Clinical trial results:
Randomized, Double-Blind, Placebo-Controlled, Three-Arm, 12-Month, Safety and Efficacy Study of Hydromethylthionine Mesylate (LMTM) Monotherapy in Subjects with Alzheimer's Disease Followed by a 12-Month Open-Label Treatment

Summary

EudraCT number	2017-003558-17
Trial protocol	GB BE PL ES FR IT
Global end of trial date	04 April 2023

Results information

Result version number	v1 (current)
This version publication date	20 April 2024
First version publication date	20 April 2024

Trial information

Trial identification

Sponsor protocol code	TRx-237-039

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03446001
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	TauRx Therapeutics Ltd
Sponsor organisation address	395 King Street, Aberdeen, United Kingdom, AB24 5RP
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	07 March 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2022
Global end of trial reached?	Yes
Global end of trial date	04 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To compare the HMTM dose of 16 mg/day with the control group on the following coprimary clinical endpoints:
a. Alzheimer's Disease Assessment Scale, 11-item version (ADAS-cog11)
b. Alzheimer's Disease Cooperative Study - Activities of Daily Living, 23-item version (ADCS-ADL23)

2. To assess the safety and tolerability of HMTM 16 mg/day given for up to 52 weeks and up to 104 weeks

3. To determine if there is a difference in disease progression on the coprimary clinical endpoints and the MRI imaging endpoint for subjects who started treatment in the double-blind phase and those who started treatment in the open-label, delayed-start phase (referred to as "early" and "late" HMTM starters, respectively)

Protection of trial subjects:

The following measures were repeatedly assessed throughout the course of the study to monitor subject safety: adverse events, clinical laboratory evaluations (serum chemistry and hematology), vital signs (blood pressure, pulse, and body weight), physical and neurological examinations, and ophthalmological examinations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2017
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	Canada: 16
Country: Number of subjects enrolled	United States: 333
Country: Number of subjects enrolled	Poland: 80
Country: Number of subjects enrolled	Spain: 44
Country: Number of subjects enrolled	United Kingdom: 54
Country: Number of subjects enrolled	France: 44
Country: Number of subjects enrolled	Italy: 27
Worldwide total number of subjects	598
EEA total number of subjects	195

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)	114
From 65 to 84 years	459
85 years and over	25

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening duration was dependent on whether subjects were receiving an acetylcholinesterase inhibitor and/or memantine at the time of consent: up to 9 weeks (non-users) or up to 15 weeks (users, to allow for a 60-day washout). A total of 1830 subjects consented, of whom 1232 were screen failures, and 598 subjects were randomized (ITT Population).

Period 1

Period 1 title	Double-Blind Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Methylthioninium chloride (MTC)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 2 to 4 blank placebo tablets (depending on the protocol versions) orally, in a twice daily regimen for up to 52 weeks in the double-blind phase. Beginning with Protocol v5.0, the placebo supplies introduced a methylthioninium chloride (MTC) 4-mg tablet intermittently (2 times per week) as a urinary colorant to preserve the blind, thus subjects in the control group who consented to Protocol v5.0 and above received MTC 8 mg/week.

Investigational medicinal product name	Blank Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 2 to 4 blank placebo tablets (depending on the protocol versions) orally, in a twice daily regimen for up to 52 weeks in the double-blind phase. Beginning with Protocol v5.0, the placebo supplies introduced a methylthioninium chloride (MTC) 4-mg tablet intermittently (2 times per week) as a urinary colorant to preserve the blind, thus subjects in the control group who consented to Protocol v5.0 and above received MTC 8 mg/week.

Arm title	HMTM 8 mg/day

Arm description: -

Arm type	Experimental

Investigational medicinal product name	Hydromethylthionine mesylate (HMTM)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received two 4-mg HMTM tablets orally, in a twice daily regimen (one in the morning and one in the evening), along with blank placebo tablets as needed to maintain the blind (depending on the protocol version) for up to 52 weeks in the double-blind phase.

Arm title	HMTM 16 mg/day

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Hydromethylthionine mesylate (HMTM)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received four 4-mg HMTM tablets orally, in a twice daily regimen (two in the morning and two in the evening) for up to 52 weeks in the double-blind phase.

Number of subjects in period 1	Control	HMTM 8 mg/day	HMTM 16 mg/day
Started	266	80	252
Completed	215	61	194
Not completed	51	19	58
Physician decision	1	1	1
Consent withdrawn by subject	30	11	30
COVID-19	1	-	-
Adverse event, non-fatal	7	5	9
Other	3	-	4
Non-compliance with study drug	-	-	1
Consent withdrawn by legally accepted rep	1	-	2
Lost to follow-up	4	2	6
Lack of efficacy	2	-	2
Consent withdrawn by study partner	2	-	3

Period 2

Period 2 title	Open-Label Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Control -> HMTM 16 mg/day

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Hydromethylthionine mesylate (HMTM)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects receiving the control in the 52-week double-blind phase then received oral, HMTM 16 mg/day in a twice daily regimen (two 4-mg tablets in the morning and two 4-mg tablets in the evening) for an additional 52 weeks in the open-label, delayed-start phase.

Arm title	HMTM 8 mg/day -> HMTM 16 mg/day

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Hydromethylthionine mesylate (HMTM)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects receiving HMTM 8 mg/day in the 52-week double-blind phase then received oral, HMTM 16 mg/day in a twice daily regimen (two 4-mg tablets in the morning and two 4-mg tablets in the evening) for an additional 52 weeks in the open-label, delayed-start phase.

Arm title	HMTM 16 mg/day -> HMTM 16 mg/day

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Hydromethylthionine mesylate (HMTM)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects receiving HMTM 16 mg/day in the 52-week double-blind phase continued to receive oral, HMTM 16 mg/day in a twice daily regimen (two 4-mg tablets in the morning and two 4-mg tablets in the evening) for an additional 52 weeks in the open-label, delayed-start phase.

Arm title	HMTM Pooled -> HMTM 16 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Hydromethylthionine mesylate (HMTM)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects receiving HMTM 8 mg/day or HMTM 16 mg/day in the 52-week double-blind phase then received oral, HMTM 16 mg/day in a twice daily regimen (two 4-mg tablets in the morning and two 4-mg tablets in the evening) for an additional 52 weeks in the open-label, delayed-start phase.

Number of subjects in period 2	Control -> HMTM 16 mg/day	HMTM 8 mg/day -> HMTM 16 mg/day	HMTM 16 mg/day -> HMTM 16 mg/day
Started	197	48	188
Completed	170	39	162
Not completed	27	9	26
Adverse event, serious fatal	3	1	1
Physician decision	1	-	2
Consent withdrawn by subject	8	7	12
Adverse event, non-fatal	6	-	3
Other	2	-	1
Non-compliance with study drug	1	-	-
Lost to follow-up	2	-	4
Lack of efficacy	4	1	2
Consent withdrawn by study partner	-	-	1

Number of subjects in period 2	HMTM Pooled -> HMTM 16 mg
Started	236
Completed	201
Not completed	35
Adverse event, serious fatal	2
Physician decision	2
Consent withdrawn by subject	19
Adverse event, non-fatal	3
Other	1
Non-compliance with study drug	-
Lost to follow-up	4
Lack of efficacy	3
Consent withdrawn by study partner	1

Baseline characteristics

Reporting groups	
Reporting group title	Control
Reporting group description: -	
Reporting group title	HMTM 8 mg/day
Reporting group description: -	
Reporting group title	HMTM 16 mg/day
Reporting group description: -	

Reporting group values	Control	HMTM 8 mg/day	HMTM 16 mg/day
Number of subjects	266	80	252
Age categorical Units: Subjects			
<75 years	152	49	145
>=75 years	114	31	107
Age continuous Units: years			
arithmetic mean	72.4	71.8	71.9
standard deviation	± 8.3	± 8.1	± 8.6
Gender categorical Units: Subjects			
Female	153	49	161
Male	113	31	91

Reporting group values	Total		
Number of subjects	598		
Age categorical Units: Subjects			
<75 years	346		
>=75 years	252		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	363		
Male	235		

End points

End points reporting groups	
Reporting group title	Control
Reporting group description: -	
Reporting group title	HMTM 8 mg/day
Reporting group description: -	
Reporting group title	HMTM 16 mg/day
Reporting group description: -	
Reporting group title	Control -> HMTM 16 mg/day
Reporting group description: -	
Reporting group title	HMTM 8 mg/day -> HMTM 16 mg/day
Reporting group description: -	
Reporting group title	HMTM 16 mg/day -> HMTM 16 mg/day
Reporting group description: -	
Reporting group title	HMTM Pooled -> HMTM 16 mg
Reporting group description: -	

Primary: Change from Baseline to Week 52 in the Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-cog)

End point title	Change from Baseline to Week 52 in the Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-cog)[1]

End point description:

End point type	Primary

End point timeframe:

52 weeks

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per the protocol (and the SAP), the primary analyses were based on comparisons of the HMTM 16 mg/day and control groups over 52 weeks. The HMTM 8 mg/day group was included in other secondary and exploratory analyses, but were not included in the primary analyses or secondary analyses of interest.

End point values	Control	HMTM 16 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	178		
Units: none				
least squares mean (confidence interval 95%)	1.661 (0.632 to 2.689)	1.239 (0.209 to 2.270)		

Statistical analyses

Statistical analysis title	ADAS-cog Primary Analysis (ITTv5 Population)
Comparison groups	Control v HMTM 16 mg/day

Number of subjects included in analysis	365
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6108
Method	Mixed models analysis

Primary: Change from Baseline to Week 52 in the Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL)

End point title	Change from Baseline to Week 52 in the Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL)[2]

End point description:

End point type	Primary

End point timeframe:

52 weeks

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per the protocol (and the SAP), the primary analyses were based on comparisons of the HMTM 16 mg/day and control groups over 52 weeks. The HMTM 8 mg/day group was included in other secondary and exploratory analyses, but were not included in the primary analyses or secondary analyses of interest.

End point values	Control	HMTM 16 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	180		
Units: none				
least squares mean (confidence interval 95%)	-0.889 (-2.448 to 0.671)	-0.527 (-2.107 to 1.052)		

Statistical analyses

Statistical analysis title	ADCS-ADL Primary Analysis (ITTv5 Population)
Comparison groups	Control v HMTM 16 mg/day
Number of subjects included in analysis	373
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8053
Method	Mixed models analysis

Secondary: Change from Baseline to Week 104 in the Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-cog)

End point title	Change from Baseline to Week 104 in the Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-cog)

End point description:

End point type	Secondary
End point timeframe: 104 weeks	

End point values	Control -> HMTM 16 mg/day	HMTM Pooled -> HMTM 16 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	146	179		
Units: none				
least squares mean (confidence interval 95%)	2.976 (2.006 to 3.946)	3.584 (2.700 to 4.468)		

Statistical analyses

Statistical analysis title	ADAS-cog Secondary Analysis (PPv5-OL Population)
Comparison groups	HMTM Pooled -> HMTM 16 mg v Control -> HMTM 16 mg/day
Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0151
Method	Mixed models analysis

Secondary: Change from Baseline to Week 104 in the Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL)

End point title	Change from Baseline to Week 104 in the Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL)
End point description:	

End point type	Secondary
End point timeframe: 104 weeks	

End point values	Control -> HMTM 16 mg/day	HMTM Pooled -> HMTM 16 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	158	187		
Units: none				
least squares mean (confidence interval 95%)	-4.901 (-6.433 to -3.370)	-3.160 (-4.575 to -1.744)		

Statistical analyses

Statistical analysis title	ADCS-ADL Secondary Analysis (PPv5-OL Population)
Comparison groups	HMTM Pooled -> HMTM 16 mg v Control -> HMTM 16 mg/day
Number of subjects included in analysis	345
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0001
Method	Mixed models analysis

Secondary: Change from Baseline to Week 104 in MRI Whole Brain Volume

End point title	Change from Baseline to Week 104 in MRI Whole Brain Volume
End point description:	
End point type	Secondary
End point timeframe:	
104 weeks	

End point values	Control -> HMTM 16 mg/day	HMTM Pooled -> HMTM 16 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	175		
Units: none				
least squares mean (confidence interval 95%)	-11852.82 (-13549.34 to -10156.30)	-10905.09 (-12419.44 to -9390.73)		

Statistical analyses

Statistical analysis title	MRI Whole Brain Volume (PPv5-OL Population)
Comparison groups	HMTM Pooled -> HMTM 16 mg v Control -> HMTM 16 mg/day
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Mixed models analysis

Secondary: Change from Baseline to Week 104 in MRI Temporoparietal Lobe Volume

End point title	Change from Baseline to Week 104 in MRI Temporoparietal Lobe Volume
End point description:	
End point type	Secondary
End point timeframe: 104 weeks	

End point values	Control -> HMTM 16 mg/day	HMTM Pooled -> HMTM 16 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	175		
Units: none				
least squares mean (confidence interval 95%)	-560.721 (-642.849 to -478.593)	-501.438 (-574.689 to -428.188)		

Statistical analyses

Statistical analysis title	MRI Temporoparietal Volume (PPv5-OL Population)
Comparison groups	HMTM Pooled -> HMTM 16 mg v Control -> HMTM 16 mg/day
Number of subjects included in analysis	313
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
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 double-blind phase (up to Week 52) and the open-label phase (up to Week 104).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Control

Reporting group description:

Subjects receiving placebo and/or MTC 8 mg/week (to maintain the blind) during the 52-week double-blind phase.

Reporting group title	HMTM 8 mg/day

Reporting group description:

Subjects receiving HMTM 8 mg/day during the 52-week double-blind phase.

Reporting group title	HMTM 16 mg/day

Reporting group description:

Subjects receiving HMTM 16 mg/day during the 52-week double-blind phase.

Reporting group title	Open-Label Phase

Reporting group description:

All on-treatment subjects received HMTM 16 mg/day during the open-label phase.

Serious adverse events	Control	HMTM 8 mg/day	HMTM 16 mg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 266 (6.77%)	6 / 80 (7.50%)	18 / 252 (7.14%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 266 (0.00%)	1 / 80 (1.25%)	0 / 252 (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
Lung neoplasm malignant			
subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (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
Malignant pleural effusion			

subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (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
Metastasis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Prostate cancer			
subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (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
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic squamous cell carcinoma			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary renal cell carcinoma			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour compression			

subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoma			
subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (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
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral venous disease			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Gait inability			
subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (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
General physical health deterioration			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (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 embolism			

subjects affected / exposed	1 / 266 (0.38%)	2 / 80 (2.50%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropsychiatric symptoms			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Femur fracture			
subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (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
Hip fracture			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haematuria			
subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (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
Subdural haematoma			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Costal cartilage fracture			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skeletal injury			

subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 266 (0.00%)	1 / 80 (1.25%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cauda equina syndrome			
subjects affected / exposed	0 / 266 (0.00%)	1 / 80 (1.25%)	0 / 252 (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
Metabolic encephalopathy			

subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (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
Parkinsonism			
subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (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
Presyncope			
subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (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
Psychomotor hyperactivity			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	1 / 252 (0.40%)
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	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (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
Cerebral haemorrhage			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Normal pressure hydrocephalus			

subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (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
Ear and labyrinth disorders			
Tympanic membrane perforation			
subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (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
Vertigo positional			
subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (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
Eye disorders			
Lens discolouration			
subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (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
Vision blurred			
subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diverticulum			
subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	2 / 266 (0.75%)	0 / 80 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal haemorrhage			
subjects affected / exposed	0 / 266 (0.00%)	1 / 80 (1.25%)	0 / 252 (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 / 266 (0.00%)	1 / 80 (1.25%)	0 / 252 (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
Abdominal pain upper			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			

subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Bladder disorder			
subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (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
Haematuria			
subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute prerenal failure			
subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc degeneration			
subjects affected / exposed	1 / 266 (0.38%)	0 / 80 (0.00%)	0 / 252 (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
Arthritis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Osteoarthritis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	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 / 266 (0.00%)	0 / 80 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	1 / 252 (0.40%)
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	0 / 266 (0.00%)	0 / 80 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corona virus infection			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	2 / 252 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 266 (0.00%)	1 / 80 (1.25%)	0 / 252 (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
Postoperative abscess			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus bronchitis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular neuronitis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	0 / 252 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 266 (0.00%)	0 / 80 (0.00%)	1 / 252 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Open-Label Phase		
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 449 (6.01%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			

subjects affected / exposed	0 / 449 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung neoplasm malignant				
subjects affected / exposed	0 / 449 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malignant pleural effusion				
subjects affected / exposed	0 / 449 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastasis				
subjects affected / exposed	0 / 449 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bladder transitional cell carcinoma				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastatic squamous cell carcinoma				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Non-small cell lung cancer				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Papillary renal cell carcinoma				

subjects affected / exposed	1 / 449 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Plasma cell myeloma			
subjects affected / exposed	1 / 449 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour compression			
subjects affected / exposed	1 / 449 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphoma			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 449 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral venous disease			
subjects affected / exposed	1 / 449 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Gait inability			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 449 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspiration			
subjects affected / exposed	1 / 449 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Agitation			
subjects affected / exposed	1 / 449 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	1 / 449 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neuropsychiatric symptoms			
subjects affected / exposed	2 / 449 (0.45%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accidental overdose			

subjects affected / exposed	0 / 449 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural haematuria				
subjects affected / exposed	0 / 449 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	0 / 449 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Costal cartilage fracture				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				

subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Head injury				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skeletal injury				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal fracture				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				

subjects affected / exposed	1 / 449 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cauda equina syndrome			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolic encephalopathy			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Parkinsonism			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychomotor hyperactivity			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 449 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			

subjects affected / exposed	1 / 449 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cerebrovascular accident			
subjects affected / exposed	1 / 449 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Normal pressure hydrocephalus			
subjects affected / exposed	1 / 449 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Tympanic membrane perforation			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vertigo positional			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Lens discolouration			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vision blurred			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Diverticulum			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hiatus hernia			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Retroperitoneal haemorrhage			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 449 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			

subjects affected / exposed	2 / 449 (0.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Bladder disorder			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	1 / 449 (0.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute prerenal failure			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc degeneration			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Arthritis				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abdominal abscess				
subjects affected / exposed	0 / 449 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 449 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis infective				
subjects affected / exposed	0 / 449 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Corona virus infection				
subjects affected / exposed	0 / 449 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 449 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative abscess				
subjects affected / exposed	0 / 449 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urosepsis				

subjects affected / exposed	0 / 449 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus bronchitis				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Urinary tract infection				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vestibular neuronitis				
subjects affected / exposed	1 / 449 (0.22%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	0 / 449 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Control	HMTM 8 mg/day	HMTM 16 mg/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 266 (22.18%)	23 / 80 (28.75%)	52 / 252 (20.63%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	11 / 266 (4.14%)	2 / 80 (2.50%)	5 / 252 (1.98%)
occurrences (all)	16	2	5
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 266 (1.88%)	3 / 80 (3.75%)	9 / 252 (3.57%)
occurrences (all)	5	3	9
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 266 (3.01%)	5 / 80 (6.25%)	10 / 252 (3.97%)
occurrences (all)	8	8	11
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 266 (1.50%)	1 / 80 (1.25%)	8 / 252 (3.17%)
occurrences (all)	4	1	10
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 266 (0.75%)	3 / 80 (3.75%)	3 / 252 (1.19%)
occurrences (all)	2	3	3
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 266 (1.88%)	3 / 80 (3.75%)	6 / 252 (2.38%)
occurrences (all)	6	3	6
Vomiting			
subjects affected / exposed	1 / 266 (0.38%)	2 / 80 (2.50%)	5 / 252 (1.98%)
occurrences (all)	1	2	5
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	2 / 266 (0.75%)	3 / 80 (3.75%)	1 / 252 (0.40%)
occurrences (all)	3	3	1
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	10 / 266 (3.76%)	2 / 80 (2.50%)	5 / 252 (1.98%)
occurrences (all)	11	2	6
Infections and infestations			
Corona virus infection			
subjects affected / exposed	11 / 266 (4.14%)	6 / 80 (7.50%)	7 / 252 (2.78%)
occurrences (all)	11	6	7
Upper respiratory tract infection			
subjects affected / exposed	2 / 266 (0.75%)	3 / 80 (3.75%)	1 / 252 (0.40%)
occurrences (all)	3	3	1
Urinary tract infection			
subjects affected / exposed	9 / 266 (3.38%)	0 / 80 (0.00%)	5 / 252 (1.98%)
occurrences (all)	9	0	5

Non-serious adverse events	Open-Label Phase		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 449 (14.03%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	14 / 449 (3.12%)		
occurrences (all)	14		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 449 (0.89%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 449 (2.00%)		
occurrences (all)	9		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 449 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 449 (1.11%)		
occurrences (all)	5		
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	6 / 449 (1.34%) 6 2 / 449 (0.45%) 2		
Psychiatric disorders Depressed mood subjects affected / exposed occurrences (all)	4 / 449 (0.89%) 4		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	11 / 449 (2.45%) 11		
Infections and infestations Corona virus infection subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	18 / 449 (4.01%) 18 1 / 449 (0.22%) 1 7 / 449 (1.56%) 7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 August 2017	In Protocol v2.1, the protocol for Study TRx-237-039 (Version 1.0 dated 23 Aug 2017) was revised to clarify the assessments that would be made at various visits as follows: the blood was to be collected during Visit 2 and Visit 3 (not at Visit 2 or Visit 3), a spelling error was corrected (dimethyl to desmethyl), clarification was made that the time of dose from the previous day was to be collected, a redundant paragraph was removed, specifications for procedure of blood collection were removed from the protocol, the Appendices were renumbered and the table of contents updated, and minor edits, such as expansion of abbreviations, were made.
31 May 2018	In Protocol v3.0, the protocol for Study TRx-237-039 (Version 2.1 dated 25 October 2017), the study duration was increased from 6 months to 9 months and the procedures and assessments associated with Visit 6 (39 weeks) were added. The study sample size increased from 180 to 375 subjects and an HMTM 16-mg/day treatment arm added: HMTM 8 mg/day, HMTM 16 mg/day, and placebo (2:1:2); the number of planned study sites was increased from 60 to at least 100. 18F-FDG-PET SUVR of temporal lobe (normalized to pons) kept as primary endpoint but a Composite Scale, to be defined, was added as the secondary endpoint. The study population was expanded from mild AD with an MMSE of 20-25 to include MCI-AD with an MMSE of 20-27; CDR 0.5 (requiring a score of >0 in one of the functional domains: Community Affairs, Home and Hobbies, or Personal Care). The inclusion criteria were changed to require an amyloid-positive PET scan and include subjects who discontinued AChEI and/or memantine at Screening; this required an extension of Screening period extended up to 6 weeks (15 weeks in total) to allow for 60-day washout of AChEI and/or memantine. The exclusion criteria were changed to exclude subjects with moderate to severe sleep apnea or any physical disability that would prevent completion of study procedures and assessments, and taking Souvenaid® and carbamazepine, but allow olanzapine. Whole blood and plasma assessed for the concentration of HMT and its metabolites and urine assessed for color determination were added as were MMSE and CDR assessments after 39 weeks or upon early termination. Brain MRI hyperintensities were also quantified.
24 August 2018	In Protocol v4.0, the protocol for Study TRx-237-039 (Version 3.0 dated 31 May 2018) has been updated to include administrative changes, as the responsible party for study management, monitoring, and pharmacovigilance has changed (previously PAREXEL International, now Syneos Health). Additional modifications and clarifications have been incorporated with respect to the Sponsor contact details, objectives and statistical analyses, background, study population (e.g., number of allowed screened subjects increased from 900 to 1500), informed consent, study assessments, documentation, data protection, and study administration.

09 July 2019	In Protocol v5.0, the protocol for Study TRx-237-039 (Version 4.1 dated 9 November 2018) has been revised primarily to include the following modifications: • The study design now includes two phases, including the double-blind treatment phase (now 12 months, extended from 9 months) with subjects randomized to HMTM 16 mg/day, HMTM 8 mg/day, or placebo, followed by an open-label, delayed-start treatment period with HMTM 16 mg/day for an additional 52 weeks; study visits and schedules of assessments have been modified accordingly • The study population now includes subjects with early to mild-moderate AD (previously only early AD), and the number of randomized subjects has been increased to approximately 450 subjects (previously 375 subjects) • The primary objectives for the double-blind treatment phase now pertain to comparing HMTM 16 mg/day with placebo for the co-primary endpoints of ADAS-cog11 and ADCS-ADL23 (difference in temporal lobe 18F-FDG-PET change in SUVR and the Composite Scale are no longer primary objectives), and for assessing safety and tolerability; secondary objectives have been modified to include comparisons of HMTM 16 mg/day with placebo in whole brain atrophy as measured by MRI, to restrict the 18F-FDG-PET endpoints to subjects with CDR 0.5 at Screening, and to compare the HMTM dose of 8 mg/day for selected endpoints Modifications have also been made to administrative information, criteria for subject enrollment and eligibility for the EAP, study drug supplies for the placebo group (now including a urinary discolorant to maintain blinding during the double-blind treatment period), and study assessments. Minor revisions have also been incorporated for clarity.
09 October 2020	In Protocol v6.0, the protocol for Study TRx-237-039 (Version 5.1 dated 05 February 2020) has been revised to incorporate modifications to the study conduct and monitoring, guidance for continued data collection and analysis, and ongoing risk assessment due to the COVID-19 Public Health Emergency. In addition, the total number of subjects to be randomized has increased, and updates have been incorporated for contact information for responsible personnel, as well as modifications and/or clarifications to investigator responsibilities, study assessments, and statistical analyses. Reference to a separate plan has been included for additional analyses to be undertaken of the blinded 18F-FDG-PET and MRI data for scientific research and quality control purposes. Additional revisions are editorial and are intended to correct typographical errors and editorial inconsistencies as well as to add clarification.
28 July 2021	In Protocol v7.0, the protocol for study TRx-237-039 (Version 6.0 dated 09 October 2020) has been revised to incorporate changes to responsible personnel; updates to the background information to reflect the most current version of the Investigator's Brochure; clarification of assessments and drug dispensing for Visit 7 of double-blind treatment (also Baseline/Day 1 of open-label phase); addition of lens discoloration as an AESI and further instruction regarding timing of slit lamp examinations; clarification that MT concentration sampling will not continue for the off-treatment on-study (TOTOS) group; and further description of composite scores and endpoints. Additional statistical analysis updates include sensitivity and subgroup analyses, and further detail provided for primary endpoints, all in response to potential impacts of COVID-19; the primary efficacy hypotheses have been clarified; and the primary estimand and five components of interest are now described. Additional revisions are editorial and are intended to correct typographical errors and editorial inconsistencies as well as to add clarification.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported