Clinical trial results:
An Open-Label, Extension Study of the Effects of Leuco-methylthioninium bis(hydromethanesulfonate) in Subjects with Alzheimer's Disease or Behavioral Variant Frontotemporal Dementia

Summary

EudraCT number	2014-002013-37
Trial protocol	GB ES FI BE HR NL
Global end of trial date	19 May 2017

Results information

Result version number	v1 (current)
This version publication date	18 November 2020
First version publication date	18 November 2020

Trial information

Trial identification

Sponsor protocol code	TRx-237-020

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 1224440905, info@taurx.com
Scientific contact	Information Desk, TauRx Therapeutics Ltd, +44 1224440905, 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	21 August 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 May 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this open-label extension study are to provide subjects who have completed participation in a Phase 2 or Phase 3 trial continued access to therapy and to evaluate the long-term safety and tolerability of leuco-methylthioninium bis(hydromethanesulfonate) (LMTM; hereafter referred to by the international nonproprietary name hydromethylthionine mesylate) given in flexible doses of up to 300 mg/day.

Protection of trial subjects:

The following measures were repeatedly assessed throughout the course of the study to monitor subject safety: adverse events, vital signs, clinical laboratory findings, electrocardiograms, and targeted physical and neurological examinations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 August 2014
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	Australia: 41
Country: Number of subjects enrolled	Canada: 51
Country: Number of subjects enrolled	Korea, Republic of: 13
Country: Number of subjects enrolled	Malaysia: 8
Country: Number of subjects enrolled	Russian Federation: 35
Country: Number of subjects enrolled	Singapore: 22
Country: Number of subjects enrolled	Taiwan: 16
Country: Number of subjects enrolled	United States: 459
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Spain: 39
Country: Number of subjects enrolled	United Kingdom: 162
Country: Number of subjects enrolled	Croatia: 11
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Finland: 18
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 12

Worldwide total number of subjects	913
EEA total number of subjects	268

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)	270
From 65 to 84 years	611
85 years and over	32

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who completed participation in a Phase 2 or 3 LMTM study were eligible to enroll, pending their ability to meet the inclusion/exclusion criteria. A total of 913 subjects enrolled; however, data for 16 subjects in Spain were excluded and 1 UK subject was enrolled but never dosed; thus, 896 subjects are included in the analyses.

Period 1

Period 1 title	Open-Label LMTM Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	LMTM 100-300 mg/day

Arm description:

The initial LMTM dose was 200 mg/day (one 100-mg tablet twice daily), except in subjects with bvFTD who were taking a reduced dose (i.e., 100 mg/day) upon entering this extension study. The dose could be increased (after at least 13 weeks of treatment) or decreased (at any time at or after 2 weeks of treatment) by the Investigator in 100-mg increments or decrements. The maximum allowable dose was 300 mg/day (or in those countries where limited by a Competent Authority or Ethics Committee, 200 mg/day).

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 flexible dosing regimen (100-300 mg/day).

Number of subjects in period 1	LMTM 100-300 mg/day
Started	913
Completed	60
Not completed	853
Adverse event, serious fatal	9
Physician decision	14
Consent withdrawn by subject	77
Study terminated by Sponsor	346
Adverse event, non-fatal	144
Other	17
Missing (Site closure)	16
Non-compliance with study drug	11

Consent withdrawn by caregiver	85
Lost to follow-up	5
Consent withdrawn by LAR	31
Lack of efficacy	98

Baseline characteristics

Reporting groups

Reporting group title	LMTM 100-300 mg/day

Reporting group description:

The initial LMTM dose was 200 mg/day (one 100-mg tablet twice daily), except in subjects with bvFTD who were taking a reduced dose (i.e., 100 mg/day) upon entering this extension study. The dose could be increased (after at least 13 weeks of treatment) or decreased (at any time at or after 2 weeks of treatment) by the Investigator in 100-mg increments or decrements. The maximum allowable dose was 300 mg/day (or in those countries where limited by a Competent Authority or Ethics Committee, 200 mg/day).

Reporting group values	LMTM 100-300 mg/day	Total	
Number of subjects	913	913	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	69.2		
full range (min-max)	39 to 89	-	
Gender categorical Units: Subjects			
Female	487	487	
Male	426	426	

Subject analysis sets

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population was composed of patients dosed with 100-300 mg LMTM who were used for analysis. Safety evaluations included intervening medical history, adverse events, concomitant medication, seated blood pressure and pulse, body weight, clinical laboratory tests including serum pregnancy testing in women of childbearing potential, 12-lead electrocardiograms, and targeted physical and neurological examinations.

Reporting group values	Safety Population		
Number of subjects	896		

Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	69.2		
full range (min-max)	39 to 89		
Gender categorical Units: Subjects			
Female	478		
Male	418		

End points

End points reporting groups

Reporting group title	LMTM 100-300 mg/day

Reporting group description:

The initial LMTM dose was 200 mg/day (one 100-mg tablet twice daily), except in subjects with bvFTD who were taking a reduced dose (i.e., 100 mg/day) upon entering this extension study. The dose could be increased (after at least 13 weeks of treatment) or decreased (at any time at or after 2 weeks of treatment) by the Investigator in 100-mg increments or decrements. The maximum allowable dose was 300 mg/day (or in those countries where limited by a Competent Authority or Ethics Committee, 200 mg/day).

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population was composed of patients dosed with 100-300 mg LMTM who were used for analysis. Safety evaluations included intervening medical history, adverse events, concomitant medication, seated blood pressure and pulse, body weight, clinical laboratory tests including serum pregnancy testing in women of childbearing potential, 12-lead electrocardiograms, and targeted physical and neurological examinations.

Primary: Incidence of Study-emergent Adverse Events

End point title	Incidence of Study-emergent Adverse Events[1]

End point description:

End point type	Primary

End point timeframe:

Study-emergent adverse events (onset of new AEs or worsening of pre-existing AEs) were recorded from the time of first dose in this study to the end of study participation.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were planned; only summary tables and listings.

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	896			
Units: subjects	734			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

As the study was terminated early, AEs were reported from the time of subject enrollment to the termination of the extended open-label period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	LMTM (100-300 mg/day)

Reporting group description: -

Serious adverse events	LMTM (100-300 mg/day)		
Total subjects affected by serious adverse events			
subjects affected / exposed	146 / 896 (16.29%)		
number of deaths (all causes)	15		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder cancer			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer recurrent			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Chronic lymphocytic leukaemia				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malignant melanoma				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Metastatic neoplasm				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Non-Hodgkin's lymphoma				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Oesophageal carcinoma				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian cancer				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal cell carcinoma				

subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of lung				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tonsil cancer				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Circulatory collapse				
subjects affected / exposed	2 / 896 (0.22%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertensive crisis				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Orthostatic hypotension				
subjects affected / exposed	2 / 896 (0.22%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Thrombosis				

subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	4 / 896 (0.45%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Uterine prolapse			
subjects affected / exposed	2 / 896 (0.22%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	4 / 896 (0.45%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Dyspnoea			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoxia			

subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	3 / 896 (0.33%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Abnormal behaviour				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aggression				
subjects affected / exposed	3 / 896 (0.33%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Agitation				
subjects affected / exposed	4 / 896 (0.45%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Delirium				

subjects affected / exposed	3 / 896 (0.33%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Hallucination, visual				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypersexuality				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mental status changes				
subjects affected / exposed	3 / 896 (0.33%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Staring				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Suicidal ideation				
subjects affected / exposed	3 / 896 (0.33%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Suicide attempt				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood glucose increased				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Liver function test abnormal				

subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Concussion				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Facial bones fracture				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	9 / 896 (1.00%)			
occurrences causally related to treatment / all	2 / 9			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	2 / 896 (0.22%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	2 / 896 (0.22%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Humerus fracture				

subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Overdose				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary contusion				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper limb fracture				

subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	2 / 896 (0.22%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	2 / 896 (0.22%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Cardiac arrest			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	2 / 896 (0.22%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 2		
Myocardial infarction			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sick sinus syndrome			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			

subjects affected / exposed	2 / 896 (0.22%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Coordination abnormal				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dementia				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Dementia Alzheimer's type				
subjects affected / exposed	3 / 896 (0.33%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 3			
Grand mal convulsion				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lacunar infarction				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Loss of consciousness				

subjects affected / exposed	2 / 896 (0.22%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Migraine				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure like phenomena				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Serotonin syndrome				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	6 / 896 (0.67%)			
occurrences causally related to treatment / all	2 / 7			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	4 / 896 (0.45%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Tremor				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
VIIth nerve paralysis				

subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemolytic anaemia			
subjects affected / exposed	2 / 896 (0.22%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis microscopic			
subjects affected / exposed	2 / 896 (0.22%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer perforation			

subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Faecaloma				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal obstruction				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis				

subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
subjects affected / exposed	2 / 896 (0.22%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Hyperhidrosis				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Bladder mass				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bladder prolapse				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cystitis noninfective				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematuria				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				
subjects affected / exposed	2 / 896 (0.22%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Nephropathy				

subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	2 / 896 (0.22%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Renal impairment				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract obstruction				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Costochondritis				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal pain				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rotator cuff syndrome				
subjects affected / exposed	2 / 896 (0.22%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Spondylolisthesis				

subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	3 / 896 (0.33%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Bacterial pyelonephritis			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis infective			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile infection			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	6 / 896 (0.67%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 1			
Sepsis				
subjects affected / exposed	4 / 896 (0.45%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	11 / 896 (1.23%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral upper respiratory tract infection				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	4 / 896 (0.45%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Diabetic ketoacidosis				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	1 / 896 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				

subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypovolaemia			
subjects affected / exposed	1 / 896 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	LMTM (100-300 mg/day)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	717 / 896 (80.02%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	20 / 896 (2.23%)		
occurrences (all)	20		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	20 / 896 (2.23%)		
occurrences (all)	23		
Immune system disorders			
Urinary tract infection			
subjects affected / exposed	49 / 896 (5.47%)		
occurrences (all)	72		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 896 (2.68%)		
occurrences (all)	24		
Psychiatric disorders			
Agitation			
subjects affected / exposed	46 / 896 (5.13%)		
occurrences (all)	59		
Anxiety			

subjects affected / exposed	32 / 896 (3.57%)		
occurrences (all)	35		
Confusional state			
subjects affected / exposed	34 / 896 (3.79%)		
occurrences (all)	39		
Depression			
subjects affected / exposed	21 / 896 (2.34%)		
occurrences (all)	21		
Insomnia			
subjects affected / exposed	19 / 896 (2.12%)		
occurrences (all)	21		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	21 / 896 (2.34%)		
occurrences (all)	21		
Creatinine renal clearance decreased			
subjects affected / exposed	33 / 896 (3.68%)		
occurrences (all)	37		
Haemoglobin decreased			
subjects affected / exposed	40 / 896 (4.46%)		
occurrences (all)	44		
Weight decreased			
subjects affected / exposed	30 / 896 (3.35%)		
occurrences (all)	31		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	62 / 896 (6.92%)		
occurrences (all)	79		
Nervous system disorders			
Dizziness			
subjects affected / exposed	23 / 896 (2.57%)		
occurrences (all)	31		
Headache			
subjects affected / exposed	29 / 896 (3.24%)		
occurrences (all)	33		
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	43 / 896 (4.80%)		
occurrences (all)	45		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	123 / 896 (13.73%)		
occurrences (all)	174		
Nausea			
subjects affected / exposed	44 / 896 (4.91%)		
occurrences (all)	56		
Constipation			
subjects affected / exposed	18 / 896 (2.01%)		
occurrences (all)	19		
Vomiting			
subjects affected / exposed	36 / 896 (4.02%)		
occurrences (all)	40		
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	55 / 896 (6.14%)		
occurrences (all)	58		
Urinary incontinence			
subjects affected / exposed	60 / 896 (6.70%)		
occurrences (all)	67		
Dysuria			
subjects affected / exposed	39 / 896 (4.35%)		
occurrences (all)	45		
Micturition urgency			
subjects affected / exposed	29 / 896 (3.24%)		
occurrences (all)	30		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	27 / 896 (3.01%)		
occurrences (all)	34		
Back pain			
subjects affected / exposed	18 / 896 (2.01%)		
occurrences (all)	21		

Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	18 / 896 (2.01%)		
occurrences (all)	21		
Nasopharyngitis			
subjects affected / exposed	27 / 896 (3.01%)		
occurrences (all)	31		
Upper respiratory tract infection			
subjects affected / exposed	27 / 896 (3.01%)		
occurrences (all)	34		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 September 2015	In Protocol Version 2.1, the exclusion and discontinuation/withdrawal criteria for subjects in Germany was modified, and the maximum allowable dose was restricted to 200 mg/day in certain countries. Storage conditions, study assessments, and procedures were further clarified, and the Global Project Lead and contact for Pharmacovigilance were changed.
28 July 2016	In Protocol Version 3.0, neurological assessments at Baseline were added; Global Project Lead, Head of Safety, and Medical Monitoring personnel were changed; and personnel responsible for new ECG assessments were added. Clarifications were made to the inclusion criteria, study assessments, and statistical analyses for safety evaluations, and other procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported