



## Clinical trial results:

### A Double-Blind, Placebo-Controlled, Randomized, Parallel Group, 12-Month Safety and Efficacy Trial of Leuco-methylthioninium bis (hydromethanesulfonate) in Subjects with Behavioral Variant Frontotemporal Dementia (bvFTD)

#### Summary

EudraCT number	2011-005529-34
Trial protocol	DE GB NL IT FI PL ES HR
Global end of trial date	22 February 2016

#### Results information

Result version number	v1 (current)
This version publication date	02 February 2020
First version publication date	02 February 2020

#### Trial information

##### Trial identification

Sponsor protocol code	TRx-237-007
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	TauRx Therapeutics Ltd
Sponsor organisation address	395 King Street, Aberdeen, United Kingdom,
Public contact	Information Desk, TauRx Therapeutics Ltd, +44 1224 440905, info@taurx.com
Scientific contact	Information Desk, TauRx Therapeutics Ltd, +44 1224 440905, info@taurx.com

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 January 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	22 February 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate the efficacy of Leuco-methylthioninium bis(hydromethanesulfonate) (hereafter referred to by the INN: hydromethylthionine mesylate) as assessed by the change from Baseline on Addenbrooke's Cognitive Examination-Revised (ACE-R), Functional Activities Questionnaire (FAQ), and reduction in decline in whole brain volume as measured by the Brain Boundary Shift Integral (BBSI) by magnetic resonance imaging (MRI) in subjects with probable bvFTD.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 May 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 15
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	United Kingdom: 21
Country: Number of subjects enrolled	Croatia: 6
Country: Number of subjects enrolled	Germany: 24
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Australia: 22
Country: Number of subjects enrolled	Canada: 26
Country: Number of subjects enrolled	Singapore: 6
Country: Number of subjects enrolled	United States: 65
Worldwide total number of subjects	220
EEA total number of subjects	101

Notes:

<b>Subjects enrolled per age group</b>	
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)	122
From 65 to 84 years	98
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Screening assessments to evaluate subject eligibility were to occur <42 days prior to Baseline. Overall, 369 subjects provided informed consent, of whom 149 subjects were screen failures. The most common reasons for screen failure were centrally rated frontotemporal atrophy score of <2 on brain MRI (7%) and MMSE of <20 (6%).

### Period 1

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

### Arms

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

Arm description:

Subjects were to be administered LMTM 100 mg tablets twice daily for 52 weeks.

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

Dosage and administration details:

LMTM 100 mg tablets were administered orally, in a twice daily regimen.

<b>Arm title</b>	LMTM 8 mg/day
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Arm description:

Subjects were to be administered LMTM 4 mg tablets twice daily for 52 weeks.

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

Dosage and administration details:

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

<b>Number of subjects in period 1</b>	LMTM 200 mg/day	LMTM 8 mg/day
Started	109	111
Completed	73	94
Not completed	36	17
Adverse event, serious fatal	2	1
Consent withdrawn by subject	7	4
Physician decision	1	-
Adverse event, non-fatal	13	4
Consent withdrawn by legal representative	-	1
Other	1	1
Consent withdrawn by caregiver	7	2
Non-compliance with study drug	2	1
Lost to follow-up	1	-
Lack of efficacy	2	2
Protocol deviation	-	1

## Baseline characteristics

### Reporting groups

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

Subjects were to be administered LMTM 100 mg tablets twice daily for 52 weeks.

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

Subjects were to be administered LMTM 4 mg tablets twice daily for 52 weeks.

Reporting group values	LMTM 200 mg/day	LMTM 8 mg/day	Total
Number of subjects	109	111	220
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	63.6 ± 7.52	63.1 ± 7.35	-
Gender categorical Units: Subjects			
Female	38	44	82
Male	71	67	138

## End points

### End points reporting groups

Reporting group title	LMTM 200 mg/day
Reporting group description:	
Subjects were to be administered LMTM 100 mg tablets twice daily for 52 weeks.	
Reporting group title	LMTM 8 mg/day
Reporting group description:	
Subjects were to be administered LMTM 4 mg tablets twice daily for 52 weeks.	

### Primary: Change from Baseline to Week 52 in the Addenbrooke's Cognitive Examination Revised (ACE-R)

End point title	Change from Baseline to Week 52 in the Addenbrooke's Cognitive Examination Revised (ACE-R)
End point description:	
End point type	Primary
End point timeframe:	
52 weeks	

End point values	LMTM 200 mg/day	LMTM 8 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	94		
Units: none				
arithmetic mean (standard deviation)	-7.4 ( $\pm$ 11.48)	-9.8 ( $\pm$ 14.71)		

### Statistical analyses

Statistical analysis title	ACE-R Primary Analysis (ITT Population)
Comparison groups	LMTM 200 mg/day v LMTM 8 mg/day
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.817
Method	Mixed models analysis

### Primary: Change from Baseline to Week 52 in the Functional Activities Questionnaire (FAQ)

End point title	Change from Baseline to Week 52 in the Functional Activities Questionnaire (FAQ)
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End point description:

End point type	Primary
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End point timeframe:

52 weeks

End point values	LMTM 200 mg/day	LMTM 8 mg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	93		
Units: none				
arithmetic mean (standard deviation)	5.1 (± 5.17)	5.1 (± 6.00)		

### Statistical analyses

Statistical analysis title	FAQ Primary Analysis (ITT Population)
Comparison groups	LMTM 200 mg/day v LMTM 8 mg/day
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.641
Method	Mixed models analysis

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were to be recorded from the time informed consent was signed and continued throughout the study, including the follow-up safety visit (Week 56).

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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### Reporting groups

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

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

Serious adverse events	LMTM 200 mg/day	LMTM 8 mg/day	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 108 (12.04%)	14 / 110 (12.73%)	
number of deaths (all causes)	3	1	
number of deaths resulting from adverse events	3	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	0 / 108 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Brain contusion			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			

subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 108 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 108 (0.93%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 108 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			

subjects affected / exposed	1 / 108 (0.93%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Nervous system disorders</b>			
Amyotrophic lateral sclerosis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
<b>Balance disorder</b>			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cerebrovascular accident</b>			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
<b>Convulsion</b>			
subjects affected / exposed	0 / 108 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Frontotemporal dementia</b>			
subjects affected / exposed	0 / 108 (0.00%)	2 / 110 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Grand mal convulsion</b>			
subjects affected / exposed	0 / 108 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastrointestinal disorders</b>			
Rectal haemorrhage			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Respiratory, thoracic and mediastinal</b>			

disorders			
Pneumonia aspiration			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	3 / 108 (2.78%)	3 / 110 (2.73%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 108 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	0 / 108 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 108 (0.93%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 108 (0.93%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	1 / 108 (0.93%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	LMTM 200 mg/day	LMTM 8 mg/day	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	103 / 108 (95.37%)	87 / 110 (79.09%)	
Investigations			
Blood folate decreased			
subjects affected / exposed	9 / 108 (8.33%)	6 / 110 (5.45%)	
occurrences (all)	11	6	
White blood cells urine positive			
subjects affected / exposed	6 / 108 (5.56%)	1 / 110 (0.91%)	
occurrences (all)	10	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	13 / 108 (12.04%)	10 / 110 (9.09%)	
occurrences (all)	16	16	
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	5 / 108 (4.63%) 7	8 / 110 (7.27%) 8	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	24 / 108 (22.22%) 45	9 / 110 (8.18%) 11	
Vomiting subjects affected / exposed occurrences (all)	9 / 108 (8.33%) 11	5 / 110 (4.55%) 5	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 108 (1.85%) 2	7 / 110 (6.36%) 8	
Psychiatric disorders Agitation subjects affected / exposed occurrences (all)	9 / 108 (8.33%) 11	9 / 110 (8.18%) 9	
Insomnia subjects affected / exposed occurrences (all)	7 / 108 (6.48%) 7	3 / 110 (2.73%) 3	
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	6 / 108 (5.56%) 6	0 / 110 (0.00%) 0	
Pollakiuria subjects affected / exposed occurrences (all)	10 / 108 (9.26%) 13	3 / 110 (2.73%) 3	
Urinary incontinence subjects affected / exposed occurrences (all)	9 / 108 (8.33%) 20	13 / 110 (11.82%) 13	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	7 / 108 (6.48%) 8	8 / 110 (7.27%) 9	
Urinary tract infection			

subjects affected / exposed occurrences (all)	13 / 108 (12.04%) 15	12 / 110 (10.91%) 14	
Metabolism and nutrition disorders Folate deficiency subjects affected / exposed occurrences (all)	6 / 108 (5.56%) 6	2 / 110 (1.82%) 2	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 December 2012	In Protocol Version 2.0, inclusion and exclusion criteria were modified; dosing and drug supplies text was revised; modifications to laboratory testing (e.g., bilirubin, Heinz bodies, folate, thyroid stimulating hormone, and oxygen content) were incorporated; and clarifications and/or modifications to other procedural activities (e.g., informed consent and subject withdrawal, unblinding, Modified ADCS-CGIC evaluations, telephone contacts, ECG assessments, physical and neurological examinations, serotonin toxicity assessments, and blood sample collection and labeling) were also incorporated.
19 February 2013	In Protocol Version 3.0, background information was modified to include new reproductive toxicity findings (the discussion of contraceptive measures was also updated accordingly) and clinical pharmacokinetic and safety data; inclusion and exclusion criteria were modified; clarifications and/or modifications to safety assessments and procedures (e.g., dosing and study continuation decisions to be made based on electrocardiogram results, Unified Parkinson's Disease Rating Scale version, Heinz body determination, serotonin toxicity assessments, pulse rate measurements, and reporting/handling of adverse events of special interest) were incorporated; and clarifications and/or modifications to other assessments and procedural activities were also incorporated.
18 October 2013	In Protocol Version 4.0, additional clinical trial sites were added in new countries; an exploratory objective/endpoint was added to evaluate the effect of LMTM as assessed by the change from Baseline on Addenbrooke's Cognitive Examination-III (ACE-III) to permit comparison of Addenbrooke's Cognitive Examination-Revised (ACE-R) and ACE-III total scores; an exploratory objective was added to determine the effect of LMTM in subjects with known genetic mutations associated with bvFTD; inclusion and exclusion criteria were modified; instructions for dose interruptions were revised; clarifications and/or modifications to safety assessments and procedures were incorporated; the definitions of serious adverse events and other medically significant events were clarified; clarifications and/or modifications to other assessments and procedural activities were incorporated; and the statistical analysis discussion was revised to incorporate an additional sensitivity analysis, revise the definition of a responder, and indicate that interim analyses may be performed.
23 December 2013	In Protocol Version 5.0, modifications were incorporated to clarify the presentation of the locations (countries and regions) of participating clinical trial sites; clarify the exclusion criterion regarding current or prior participation in a clinical trial of a product for cognition; allow any suitable laboratory to be used for measurement of glucose-6-phosphate dehydrogenase for deficiency screening; and address comments received from participating Member States in the Voluntary Harmonisation Procedure to restore the exclusionary creatinine clearance to <50 mL/min and to unblind treatment allocation for Suspected Unexpected Serious Adverse Reaction reporting to the pertinent regulatory authorities.
21 July 2014	In Protocol Version 6.0, modifications were incorporated to no longer require routine magnetic resonance imaging (MRI) monitoring for evaluation of amyloid related imaging abnormalities based on correspondence received from the United States Food and Drug Administration. Additional modifications were included with regards to concomitant medications and study drug storage temperature conditions.

22 October 2015	<p>In Protocol Version 8.0, modifications (relative to Protocol Version 6.0) were incorporated for the clinical efficacy endpoints, imaging endpoints, and statistical analyses in light of newly emerging regulatory guidances and data available from other studies. These modifications were introduced in an interim protocol amendment (Version 7.0 dated 29 June 2015) and were incorporated in the last protocol amendment for this study (Version 8.0). Protocol Version 7.0 was not distributed for implementation at the clinical sites and was superseded by Protocol Version 8.0.</p> <p>The primary, secondary, and exploratory endpoints and statistical analyses were modified as follows: symptomatic effect as reflected by the Functional Activities Questionnaire (FAQ) and disease-modifying effect based on reduction in decline in whole brain volume (WBV) by magnetic resonance imaging (MRI) became primary endpoints, the Modified Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change became a secondary endpoint, and disease modification by reduction in the rate of atrophy in frontal and temporal lobes as well as ventricular volume by MRI imaging was added as an exploratory endpoint. As the Addenbrooke's Cognitive Examination-III (ACE-III) and Addenbrooke's Cognitive Examination-Revised (ACE-R) are highly correlated, in the few instances where only ACE-III may have been obtained at Baseline, the change in total score (out of 100) from Baseline ACE-III to subsequent ACE-R was to be used to compute the change in ACE-R.</p> <p>Additional changes from the last implemented protocol included updates to administrative and background information, modifications and clarifications to safety assessments and other procedures including quality assurance and clinical monitoring, as well as other minor revisions to provide further clarification.</p>
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Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported