Clinical trial results:
XanADu: A Phase II, Double-Blind, 12-Week, Randomised, Placebo-Controlled Study to Assess the Safety, Tolerability and Efficacy of Xanamem™ in Subjects with Mild Dementia due to Alzheimer's Disease (AD)

Summary

EudraCT number	2016-001049-24
Trial protocol	GB
Global end of trial date	15 March 2019

Results information

Result version number	v1 (current)
This version publication date	07 May 2022
First version publication date	07 May 2022

Trial information

Trial identification

Sponsor protocol code	ACW0002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02727699
WHO universal trial number (UTN)	U1111-1177-5932

Notes:

Sponsors

Sponsor organisation name	ICON Clinical Research Pty Ltd
Sponsor organisation address	South County Business Park, Leopardstown, Dublin, Ireland, 18
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Scientific contact	Project Management, ICON Clinical Research Pty Ltd, +61 298593907, tom.olson@iconplc.com
Sponsor organisation name	Actinogen Medical Limited
Sponsor organisation address	SUITE 901, LEVEL 9, 109 PITT STREET, SYDNEY, Australia, 2000
Public contact	Miriam Roesner, Actinogen Medical, +61 289647401, miriam.roesner@actinogen.com.au
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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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 March 2019
Global end of trial reached?	Yes
Global end of trial date	15 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the extent to which Xanamem™ improves performance from Baseline to end of treatment (EOT) compared to placebo, as measured by changes in AD COMposite Scores (ADCOMs, composite data derived from Alzheimer's Disease Assessment Scales - Cognitive subscale version 14 [ADAS-Cog v14], Clinical Dementia Rating Scale - Sum of Boxes [CDR-SOB], and Mini-Mental Status Examination [MMSE]) and ADAS-Cog v14 as primary endpoints in subjects with mild dementia due to probable AD.

Protection of trial subjects:

Data Safety Monitoring Board
A DSMB consisting of two sponsor-independent clinical experts and one sponsor independent statistical expert will be established. The DSMB will periodically meet for the review of accumulating study data, including safety (AE and laboratory data), PD data and NFM data, and will also be involved in the interim efficacy analysis.
The DSMB will have access to unblinded data.
The DSMB will submit its recommendations in writing to Actinogen Medical who are responsible for responding to the recommendations of the DSMB and taking appropriate action. The investigators will only be informed by Actinogen Medical/ICON if the study is stopped or if additional PD subjects need to be enrolled. The DSMB may choose to make additional evaluations at any time if they feel this is warranted from a safety point of view.

Data Safety Monitoring Board Nerve Function Monitoring Sub-committee
The DSMB Nerve Function Monitoring sub-committee consists of two experts in neurophysiology, one of which will be the DSMB Chairperson. The unblinded NFM data will be primarily reviewed by the DSMB Nerve Function Monitoring sub committee. When there is a confirmed nerve safety signal, this is escalated to the DSMB for consideration and recommendations for the study.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	23 March 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	United Kingdom: 29
Country: Number of subjects enrolled	Australia: 48
Country: Number of subjects enrolled	United States: 108

Worldwide total number of subjects	185
EEA total number of subjects	0

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)	43
From 65 to 84 years	142
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

At study start, it was planned that 20 study sites would be initiated in three countries (Australia, the United Kingdom [UK] and the United States of America [USA]). Following amendments to the study and the protocol, a total of 27 study sites were initiated (6 in Australia, 6 in the UK, and 15 in the USA). Recruitment period: 23Mar2017-08Oct2018.

Pre-assignment

Screening details:

It was planned that approximately 174 subjects would be enrolled to ensure 156 subjects would complete the 12 week double-blind study period (78 subjects in each treatment group). At study-end, in total, 457 subjects were screened, of whom 185 subjects were randomised (91:94 Xanamem to placebo) to the study with 171 subjects completed.

Period 1

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

Blinding implementation details:

To ensure blinding, the study drug (Xanamem™ capsules) and the matching placebo have the same shape and size. Labels on the study drug containers will not identify treatment a subject is randomised to. Traceability of the treatment is ensured by the study drug number.

Arms

Are arms mutually exclusive?	Yes
Arm title	Xanamem™

Arm description:

Oral Xanamem™ capsules 10mg, to be administered once daily

Xanamem™: Xanamem™ is formulated in green and cream coloured size 3, Coni-Snap shaped gelatin capsules as an excipient blend at a dose of 10mg. It contains active pharmaceutical ingredient of UE2343 (Laboratory code for Xanamem)

Arm type	Experimental
Investigational medicinal product name	Xanamem (UE2343)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One capsule of Xanamem was administered orally with approximately 200 mL of preferably warm water QD, preferably with food in the morning, to eligible subjects from Baseline (Week 0) to EOT (Week 12) for a total of 12 weeks.

Arm title	Placebo

Arm description:

Matching placebo which is identical in appearance to the test product except that it contains no active ingredient, to be administered once daily

Placebo (for Xanamem™): Excipient blend capsules manufactured to mimic Xanamem™ capsules

Arm type	Placebo

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

Dosage and administration details:

One capsule of the matching placebo was administered orally with approximately 200 mL of preferably warm water QD, preferably with food in the morning, to eligible subjects from Baseline (Week 0) to EOT (Week 12) for a total of 12 weeks.

Number of subjects in period 1	Xanamem™	Placebo
Started	91	94
Completed	82	89
Not completed	9	5
Consent withdrawn by subject	5	3
Physician decision	-	1
Adverse event, non-fatal	2	-
Sponsor decision	1	-
Lack of efficacy	1	-
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Xanamem™

Reporting group description:

Oral Xanamem™ capsules 10mg, to be administered once daily

Xanamem™: Xanamem™ is formulated in green and cream coloured size 3, Coni-Snap shaped gelatin capsules as an excipient blend at a dose of 10mg. It contains active pharmaceutical ingredient of UE2343 (Laboratory code for Xanamem)

Reporting group title	Placebo

Reporting group description:

Matching placebo which is identical in appearance to the test product except that it contains no active ingredient, to be administered once daily

Placebo (for Xanamem™): Excipient blend capsules manufactured to mimic Xanamem™ capsules

Reporting group values	Xanamem™	Placebo	Total
Number of subjects	91	94	185
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	19	24	43
From 65-84 years	0	0	0
85 years and over	0	0	0
<= 18 years	0	0	0
Between 18 and 64 years	0	0	0
>= 65 years	72	70	142
Age continuous Units: years			
arithmetic mean	71.3	70.8	
standard deviation	± 8.71	± 8.20	-
Gender categorical Units: Subjects			
Female	52	54	106
Male	39	40	79
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	4	3	7
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	18	19	37
White	69	70	139
Unknown or Not Reported	0	2	2

Height Units: cm arithmetic mean standard deviation	 165.49 ± 9.665	 166.36 ± 8.964	 -
Body mass index (BMI) Units: kg/m^2 arithmetic mean standard deviation	 27.31 ± 5.024	 27.08 ± 6.570	 -
Weight Units: kg arithmetic mean standard deviation	 74.90 ± 15.964	 74.88 ± 18.774	 -

End points

End points reporting groups

Reporting group title	Xanamem™

Reporting group description:

Oral Xanamem™ capsules 10mg, to be administered once daily

Xanamem™: Xanamem™ is formulated in green and cream coloured size 3, Coni-Snap shaped gelatin capsules as an excipient blend at a dose of 10mg. It contains active pharmaceutical ingredient of UE2343 (Laboratory code for Xanamem)

Reporting group title	Placebo

Reporting group description:

Matching placebo which is identical in appearance to the test product except that it contains no active ingredient, to be administered once daily

Placebo (for Xanamem™): Excipient blend capsules manufactured to mimic Xanamem™ capsules

Primary: ADAS-Cog v14

End point title	ADAS-Cog v14

End point description:

Change in Alzheimer's Disease Assessment Scales - Cognitive Subscale Score, version 14 (ADAS-Cog v14). Total scores of ADAS Cog 14 range from 0 to 90, with higher scores indicating greater disease severity.

End point type	Primary

End point timeframe:

Baseline, Week 12

End point values	Xanamem™	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	92		
Units: Change in score				
arithmetic mean (standard deviation)	-1.5 (± 6.47)	-0.7 (± 6.65)		

Statistical analyses

Statistical analysis title	ADAS-Cog Score

Statistical analysis description:

ADAS-Cog v14 score is sum of all 14 items of ADAS-Cog v14. An analysis of covariance model was used to assess the change in ADAS-Cog v14 score from Baseline (Week 0) to EOT (Week 12). The ANCOVA model included treatment group as fixed effects and the Baseline value as a covariate. The primary efficacy hypothesis was: H0: $\mu P \leq \mu X$; H1: $\mu P > \mu X$, where μP and μX denoted the change from Baseline to EOT in ADAS-Cog v14 for placebo and Xanamem, respectively.

Comparison groups	Xanamem™ v Placebo

Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.343
Method	ANCOVA

Notes:

[1] - The test was performed at a type I error rate of 0.05 one-sided, with a priori hierarchical handling of multiplicity, based on the least squares (LS) means for EOT (Week 12). ANCOVA was used to derive 90% and 95% confidence intervals with Baseline ADCOMs score and treatment as covariates. The primary efficacy analysis did not replace missing EOT (Week 12).

Primary: AD COMposite Scores

End point title	AD COMposite Scores

End point description:

Change in AD COMposite Scores (ADCOMs- ADCOMs, composite score is derived from a weighted linear combination of items from commonly used outcome scales Cognitive Subscale Version 14 [ADAS-Cog v14], Clinical Dementia Rating Scale - Sum of Boxes [CDR-SOB], and Mini-Mental Status Examination [MMSE]. Th ADCOMs range: 0 - 1.97, whereas a lover score is interpreted as a better result.

Included scales:

ADAS-Cog v14 (range: 0-90): A lower score is indicative of better cognition, a higher score indicates higher cognitive impairment.

CDR-SUB (range: 0-18): A lower score is indicative of better cognition, a higher score indicates higher cognitive impairment.

MMSE (range: 0-30): A higher score is indicative of better cognition, a lower score indicates higher cognitive impairment.

End point type	Primary

End point timeframe:

Baseline, Week 12

End point values	Xanamem™	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	92		
Units: Change in score				
arithmetic mean (standard deviation)	0.02472 (± 0.144135)	0.01908 (± 0.151502)		

Statistical analyses

Statistical analysis title	ADCOMs

Statistical analysis description:

An analysis of covariance model was used to assess the change in ADCOMs score from Baseline (Week 0) to EOT (Week 12). The ANCOVA model included treatment group as fixed effects and the Baseline value as a covariate. The primary efficacy hypothesis was: H0: μP ≤ μX; H1: μP > μX, where μP and μX denoted the change from Baseline to EOT in ADCOMs for placebo and Xanamem, respectively.

Comparison groups	Xanamem™ v Placebo

Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.795
Method	ANCOVA

Notes:

[2] - The test was performed at a type I error rate of 0.05 one-sided, with a priori hierarchical handling of multiplicity, based on the least squares (LS) means for EOT (Week 12). ANCOVA was used to derive 90% and 95% confidence intervals with Baseline ADCOMs score and treatment as covariates. The primary efficacy analysis did not replace missing EOT (Week 12).

Secondary: RAVLT - Recall list A

End point title	RAVLT - Recall list A

End point description:

Change in Rey Auditory Verbal Learning Test (RAVLT) RAVLT will be administered using five trials, with individual scores from 0-15. The total score is the combined score of all five trials, ranging from 0 to 75, whereas a lower score is considered a worse outcome and a higher score a better outcome.
Recall List A - Total number of correct words

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Xanamem™	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	90		
Units: Change in score				
arithmetic mean (standard deviation)	0.3 (± 6.54)	0.4 (± 6.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: RAVLT - Recall list B

End point title	RAVLT - Recall list B

End point description:

Change in Rey Auditory Verbal Learning Test (RAVLT) RAVLT will be administered using five trials, with individual scores from 0-15. The total score is the combined score of all five trials, ranging from 0 to 75, whereas a lower score is considered a worse outcome and a higher score a better outcome.
Recall List B - Number of correct words

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Xanamem™	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	90		
Units: Change in words				
arithmetic mean (standard deviation)	0.3 (± 1.63)	0.1 (± 1.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: RAVLT - Final recall of List A

End point title	RAVLT - Final recall of List A

End point description:

Change in Rey Auditory Verbal Learning Test (RAVLT) RAVLT will be administered using five trials, with individual scores from 0-15. The total score is the combined score of all five trials, ranging from 0 to 75, whereas a lower score is considered a worse outcome and a higher score a better outcome.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Xanamem™	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	90		
Units: Change in words				
arithmetic mean (standard deviation)	0.2 (± 3.14)	0.4 (± 2.40)		

Statistical analyses

No statistical analyses for this end point

Secondary: CDR-SOB

End point title	CDR-SOB

End point description:

Change in Clinical Dementia Rating Scale - Sum of Boxes (CDR-SOB) The CDR is obtained through semi-structured interviews of patients and informants, and cognitive functioning is rated in six domains of functioning: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care.

Each domain is rated on a five-point scale of functioning as follows: 0, no impairment; 0.5, questionable impairment; 1, mild impairment; 2, moderate impairment; and 3, severe impairment.

The CDR-SOB is based on summing each of the domain box scores, with scores ranging from 0-18, whereas lower scores represent better outcomes and higher scores worse outcomes.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Xanamem™	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	91		
Units: Score				
arithmetic mean (standard deviation)	0.25 (± 1.276)	0.16 (± 1.325)		

Statistical analyses

No statistical analyses for this end point

Secondary: MMSE

End point title	MMSE

End point description:

Change in Mini-Mental Status Examination (MMSE) MMSE total score (0 - 30) is a sum of all 30 point questionnaire of MMSE. A score of 20 to 24 suggests mild dementia, 13 to 20 suggests moderate dementia, and less than 12 indicates severe dementia.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Xanamem™	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	91		
Units: Score				
arithmetic mean (standard deviation)	0.2 (± 3.09)	-0.2 (± 2.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: NPI (Neuropsychiatric Inventory)

End point title	NPI (Neuropsychiatric Inventory)

End point description:

Change in Neuropsychiatric Inventory (NPI) The NPI includes questions to ten behavioural and two neurodegenerative domains.

Raters recorded neuropsychiatric symptoms using a 1-4 scale for frequency and a 1-3 scale for severity for each item in the instrument, with the score for each domain being: domain score = frequency x severity.

The total score is calculated by adding the scores of the first 10 domain scores.

The two neurodegenerative items are not included in the NPI total score as they form part of the depression syndrome in some patients and were specifically excluded from the dysphoria subscale of the NPI in order to allow that subscale to focus on mood symptoms.

The total NPI-score minimum is 0 and the maximum 144. A lower score is considered a better outcome, a higher score a worse outcome.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Xanamem™	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	92		
Units: Score				
arithmetic mean (standard deviation)				
NPI Total Score	0.9 (± 8.67)	0.8 (± 9.09)		
Delusions	0.0 (± 0.38)	0.1 (± 0.87)		
Hallucinations	0.1 (± 0.60)	0.0 (± 0.36)		
Agitation/Aggression	0.2 (± 2.02)	0.2 (± 1.91)		
Depression/Dysphoria	0.0 (± 1.34)	0.0 (± 1.91)		
Anxiety	0.1 (± 1.70)	-0.4 (± 2.08)		
Elation/Euphoria	0.1 (± 0.92)	0.0 (± 0.67)		
Apathy/Indifference	0.0 (± 2.18)	0.3 (± 2.11)		
Disinhibition	0.1 (± 1.15)	0.1 (± 1.03)		
Irritability/Lability	0.1 (± 1.94)	0.5 (± 2.17)		
Aberrant Motor Behaviour	-0.1 (± 2.98)	0.2 (± 2.37)		
Sleep	0.2 (± 2.47)	0.0 (± 1.83)		
Appetite and Eating Disorders	0.1 (± 3.18)	-0.1 (± 2.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: NTB - Executive Domain

End point title	NTB - Executive Domain

End point description:

Change in Neuropsychological Test Batteries (NTB) - Executive Domains: Controlled Oral Word Association - Test (COWAT) and Total Correct Response (CFT) Total NTB score is the sum of COWAT and CFT. During the COWAT test, the subject is asked to mention as many words as possible beginning with different letters (F, A, S) within 1 minute each. The number of words for each letter is recorded, the score is the sum of all words. There is no minimum or maximum score, whereas more words indicate a better outcome.

During the CFT test, the subject is given 1 minute to produce as many unique words as possible within a semantic category. The subject's score is the number of unique correct words.

There is no minimum or maximum score whereas a score of under 14 is interpreted as concerning regarding cognition.

End point type	Secondary

End point timeframe:
Baseline, Week 12

End point values	Xanamem™	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	91		
Units: Score				
arithmetic mean (standard deviation)				
COWAT Total Correct Words	0.5 (± 8.08)	0.5 (± 8.12)		
CTF Total Correct Responses	0.3 (± 8.53)	-0.7 (± 6.28)		
NTB Total Score	0.8 (± 11.50)	-0.2 (± 9.84)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Median treatment duration (weeks) was 12 weeks (range: 0.14, 13.0 weeks) for subjects in the Xanamem group and 12 weeks (range: 0.14, 13.1 weeks) for subjects in the placebo group.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Xanamem™

Reporting group description:

Oral Xanamem™ capsules 10mg, to be administered once daily

Xanamem™: Xanamem™ is formulated in green and cream coloured size 3, Coni-Snap shaped gelatin capsules as an excipient blend at a dose of 10mg. It contains active pharmaceutical ingredient of UE2343

Reporting group title	Placebo

Reporting group description:

Matching placebo which is identical in appearance to the test product except that it contains no active ingredient, to be administered once daily

Placebo (for Xanamem™): Excipient blend capsules manufactured to mimic Xanamem™ capsules

Serious adverse events	Xanamem™	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 91 (4.40%)	4 / 94 (4.26%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Vibration test abnormal			
subjects affected / exposed	1 / 91 (1.10%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 91 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			

subjects affected / exposed	0 / 91 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 91 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 91 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary cavitation			
subjects affected / exposed	1 / 91 (1.10%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 91 (1.10%)	0 / 94 (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			
Pneumonia			
subjects affected / exposed	2 / 91 (2.20%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 91 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Xanamem™	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 91 (36.26%)	32 / 94 (34.04%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 91 (3.30%)	6 / 94 (6.38%)	
occurrences (all)	4	6	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 91 (9.89%)	10 / 94 (10.64%)	
occurrences (all)	11	11	
Dizziness			
subjects affected / exposed	8 / 91 (8.79%)	4 / 94 (4.26%)	
occurrences (all)	8	4	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 91 (6.59%)	5 / 94 (5.32%)	
occurrences (all)	7	5	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 91 (1.10%)	5 / 94 (5.32%)	
occurrences (all)	1	5	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	6 / 91 (6.59%)	2 / 94 (2.13%)	
occurrences (all)	9	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 August 2016	Protocol Amendment 1 was implemented on 8 August 2016 to include comprehensive nerve function monitoring in all randomised subjects and not just a sub-set of subjects, amendment of the dosing schedule to a once daily dose up-titration regimen in order to reduce plasma exposure; clarification around the cerebrospinal fluid sampling; amendment of pharmacokinetic sampling with sparse pharmacokinetic sampling being conducted in all randomised subjects; addition of procedures used to measure orthostatic changes in blood pressure and heart rate.
16 October 2017	Protocol Amendment 4 was implemented on 16 October 2017. The primary reason for this protocol amendment was to implement an interim and efficacy analysis of 50 completed, evaluable participants to coincide with the scheduled Data Safety Monitoring Board review of the same subjects' safety data. Blood chemistry parameters have been slightly broadened to increase participant eligibility for the study. The proposed new blood chemistry parameters are still within safe limits. Explicit exclusion criteria were also introduced to ensure that potential participants with a functional deficit at foot level were not enrolled into the study. Additional exclusion criteria were also added to exclude participants with disorders affecting hypothalamic-pituitary-adrenal axis function or with uncontrolled conditions relating to glucose and lipid metabolism.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported