
Male	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**

<b>Statistical analysis title</b>	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

<b>Statistical analysis title</b>	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
<b>Gastrointestinal disorders</b>			
<b>Abdominal pain</b>			
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
<b>Abdominal pain upper</b>			
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
<b>Diarrhoea</b>			
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
<b>Duodenal ulcer haemorrhage</b>			
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
<b>Enteritis</b>			
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
<b>Gastric disorder</b>			
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
<b>Ileus</b>			
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
<b>Inguinal hernia</b>			

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 %

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