1 TITLE PAGE

AMENDED CLINICAL STUDY PROTOCOL

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)

Protocol Number:	**ACW0002**
Project Name:	**XanADu**
Universal Trial Number:	**U1111-1177-5932**
Test Product:	**Xanamem™ (UE2343)**
Indication:	**Mild Dementia due to Alzheimer's disease**
Sponsor:	**Actinogen Medical, Level 9, Suite 1, 68 Pitt Street, Sydney, New South Wales 2000, Australia**
Development Phase:	**Phase II**
Date of the Final Protocol:	**08-Mar-2016**
Version of the Final Protocol:	**Final Version 2**
Date of Protocol Amendment 1:	**08-Aug-2016**
Date of Protocol Amendment 2:	**24-Nov-2016**
Date of Protocol Amendment 3:	**27-Jan-2017 (United Kingdom only)**
Date of Protocol Amendment 4:	**16-Oct-2017**
Date of Non-Substantial Amendment 5:	**18-Jul-2018**

2 SIGNATURE PAGES

SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: **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)**

PROTOCOL NUMBER: **ACW0002**

I have read and understood the protocol entitled as above and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

Actinogen Medical

Vincent Ruffles
Vice President of Drug Development
Actinogen Medical

25 July 2018
Date (day/month/year)

Professor Alan Boyd, MD
Sponsor's Responsible Physician
Actinogen Medical

26th July 2018.
Date (day/month/year)

CLINICAL RESEARCH ORGANISATION SIGNATURE PAGE

PROTOCOL TITLE: **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)**

PROTOCOL NUMBER: **ACW0002**

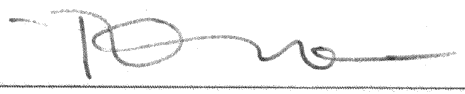
I have read and understood the protocol entitled as above and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

ICON Clinical Research Ltd

26 July 2017

Dr Peter Schueler, MD
Senior Vice President, Drug Development Services CNS
ICON Clinical Research Ltd

Date (day/month/year)



27/JUL/2018

Tom Olson
Project Manager
ICON Clinical Research Ltd

Date (day/month/year)

SIGNATURE OF INVESTIGATOR

I have read the protocol entitled "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)" and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

I agree to conduct the study outlined above in accordance with the terms and conditions of the protocol, International Conference on Harmonisation guidelines on Good Clinical Practice and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

Changes to the protocol will only be implemented after written approval is received from Actinogen Medical and the Institutional Review Board or Independent Ethics Committee (as appropriate), with the exception of medical emergencies.

I will ensure that study staff fully understand and follow the protocol.

_____ _____

(Name, job title and institution) Date (day/month/year)

_____

(Signature)

3 GENERAL INFORMATION

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)

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Sponsor:	**Actinogen Medical** **Level 9, Suite 1** **68 Pitt Street** **Sydney, New South Wales 2000** **Australia**
Clinical Research Organisation:	**ICON Clinical Research Pty Ltd** **Suite 201, Level 2** **2-4 Lyon Park Road** **North Ryde, New South Wales 2113** **Australia**
Sponsor's Legal Representative in the European Union:	**ICON Clinical Research UK Ltd** **Concept House 6** **Stoneycroft Rise** **Chandlers Ford** **Eastleigh, Hampshire SO53 3LD** **United Kingdom**
Sponsor Signatory:	**Vincent Ruffles** **Vice President of Drug Development** **Actinogen Medical** **Level 9, Suite 1** **68 Pitt Street** **Sydney, New South Wales 2000** **Australia** **Tel No.: +61 2 8964 7401** **Fax No.: +61 2 8964 7588**

Sponsor Medical Expert:	**Professor Alan Boyd** **Sponsor's Responsible Physician** **Actinogen Medical** **Level 9, Suite 1** **68 Pitt Street** **Sydney, New South Wales 2000** **Australia** **Tel No.: +61 2 8964 7401** **Fax No.: +61 2 8964 7588**
Central Clinical Laboratory:	**ICON Laboratory Services** **South County Business Park** **Leopardstown, Dublin 18** **Ireland**
Secondary Clinical Laboratory:	**Edinburgh Clinical Research Facility** **Queen's Medical Research Institute** **47 Little France Crescent** **Edinburgh EH16 4TJ** **Scotland UK**

4 STUDY SYNOPSIS

Name of Sponsor/Company: Actinogen Medical	**Individual Study Table Referring to Part of the Dossier:**	**(For National Authority Use Only)**
Name of Product: Xanamem™		
Name of Active Ingredient: (5-(1H-Pyrazol-4-yl)thiophen-3-yl)(3-hydroxy-3-(pyrimidin-2-yl)-8 azabicyclo[3.2.1]octan-8-yl)methanone	**Volume:** **Page:**	

Title of Study:
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)

Study Sites:
It is planned that approximately 20 study sites will be initiated for this study in three countries (Australia, United Kingdom and United States of America).

Publication(s):
None.

Planned Study Period:	**Development Phase:**
March 2017 to February 2019 (last subject last visit)	Phase II

Objectives:
Primary Objective:
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.
Secondary Objectives:
Secondary objectives of this study are to assess the extent to which Xanamem™ improves performance from Baseline to EOT compared to placebo, as measured by changes to:

- Rey Auditory Verbal Learning Test (RAVLT)
- CDR-SOB
- MMSE
- Neuropsychiatric Inventory (NPI)
- Neuropsychological Test Batteries (NTB) – Executive Domain

Methodology:
This is a randomised, double-blind, placebo-controlled Phase II proof-of-concept study.

Number of Subjects:
It is planned that approximately 174 subjects will be enrolled to ensure that 156 subjects would complete the 12-week double-blind study period (78 subjects in each treatment group). A 10% drop-out rate is expected.

Diagnosis and Main Criteria for Inclusion:
1. Males and females aged 50 years or older at the time of informed consent.
2. Female subjects:
   a) Post-menopausal women, defined as no menses for 12 months without an alternative medical cause. If there is any concern about the menopausal status of a prospective female subject, a follicle-stimulating hormone test (FSH) should be requested to confirm post-menopausal status. Post-menopausal women confirmed by FSH level > 40 mIU/mL, will be confirmed by central laboratory.
   b) Women of childbearing potential (WOCBP) must have a negative pregnancy test at Screening and Baseline, and be willing to use highly effective methods of contraception from the Screening visit

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until 3 months after last dose of study drug. The central laboratory will flag positive serum human chorionic gonadotropin as exclusionary at Screening (re-test of Screening if required). In such cases, the site will perform a local urine pregnancy test at Baseline to determine if the subject can continue to randomisation.

c) Are permanently sterile or have had a hysterectomy, bilateral salpingectomy or bilateral oophorectomy.

d) Women must not be breastfeeding.

3. Male Subjects:
   a) Who are sexually active, fertile men must use highly effective methods of contraception from Day 1 until 3 months after last dose of study drug if their partners are WOBC.
   b) Who are permanently sterile or have had bilateral orchiectomy.
4. Diagnosis of mild dementia due to probable AD with increased level of certainty (provided by evidence of clinical deterioration within the 6 months preceding Screening, as assessed by the investigator) as determined by the National Institute of Ageing and the Alzheimer's Association workgroup. Individual criteria will be included in the electronic case report form.
5. Mild dementia due to probable AD with MMSE of 20 to 26 (inclusive).
6. CDR Global Score of 0.5 to 1.0.
7. A brain magnetic resonance imaging or computed tomography scan in the 12 months preceding Screening (a wider window may be accepted but requires written approval by the ICON Medical Monitor) that, in the investigator's opinion, is consistent with AD as the principal aetiology of the dementia with no other clinically significant abnormality, e.g. another principal underlying aetiology of the subject's dementia, or a lesion which could affect cognition e.g. a brain tumour or large stroke.
8. On stable dose of acetylcholinesterase inhibitor (AChEI) and/or memantine (at least 3 months prior to Screening) OR treatment-naïve. Initiating AChEIs or memantine during the study will not be permitted.
9. Apart from a clinical diagnosis of mild dementia due to probable AD, the subject must be in good health as determined by the investigator, based on medical history and screening assessments.
10. Has a consenting study partner who, in the investigator's judgement, has frequent and sufficient contact with the subject to be able to provide accurate information as to the subject's cognitive and functional abilities. The study partner must be available to provide information to the investigator and study site staff about the subject and agrees to attend all study site visits in person for scale completion. A study partner should be available for the duration of the study. The measure of adequate availability will be at the investigator's discretion.
11. Must be willing and able to comply with the requirements of the protocol and must be available to complete the study.
12. Must satisfy a medical examiner about their fitness to participate in the study.
13. Must provide written informed consent to participate in the study.

Exclusion Criteria

1. Clinically significant abnormalities in vital signs (blood pressure, heart rate, respiration rate and oral temperature), as determined by the investigator.
2. Clinically significant abnormal haematology, biochemistry and urine examination values, as determined by the investigator. Additionally, abnormal liver and renal function and Vitamin B12 levels below lower threshold may impact cognitive function. The following values will have an alert flag on the laboratory report and are specifically excluded:
   a) Vitamin B12 < 176 pg/mL
   b) Haemoglobin < 11 g/dL for females and < 12 g/dL for males
   c) Aspartate aminotransferase > 3 x upper limit of normal (ULN)

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d) Alanine aminotransferase > 3 x ULN
e) Serum creatinine > 2 x ULN
f) Urine benzodiazepines when positive: One re-test will be allowed in cases where the subject's intake of benzodiazepines is within the allowed dose. Re-tests must be performed within 7 days of the last benzodiazepine dose prior to the Baseline visit. A positive re-test for urine benzodiazepines is exclusionary.

Re-testing of laboratory parameters that requires a confirmatory value within the screening period will be permitted in an effort to find all possible well-qualified subjects. The most current result prior to randomisation is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state. Consultation with the ICON Medical Monitor (MM) is advised, to identify whether repeat testing of any particular parameter is acceptable and clinically relevant.

3. Has had a significant systemic illness or infection within the past 4 weeks prior to randomisation, as determined by the investigator.
4. Clinically significant neurological disease other than AD, such as (but not limited to) Parkinson's disease, multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, brain tumour, progressive supranuclear palsy, seizure disorder, subdural haematoma, multiple sclerosis or a history of significant head trauma followed by persistent neurologic defaults or known structural brain abnormalities.
5. Subjects with clinical evidence of peripheral neuropathy or historical evidence of clinically significant nerve conduction abnormalities. Clinical evidence of neuropathy is defined as:
   a) Inability to sense a stimulus even at the secondary (more proximal) skin area for pinprick, light touch, and vibration or temperature at the foot, in at least one extremity (in case neurography measures are normal, the case will be discussed with the ICON MM to assess subject eligibility)
   b) Nerve conduction abnormalities beyond local normal values or inability to measure Sensory Nerve Action Potential or Compound Muscle Action Potential in the primary or a secondary (back-up) nerve
   c) Neuropathy Total Symptom Score (NTSS)-6 score > 6, but note that subjects are eligible even if they show:
      - Missing reflexes of the Achilles tendon (ankle), but a positive patellar (knee) tendon reflex
      - Missing ability to name toe or thumb position
6. Has had a stroke within the year prior to randomisation, as determined by the investigator.
7. Has a lifetime diagnosis of a major psychiatric disorder (other than dementia), based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria. This includes but is not limited to schizophrenia, schizoaffective disorder, bipolar affective disorder, alcohol dependence syndrome or major depressive disorder.
8. Has a history of disease directly related to the hypothalamus, the pituitary and/or the adrenal glands which affect the hypothalamic-pituitary-adrenal axis function.
9. Has uncontrolled clinical conditions relating to glucose and lipid metabolism.
10. Clinically significant electrocardiogram (ECG) abnormalities, including QTc interval > 450 msec, following ECG tracings at Screening. A single repeat evaluation will be allowed if the investigator or designee has reason to believe the reading is faulty or to help assess the clinical significance of an abnormality. Any other ECG abnormality that is seen as exclusionary will first be discussed with the ICON MM.
11. Use of any prohibited medication.
12. Participation in another clinical study of an investigational drug or device whereby the last drug/device administration is within 60 days of Screening.
13. Inability to communicate well with the investigator (i.e. language problem, non-fluent English [as scales will be provided in English only], poor mental development or impaired cerebral function).

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14. Subject will undergo the tests, ADAS-Cog v14, CDR-SOB, MMSE, NTB (executive domain) and RAVLT at the indicated time-points to avoid uncontrolled learning effects. Subjects who need to perform these tests externally to and in parallel with this study will be excluded.
15. Subject has ingested any food or drink containing grapefruit, Seville oranges, star fruit, or derived products (e.g. fruit juice), for at least 3 days prior to the first administration of study drug. Subjects must be willing to abstain from ingesting these foods and drinks throughout the study, as it may interfere with the activity of Xanamem™.

Test Product, Dose and Mode of Administration:

Oral Xanamem™ capsules, 10 mg administered once a day (QD).

Dosing:

At Week 0, eligible subjects will be randomised to 10 mg/matching placebo QD with a 1:1 allocation ratio.

Reference Therapy, Dose and Duration of Administration:

Matching placebo which is identical in appearance to the test product except that it contains no active ingredient.

Duration of Treatment:

Subjects should participate in the study for 17 to 20 weeks, including a treatment period of 12 weeks.

Assessments:

Efficacy

- ADAS-Cog v14
- RAVLT
- CDR-SOB
- MMSE
- NPI
- NTB – Executive Domain

Safety

- Change in clinical safety laboratory values from Baseline (Week 0) to EOT (Week 12)
- Incidence of adverse events (AEs)
- ECG
- NTSS-6
- Neurological examination: This will cover all aspects of the Toronto Clinical Neuropathy Score (TCNS):
  - Muscle strength/weakness in arms and legs
  - Ataxia (gait, stance and finger-nose coordination)
  - Light touch (upper and lower extremity)
  - Pinprick (upper and lower extremity)
  - Position sense (toes and thumbs)
  - Reflexes (knee and ankle)
- Nerve Function Monitoring (NFM): This includes the abovementioned scales (NTSS-6 and TCNS), as well as neurography (nerve conduction velocity and amplitude) of peripheral sensory and motor nerves. The NFM should follow existing local standards and procedures and should be run in a consistent fashion. The test must be undertaken and reviewed by suitably qualified and experienced personnel.
- Columbia Suicide Severity Rating Scale (CSSRS)
- Physical examination

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- Vital signs

Ad hoc telephone contact may occur at any time-point throughout the study, if deemed necessary by the investigator/study nurse, or if the subject wishes to report an adverse event (AE).

Pharmacokinetics/Pharmacodynamics

- **Pharmacokinetic (PK) assessment**: PK blood samples will be taken from all enrolled subjects.
- **Optional pharmacodynamic (PD) assessment:** PD blood samples will be taken from approximately 50 subjects enrolled into the main study, who also volunteer to take part in the PD sub-study, unless a higher number is defined as a result of the analysis of the PD data, by the Data Safety Monitoring Board (DSMB). Samples will be taken pre-dose from subjects in a fasted state, to evaluate the adrenocorticotropic hormone, dehydroepiandrosterone sulfate, androstenedione and testosterone at the Baseline (Week 0), Interim visits (Week 4 and Week 8), EOT (Week 12) and Follow-up (4 weeks post last dose of study drug) visits. For optimal results, the sample for androstenedione analysis should be taken between 6 am and 10 am.

Other Exploratory Assessments

- **Metabolic function** (lipids, blood pressure, glucose, haemoglobin A1c [HbA1c], body weight, body mass index [BMI]) analysis will be performed on all enrolled subjects.

Statistical Methods:

Analysis sets

The safety analysis set will consist of all subjects who receive at least one dose of study drug. Subjects will be analysed according to the treatment they actually received. The safety analysis set will be the primary analysis set for safety analyses.

The full analysis set (FAS) will consist of all subjects randomised who received at least one dose of study drug. Subjects will be analysed in the treatment group they were randomised to even if they received incorrect study drug. Where changes from Baseline are analysed, subjects will be included only if both a Baseline and at least one valid post-Baseline measurement are available. The FAS will be the primary analysis set for efficacy analyses.

The per protocol (PP) analysis set is a subset of the FAS, and will consist of all randomised subjects for whom no key protocol violation is documented. The PP analysis set will provide supportive data for the efficacy analyses. Allocation of subjects to the PP analysis set will be performed before unblinding of the study.

The PK set will consist of all subjects in the safety population who have at least one post-dose PK assessment. PK analyses will be performed using the PK set.

The PD set will consist of all subjects in the safety population who have at least one post-dose PD assessment. PD analyses will be performed using the PD set.

Statistical Analysis

For analysis of the primary efficacy variables, an analysis of covariance (ANCOVA) model will be used to assess the change in ADCOMs/ADAS-Cog v14 score from Baseline (Week 0) to Week 12 (EOT). Treatment group will be used as fixed effect and the baseline value as a covariate. Least squares means from the ANCOVA model will be used to derive 90% and 95% confidence intervals. The analysis described above will be repeated on the PP set for supportive evidence. There will be no imputation of missing Week 12/EOT values in the primary efficacy analysis.

Sensitivity analyses aim at assessing the robustness of the primary efficacy analysis. The following two analyses will be performed:

- An additional ANCOVA, imputing missing Week 12/EOT data based on resampling from the placebo subjects, taking baseline values into account.
- An additional ANCOVA, adding site as a factor. Sites contributing few subjects may be pooled. Any decision on pooling sites will be undertaken before unblinding.

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For secondary efficacy variables, summary statistics according to the endpoints' scale will be presented and treatment groups will be compared in an exploratory fashion.

Safety variables will be analysed as follows: Clinical laboratory measurements, AEs, vital signs, physical examination and ECG data will be summarised following usual practice. NFM and CSSRS variables will be presented using summary statistics according to each variable's scale and treatment groups will be compared in an exploratory fashion. Special attention will be directed at intra-subject changes over the course of the study.

Interim Analysis

There is one planned interim analysis after 50 completed subjects. The following endpoints will be analysed in this interim analysis:

Efficacy:

- ADAS-Cog
- MMSE
- CDR-SOB
- ADCOMS
- RAVLT
- NPI
- NTB – Executive domain (Controlled Word Association Test and Category Fluency Test)

Safety:

- Laboratory values
- Incidence of AEs
- NFM

PK/PD:

- Plasma concentrations of Xanamem™

This interim efficacy analysis aims at providing additional information on the efficacy parameters to the DSMB, including both descriptive and inferential statistics. No study adaptations are planned based on these analyses. Should there be evidence of an overwhelming effect, the DSMB may recommend stopping early for success. For control of the type I error rate, the Haybittle-Peto approach will be used, thus setting the stopping boundary at a one-sided 0.001, leaving the full type I error rate of a one-sided 0.05 for the final analysis.

Date of the Non-Substantial Amendment to Protocol: 18-Jul-18

5 TABLE OF CONTENTS

5.1 List of Tables

5.2 List of Appendices and Supplements

6 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AA	Alzheimer's Association
AChEI	Acetylcholinesterase inhibitor
ACTH	Adrenocorticotropic Hormone
AD	Alzheimer's disease
ADAS-Cog v14	Alzheimer's Disease Assessment Scale - Cognitive subscale, version 14
ADCOMs	AD COMposite Score
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
$AUC_{0\text{-}24hr}$	Area under the plasma concentration-time curve from 0 to 24 hours
BMI	Body mass index
CDR	Clinical Dementia Rating scale
CDR-SOB	Clinical Dementia Rating scale - Sum of Boxes
CFT	Category Fluency Test
C_{max}	Maximum concentration
CMAP	Compound Muscle Action Potential
C_{min}	Minimum concentration
CNS	Central nervous system
COWAT	Controlled Word Association Test
CSF	Cerebrospinal fluid
CSSRS	Columbia Suicide Severity Rating Scale
CT	Computed tomography
CYP3A4	Cytochrome P450 3A4
DHEAS	Dehydroepiandrosterone sulfate
DSMB	Data Safety Monitoring Board
eCRF	Electronic case report form
ECG	Electrocardiogram
EOT	End of Treatment
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
HbA1c	Haemoglobin A1c
11β-HSD1	1β-hydroxysteroid dehydrogenase Type 1
IC_{50}	Inhibitory concentration of 50%
ICF	Informed consent form

ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IMP	Investigational medicinal product
IRB	Institutional review board
IWRS	Interactive Web Response System
LS	Least squares (means)
MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
MM	Medical Monitor
MMSE	Mini-Mental Status Examination
MRI	Magnetic resonance imaging
NCV	Nerve conduction velocity
NFM	Nerve Function Monitoring
NIA	National Institute of Ageing
NPI	Neuropsychiatric Inventory
NTB	Neuropsychological Test Batteries
NTSS	Neuropathy Total Symptom Score
pCOA	Pre-dementia Clinical Outcome Assessments
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per protocol
PV	Pharmacovigilance
QD	Once a day
QTcB	QT time using the Bazett's correction
QTcF	QT time using the Fridericia's correction
RAVLT	Rey Auditory Verbal Learning Test
SAE	Serious adverse event
SAP	Statistical analysis plan
SNAP	Sensory Nerve Action Potential
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
TCNS	Toronto Clinical Neuropathy Score
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
WOCBP	Women of childbearing potential

7 INTRODUCTION

7.1 Background

Alzheimer's disease (AD) is emerging as one of the most important global public health issues to face modern humanity. With the ageing population and success of medical interventions in many other disease areas, the prevalence of AD is rapidly increasing. Data from the 2015 World Alzheimer's Report[1] estimates there are 47 million people globally affected by AD, with the number set to double every 20 years. The burden of the disease is global, with nearly 70% of the increase expected to be in middle and low income countries.

In Australia, more than 342,800 people are living with dementia. Without a medical breakthrough, the number of people with dementia is expected to be almost 900,000 by 2050. Each week, there are more than 1,800 new cases of dementia in Australia, and approximately 25,100 people with younger onset dementia (a diagnosis of dementia under the age of 65; including people as young as 30[2]). The number of people with AD in the United Kingdom (UK) has increased since the late 1990s and is a major cause of morbidity and mortality. This increase has been associated primarily with an increasing incidence of elderly people[3] and better case ascertainment.

Of the 5.3 million Americans with AD, an estimated 5.1 million are aged 65 years and older, and approximately 200,000 are under the age of 65. The number of Americans with AD and other dementias will increase each year as the size and proportion of the population of the United States of America (USA) aged 65 years and older continues to increase. By 2025, the number of people aged 65 and older with AD is estimated to reach 7.1 million - a 40% increase from the 5.1 million aged 65 and older affected in 2015. By 2050, this number could triple to a projected 13.8 million, barring the development of medical breakthroughs to prevent or cure the disease[4].

The cost of treating AD is approaching one trillion dollars and if dementia care was a country it would be the 18th largest economy. AD is one of the leading causes of death in the developed world, and in Australia is second only to ischemic heart disease. Compounding this societal burden is the relative limited benefit provided by the currently available treatment options. None of the four registered drugs (donepezil, rivastigmine, galantamine and memantine, which are available in a number of different formulations), provide much more than short-term symptomatic benefit, and significantly, none are disease-modifying. The AD community desperately needs new alternative treatment options, and ideally, drugs with a disease-modifying potential.

The Food and Drug Administration (FDA) in the USA has recently updated draft guidelines for the treatment of AD. However, despite the FDA encouraging the development of new agents to be tested clinically in patients with early symptoms of the disease[5], 99.6% of the 244 agents tested from 2002 to 2012 failed to achieve their primary endpoints[6]. Only one drug tested during that period, the N-methyl-D-aspartate-receptor antagonist memantine, was approved, and then only for the treatment of moderate to severe AD. Therefore, there is a

high medical need for alternative therapies, and particularly those with the potential for disease modification.

The pre-clinical evidence to date would indicate that Xanamem™ could be an effective symptomatic and disease-modifying treatment for mild AD. This XanADu Phase II study in mild AD is a proof-of-concept study, designed to demonstrate the efficacy and safety of Xanamem™ in mild AD.

7.2 Rationale

The steroid-converting enzyme, 11β-hydroxysteroid dehydrogenase Type 1 (11β-HSD1), is found predominantly in the liver, adipose and brain. It catalyses the reduction of inert cortisone to the active glucocorticoid hormone, cortisol. There is comprehensive evidence from studies in rodents and in humans that regulation of cortisol levels via inhibition of 11β-HSD1 provides a therapeutic strategy to treat metabolic diseases such as Type 2 diabetes and central nervous system (CNS) conditions such as cognitive impairment and AD[7,8,9,10,11].

In the brain, 11β-HSD1 is highly expressed in regions such as the hippocampus, frontal cortex and cerebellum. These regions are important for cognition and the hippocampus, in particular, has high expression of glucocorticoid receptors. There is substantial evidence that elevated glucocorticoid levels contribute to cognitive dysfunction, are neurotoxic and may contribute to AD[12,13,14,15].

For example:

- In vivo, in rats, corticosterone administration causes regression of hippocampal neuronal dendrites[16].
- In primates, long-term (1 year) implantation of cortisol pellets in the hippocampus causes shrinkage and dendritic atrophy[13]. 11β-HSD1 knock-out mice are protected against glucocorticoid-associated, age-related cognitive dysfunction on two different genetic backgrounds[17,18]. Long-term potentiation (the probable cellular/synaptic electrophysiological basis of memory) is enhanced in hippocampal slices from these mice.
- In three separate and independent studies pharmacological inhibition of 11β-HSD1 leads to improvements in cognition in wild-type aged and young rodents and in the Tg2576 model of AD[9,10,11].
- In rodent models of AD, corticosterone is elevated, whilst treatment with glucocorticoids has been shown to elevate Aβ[15].
- Studies from the University of Edinburgh found that the 11β-HSD1 enzyme amplified glucocorticoid production in target tissues (such as adipose and the hippocampus). Overexpression of the gene in adipose resulted in obesity whilst genetic deletion of the gene protected against age-related memory impairment, leading to the hypothesis that inhibitors of 11β-HSD1 could have the potential to treat metabolic disease and cognitive impairment by safely reducing glucocorticoid levels in these target tissues. The original proof-of-concept studies in humans at the University of Edinburgh utilised the prototype, non-selective, 11β-HSD1 inhibitor carbenoloxone, which significantly improved

cognition in healthy elderly men and in subjects with Type 2 diabetes by significantly ($p<0.01$) improving verbal fluency and memory at 4 to 6 weeks compared to placebo[19].

Reducing glucocorticoid action in the CNS has therefore emerged as an important therapeutic goal in the treatment of age-associated cognitive impairment and AD.

Xanamem™ (former designation UE2343) is a new investigational medicinal product, under development for the treatment of mild AD with the potential for both symptomatic and disease-modifying effects. Xanamem™ displays high potency and selectivity for human 11β-HSD1 when compared to related hydroxysteroid dehydrogenase enzymes and receptors. Based on pre-clinical data from rodent models of AD and age-related cognitive impairment it is anticipated that Xanamem™ will have a beneficial effect on the cognitive decline associated with AD. Additionally, pre-clinical data also indicate that treatment may slow the progression of β-amyloid plaque deposition in the brain.

Two Phase I studies (RD 656/25368 [a Single Ascending Dose study] and ACW0001 [a Multiple Ascending Dose, Fed-Fasted and CNS study]) in 88 healthy volunteers established the pharmacokinetic (PK) and pharmacodynamic (PD) parameters of Xanamem™ and concluded that the drug was safe and well tolerated in doses from 2 to 35 mg twice daily, and that it should preferably be taken with food. The presence of the drug in the cerebrospinal fluid (CSF) confirmed that it crosses the blood brain barrier. PK/PD modelling of the CSF to plasma ratios obtained in the multiple ascending dose study were used to select the optimum dose regimen for this Phase II study in mild AD.

This Phase II study will assess the safety, tolerability and efficacy of oral Xanamem™ for 12 weeks in male and female subjects aged 50 years and older with mild dementia due to AD. This study will be conducted in compliance with the protocol, International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and applicable local regulatory requirements and laws.

In this study design, subjects will be randomised to receive either 10 mg once a day (QD) Xanamem™ or matching placebo for a 12-week period.

To support the selection of this dose, PK modelling was conducted based on the Multiple Ascending Dose (MAD) study results obtained from human volunteers, when 10, 20 and 35 mg of Xanamem™ was administered twice daily for 10 days. From this modelling, predicted PK values in plasma for maximum concentration (C_{max}), minimum concentration (C_{min}) and area under the plasma concentration-time curve from 0 to 24 hours ($AUC_{0\text{-}24hr}$) and for CSF C_{max}, C_{min} were estimated at steady state for 10, 20 and 30 mg Xanamem™ administered QD. This modelling confirmed that any of these doses would achieve consistent Xanamem CSF levels above the inhibitory concentration of 50% (IC_{50}) (the optimal target threshold) for the 11β-HSD1 enzyme.

More information can be found in the Investigator's Brochure[20].

8 STUDY OBJECTIVES

8.1 Primary Objectives

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.

8.2 Secondary Objectives

Secondary objectives of this study are to assess the extent to which Xanamem™ will improve performance from Baseline to EOT compared to placebo, as measured by changes to:

- Rey Auditory Verbal Learning Test (RAVLT)
- CDR-SOB
- MMSE
- Neuropsychiatric Inventory (NPI)
- Neuropsychological Test Batteries (NTB) – Executive Domain

8.3 Efficacy Assessments

See Section 11.1 for details of the efficacy assessments.

- ADAS-Cog v14
- RAVLT
- CDR-SOB
- MMSE
- NPI
- NTB – Executive Domain (Controlled Word Association Test [COWAT] and Category Fluency Test [CFT])

ADCOMs-related assessments (ADAS-Cog v14, CDR-SOB and MMSE), RAVLT, NPI and NTB – Executive Domain, will be performed at the Baseline (Week 0) and the EOT (Week 12) visits to minimise burden for rater and subject.

MMSE and CDR-SOB will also be performed at Screening.

8.4 Safety Assessments

- Change in clinical safety laboratory values from Baseline (Week 0) to EOT (Week 12)
- Incidence of adverse events (AEs)

- Electrocardiogram (ECG) (study sites' local equipment will be used and ECG will be read locally by an appropriately qualified and experienced ECG reader; the same equipment should be used throughout the study at that study site)
- Neuropathy Total Symptom Score (NTSS)-6: The six questions of NTSS-6 should be completed as part of the assessment of subjects' medical history, also asking for input from the caregiver to make sure no information is lost. Each item will also be graded for its frequency and intensity, adding up to a total score from "0" to "21.96" points. A total score of > 6 would exclude the subject from the study.
- The neurological examination will cover all aspects of the Toronto Clinical Neuropathy Score (TCNS). See Section 12.5 for details of this examination.
- Nerve Function Monitoring (NFM). See Section 12.7 for details of NFM.
- Columbia Suicide Severity Rating Scale (CSSRS)
- Physical Examination
- Vital signs

All evaluations will be performed as detailed in the Schedule of Assessments (Table 1). Ad hoc telephone contact may occur at any time-point throughout the study, if deemed necessary by the investigator/study nurse, or if the subject wishes to report an adverse event (AE).

8.5 Pharmacokinetics/Pharmacodynamics

- **PK assessment**: PK blood samples will be taken from all enrolled subjects.
- **Optional PD assessment**: PD blood samples will be taken from approximately 50 subjects enrolled into the main study who also volunteer to take part in the PD sub-study, unless a higher number is defined as a result of the analysis of the PD data, by the Data Safety Monitoring Board (DSMB). Samples will be taken pre-dose from subjects in a fasted state, to evaluate the adrenocorticotropic hormone (ACTH), dehydroepiandrosterone sulfate (DHEAS), androstenedione and testosterone at the Baseline (Week 0) visit, Interim visits (Week 4 and Week 8), EOT (Week 12) and Follow-up (4 weeks post last dose of study drug) visits. For optimal results, the sample for androstenedione analysis should be taken between 6 am and 10 am.

Note: results of the PK and PD (biomarkers) analyses will not be disclosed to study sites to avoid unintended subject treatment unblinding (for further details refer to the XanADu Laboratory Manual).

8.6 Other Exploratory Assessments

- **Metabolic function** (lipids, blood pressure, glucose, haemoglobin A1c [HbA1c], body weight, body mass index [BMI]) analysis will be performed on all enrolled subjects.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

9.1.1 Description

This is a Phase II, randomised, multi-centre, double-blind, placebo-controlled proof-of-concept study to assess the safety, tolerability and efficacy of oral Xanamem™ QD in adult subjects with mild dementia due to AD.

It is planned to randomise approximately 174 subjects at approximately 20 study sites in three countries (Australia, UK, and USA), with the aim to enrol 7 to 10 subjects at each study site. Subject enrolment will be competitive but a cap of 20 subjects per study site is to be established to avoid any site effects. In case data quality at one study site is creating concerns, an enrolment stop can also occur at fewer than 20 subjects.

The DSMB will periodically meet for the review of accumulating safety study data and will also be involved in the interim efficacy analysis (see Section 15.2.4 for details).

At the Baseline visit (Week 0), eligible subjects will be randomised on a 1:1 ratio to receive either Xanamem™ administered orally, QD (treatment group) or matching placebo (placebo group). Subjects will return to the study site for the Interim visits (Week 4 and Week 8), EOT (Week 12) and Follow-up (4 weeks post last dose of study drug) visits, at which study assessments, as detailed in Table 1 (Schedule of Assessments), will be performed. For further details on the dosing and treatment of subjects, refer to Section 10.

Ad hoc telephone contact may occur at any time-point throughout the study, if deemed necessary by the investigator/study nurse, or if the subject wishes to report an AE.

Subjects will be interviewed and examined at the study site at each visit, and will complete a variety of questionnaires and routine safety evaluations.

Selected subjects will undergo additional PD sampling at specific visits after providing appropriate informed consent. Subjects who do not provide consent for this optional assessment, will still be eligible for the main study.

The overall study duration for an individual subject will be 17 to 20 weeks, including a screening period of 1 to 4 weeks, a double-blind treatment period of 12 weeks, and a follow-up period of 4 weeks. The total duration of the study is expected to be approximately 2 years (last subject last visit).

9.2 Discussion of Study Design

This study is designed to investigate the safety, tolerability and efficacy of Xanamem™ in subjects with mild dementia due to AD.

Based on Xanamem™'s mode of action on the hippocampal function, amnestic symptoms may respond best, thus favouring the inclusion of mild dementia due to AD, with given evidence of disease progression. Subjects will be treated in a double-blind fashion, where both the investigators and subjects will be unaware of the treatment assignments, to minimise any subjective or unrecognised bias carried by the investigators and subjects. Placebo will be

used as the comparator in this study. In this study, Xanamem™ will be administered in conjunction with current standard therapy (see Sections 9.3.1 and 9.3.2).

Recognising that no animal toxicology reproductive or development studies have been performed with Xanamem™ as yet, women of childbearing potential (WOCBP) who have a positive pregnancy test at Screening and/or Baseline, or those who are not willing to use highly effective methods of contraception or who are not permanently sterile or have not had a hysterectomy, bilateral salpingectomy or bilateral oophorectomy, will be excluded from the study.

Subjects should aim to take the study drug at the same time each morning with meals (i.e. not in fasted condition) due to an approximately 25% higher bioavailability observed when taken in a fed state. Drug intake when fasted has no safety concern and will not be treated as a protocol deviation.

A variety of scales will be employed in this study for the assessment of efficacy. ADCOMs (composite data derived from ADAS-Cog v14, CDR-SOB and MMSE) are used to determine the primary efficacy endpoint as these scales have a higher sensitivity for domains affected by early AD and episodic memory problems than other scales[21]. ADAS-Cog will be a co-primary endpoint since this is the most established and widely validated scale. RAVLT is used to determine the most important secondary efficacy endpoint as this scale has the highest expected sensitivity for change in episodic memory, which is the most probable target of Xanamem™ effects. Although many scales will be employed during this study, subjects will not complete all of them at every visit. This is to ensure no learning effect between two adjacent visits, to reduce the total number of assessments, to minimise burden for raters and subjects and thus increase study compliance and to allow more focus on critical parameters.

Sparse PK blood samples will be taken from all subjects who participate in the main study. The PK samples will be taken pre-dose and between 3 and 5 hours post-dose (as required per Table 1), i.e. the time interval during which peak concentrations were observed in the Phase I studies. In addition, a PK sample will be collected from each subject in whom a serious AE (SAE) occurs, noting the time of the last dose of study drug administered relative to the time at which the PK sample was collected.

PD blood samples will be collected from a sub-group of approximately 50 subjects (unless a higher number is defined as a result of the DSMB analysis of the PD data). The PD sampling in this study will complement the previously reported Phase I data, in which most of the subjects were male and only a small number of subjects were aged 50 years or older. If, after evaluation of the PD data by the DSMB, it is considered that an insufficient number of subjects are on active drug, further PD data will be collected.

NFM, including vibration detection threshold, thermal (cold and warm) detection, and nerve conduction, is required to rule out any impact of Xanamem™ on nerve conduction in an elderly population, and to exclude long-term neurotoxic effects. Subjects with clinically symptomatic peripheral nerve damage at the Screening visit (e.g. polyneuropathy) will be excluded from the study to avoid confusion with the Xanamem™ safety profile.

Other efficacy/safety endpoints used in this study are well-established and well-accepted measurements for AD studies.

Interim visits are scheduled at Week 4 and Week 8 to allow the observation of potential adverse reactions.

9.2.1 Dose Rationale

In this study design, subjects will be randomised to receive either 10 mg QD Xanamem™ or matching placebo for a 12-week period.

To support the selection of this dose, PK modelling was conducted based on the MAD study results obtained from human volunteers, when 10, 20 and 35 mg of Xanamem™ was administered twice daily for 10 days. From this modelling, predicted PK values in plasma for C_{max}, C_{min} and $AUC_{0\text{-}24hr}$ and for CSF C_{max}, C_{min} were estimated at steady state for 10, 20 and 30 mg Xanamem™ administered QD. This modelling confirmed that any of these doses would achieve consistent Xanamem CSF levels above the IC_{50} (the optimal target threshold) for the 11β-HSD1 enzyme.

More information on the dose recommendation can be found in the Investigator's Brochure[20].

9.2.2 Risk/Benefit and Ethical Assessment

Xanamem™'s mechanism of action suggests a main role on hippocampal function, which may improve amnestic symptoms that are the main symptoms in subjects of mild AD. Furthermore, Xanamem™ may slow the progression of amyloid plaque deposition in the brain. Therefore, Xanamem™ has the potential for both symptomatic and disease-modifying effects in subject with mild AD.

Xanamem™ is an inhibitor of the 11β-HSD1 enzyme. Compounds which inhibit 11β-HSD1 are intended to affect the intracellular cortisone-cortisol balance, resulting in altered glucocorticoid action. It is therefore expected that AEs seen following the administration of Xanamem™ may be related to effects on glucose and fatty acid metabolism, or loss of suppression of innate immunity. In addition, inhibition of 11β-HSD1 results in enhanced cortisol clearance and potentially a compensatory increase in ACTH and cortisol secretion to maintain normal cortisol levels. As a result, ACTH-dependent secretion of adrenal androgens may be increased.

To date, Xanamem™ has an acceptable safety profile: in the MAD study[22], all treatment-emergent AEs (TEAEs) were either mild or moderate in intensity. A total of 6/24 (25.0%) subjects reported at least one TEAE possibly related to study drug, whilst all the other TEAEs were reported as unrelated or unlikely to be related to study drug.

Of the five TEAEs considered to be moderate in intensity, one event of diarrhoea (20 mg UE2343) and one event of headache (35 mg UE2343) were considered as possibly related to study drug. The other moderate TEAEs were all unrelated or unlikely to be related to study drug. The laboratory parameters were within normal range and no clinically significant abnormalities were recorded. In the subsequent fed-fasted study[22] in 12 subjects, the most commonly reported TEAE by preferred term was "Abnormal dreams", with a total of

five events reported by 5/12 (41.7%) subjects. These were considered possibly related to study drug (two events under fed conditions, one under fasted conditions and two across both the fed and fasted period), all mild in intensity and resolved.

Overall, there were no clinically significant abnormalities noted in nerve conduction studies for any of the subjects in the MAD cohorts.

Post-study, a total of six subjects experienced QT time increases of > 30 msec from Baseline using the Bazett's correction (QTcB). QTcB increases of > 60 msec were reported on one subject in the placebo group (change from Baseline to Day 10 [4 hours post-dose]) and one subject in the 20 mg Xanamem™ group (change from Baseline to post-study).

The potential benefits of Xanamem™ are therefore considered to outweigh the potential risks.

Close monitoring of safety, including potential effect on metabolic and nerve function, will be conducted throughout this study.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

A subject will be eligible for enrolment in the study if ALL of the following criteria apply:

1. Males and females aged 50 years or older at the time of informed consent.
2. Female subjects:
    a) Post-menopausal women, defined as no menses for 12 months without an alternative medical cause. If there is any concern about the menopausal status of a prospective female subject, a follicle-stimulating hormone (FSH) test should be requested to confirm post-menopausal status. Post-menopausal women confirmed by FSH level > 40 mIU/mL, will be confirmed by central laboratory.
    b) WOCBP must have a negative pregnancy test at Screening and Baseline, and be willing to use highly effective methods of contraception from the Screening visit until 3 months after last dose of study drug. The central laboratory will flag positive serum human chorionic gonadotropin as exclusionary at Screening (re-test of Screening if required). In such cases, the site will perform a local urine pregnancy test at Baseline to determine if the subject can continue to randomisation (see Appendix IV for more information).
    c) Are permanently sterile or have had a hysterectomy, bilateral salpingectomy or bilateral oophorectomy.
    d) Women must not be breastfeeding.
3. Male subjects:
    a) Who are sexually active, fertile men must use highly effective methods of contraception from Day 1 until 3 months after last dose of study drug if their partners are WOCBP (see Appendix IV for more information).
    b) Who are permanently sterile or have had bilateral orchiectomy.

4. Diagnosis of mild dementia due to probable AD with increased level of certainty (provided by evidence of clinical deterioration within the 6 months preceding Screening, as assessed by the investigator) as determined by the National Institute of Ageing (NIA) and the Alzheimer's Association (AA) workgroup, detailed in Section 4.1 and 4.2.1[23]. Individual criteria will be included in the electronic case report form (eCRF).
5. Mild dementia due to probable AD with MMSE of 20 to 26 (inclusive).
6. CDR Global Score of 0.5 to 1.0.
7. A brain magnetic resonance imaging (MRI) or computed tomography (CT) scan in the 12 months preceding Screening (a wider window may be accepted but requires written approval by the ICON Medical Monitor [MM]) that, in the investigator's opinion, is consistent with AD as the principal aetiology of the dementia with no other clinically significant abnormality, e.g. another principal underlying aetiology of the subject's dementia, or a lesion which could affect cognition e.g. a brain tumour or large stroke.
8. On stable dose of acetylcholinesterase inhibitor (AChEI) and/or memantine (at least 3 months prior to Screening) OR treatment-naïve. Initiating AChEIs or memantine during the study will not be permitted.
9. Apart from a clinical diagnosis of mild dementia due to probable AD, the subject must be in good health as determined by the investigator, based on medical history and screening assessments.
10. Has a consenting study partner who, in the investigator's judgement, has frequent and sufficient contact with the subject to be able to provide accurate information as to the subject's cognitive and functional abilities. The study partner must be available to provide information to the investigator and study site staff about the subject and agrees to attend all study site visits in person for scale completion. A study partner should be available for the duration of the study. The measure of adequate availability will be at the investigator's discretion.
11. Must be willing and able to comply with the requirements of the protocol and must be available to complete the study.
12. Must satisfy a medical examiner about their fitness to participate in the study.
13. Must provide written informed consent to participate in the study.

9.3.2 Exclusion Criteria

A subject will NOT be eligible for this study if ANY of the following criteria apply:

1. Clinically significant abnormalities in vital signs (blood pressure, heart rate, respiration rate and oral temperature), as determined by the investigator.
2. Clinically significant abnormal haematology, biochemistry and urine examination values, as determined by the investigator. Additionally. abnormal liver and renal function and Vitamin B12 levels below lower threshold may impact cognitive function. The following values will have an alert flag on the laboratory report and are specifically excluded:

a) Vitamin B12 < 176 pg/mL

b) Haemoglobin < 11 g/dL for females and < 12 g/dL for males

c) Aspartate aminotransferase > 3 x upper limit of normal (ULN)

d) Alanine aminotransferase > 3 x ULN

e) Serum creatinine > 2 x ULN

f) Urine benzodiazepines when positive: One re-test will be allowed in cases where the subject's intake of benzodiazepines is within the allowed dose. Re-tests must be performed within 7 days of the last benzodiazepine dose prior to the Baseline visit. A positive re-test for urine benzodiazepines is exclusionary.

Re-testing of laboratory parameters that requires a confirmatory value within the screening period will be permitted in an effort to find all possible well-qualified subjects. The most current result prior to randomisation is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state. Consultation with the ICON MM is advised, to identify whether repeat testing of any particular parameter is acceptable and clinically relevant.

3. Has had a significant systemic illness or infection within the past 4 weeks prior to randomisation, as determined by the investigator.
4. Clinically significant neurological disease other than AD, such as (but not limited to) Parkinson's disease, multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, brain tumour, progressive supranuclear palsy, seizure disorder, subdural haematoma, multiple sclerosis or a history of significant head trauma followed by persistent neurologic defaults or known structural brain abnormalities.
5. Subjects with clinical evidence of peripheral neuropathy or historical evidence of clinically significant nerve conduction abnormalities. Clinical evidence of neuropathy is defined as:

   a) Inability to sense a stimulus even at the secondary (more proximal) skin area for pinprick, light touch, and vibration or temperature at the foot, in at least one extremity (in case neurography measures are normal, the case will be discussed with the ICON MM to assess subject eligility)

   b) Nerve conduction abnormalities beyond local normal values or inability to measure SNAP or CMAP in the primary or a secondary (back-up) nerve

   c) NTSS-6 score > 6, but note that subjects are eligible even if they show:

      - Missing reflexes of the Achilles tendon (ankle), but a positive patellar (knee) tendon reflex
      - Missing ability to name toe or thumb position

6. Has had a stroke within the year prior to randomisation, as determined by the investigator.
7. Has a lifetime diagnosis of a major psychiatric disorder (other than dementia), based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria. This

includes but is not limited to schizophrenia, schizoaffective disorder, bipolar affective disorder, alcohol dependence syndrome or major depressive disorder.

8. Has a history of disease directly related to the hypothalamus, the pituitary and/or the adrenal glands which affect the hypothalamic-pituitary-adrenal axis function.
9. Has uncontrolled clinical conditions relating to glucose and lipid metabolism.
10. Clinically significant ECG abnormalities, including QTc interval > 450 msec, following ECG tracings at Screening. A single repeat evaluation will be allowed if the investigator or designee has reason to believe the reading is faulty or to help assess the clinical significance of an abnormality. Any other ECG abnormality that is seen as exclusionary will first be discussed with the ICON MM.
11. Use of any prohibited medication (see Section 10.8 for details).
12. Participation in another clinical study of an investigational drug or device whereby the last drug/device administration is within 60 days of Screening.
13. Inability to communicate well with the investigator (i.e. language problem, non-fluent English [as scales will be provided in English only], poor mental development or impaired cerebral function).
14. Subject will undergo the tests, ADAS-Cog v14, CDR-SOB, MMSE, NTB (executive domain) and RAVLT at the indicated time-points to avoid uncontrolled learning effects. Subjects who need to perform these tests externally to and in parallel with this study will be excluded.
15. Subject has ingested any food or drink containing grapefruit, Seville oranges, star fruit, or derived products (e.g. fruit juice), for at least 3 days prior to the first administration of study drug. Subjects must be willing to abstain from ingesting these foods and drinks throughout the study, as it may interfere with the activity of Xanamem™.

9.4 Schedule of Assessments

The Schedule of Assessments is presented in Table 1.

Table 1 Schedule of Assessments

Visit name	**Screening [1]**	**Baseline [1]**	**Interim [1]**		**Telephone Contact [14]**	**EOT [1,2]**	**Follow-up [1]**	**Unscheduled Safety Visit [15]**
Visit time and variance	**Weeks -1 to -4**	**Week 0**	**Week 4 ± 4 days**	**Week 8 ± 4 days**	**Ad hoc**	**Week 12 ± 4 days**	**4 Weeks Post Last Dose of Study Drug ± 4 days**	
Informed consent (subject and caregiver)	X							
Inclusion and exclusion criteria	X	X						
Demographics	X							
Medical history	X							
Prior/concomitant medications	X	X	X	X	X	X	X	X
MMSE (subject only) and CDR-SOB (subject and caregiver)	X	X				X		
ADAS-Cog v14 (subject only), RAVLT (subject only), NTB (subject only) and NPI (caregiver only)		X				X		
NTSS-6 (subject and caregiver) [3]	X	X	X	X	X	X	X	X
CSSRS (subject and caregiver)	X		X	X		X	X	
Physical and neurological examination (including TCNS), weight, vital signs [4]	X	X	X	X		X	X	X
NFM (including clinician-rated outcome in TCNS) [5]	X	X	X	X		X	X	
Height	X							
BMI		X				X		
Brain MRI/CT [6]	X							
Randomisation		X						

Visit name	**Screening** [1]	**Baseline** [1]	**Interim** [1]		**Telephone Contact** [14]	**EOT** [1,2]	**Follow-up** [1]	**Unscheduled Safety Visit** [15]
Visit time and variance	**Weeks -1 to -4**	**Week 0**	**Week 4 ± 4 days**	**Week 8 ± 4 days**	**Ad hoc**	**Week 12 ± 4 days**	**4 Weeks Post Last Dose of Study Drug ± 4 days**	
PK blood sample [7, 15]		X	X	X		X		X
Safety laboratory sample (biochemistry, haematology and urine examination)	X	X	X	X		X	X	
Vitamin B12	X							
Sample for metabolic function testing: glucose and lipids, HbA1c [8]		X				X		
Pregnancy test [9]	X	X	X	X		X	X	
FSH test [10]	X							
Benzodiazepines screening [11]	X							
Optional PD sample for adrenocorticotropic hormone, dehydroepiandrosterone sulfate, androstenedione and testosterone [12]		X	X	X		X	X	
ECG	X	X [13]	X	X		X	X	
Daily Drug Intake Diary		X	X	X		X		
Drug dispense		X	X	X				
Adverse event capture	X	X	X	X	X	X	X	X
Drug accountability			X	X		X		
IWRS	X	X	X	X				

Abbreviations: ADAS-Cog v14=Alzheimer's Disease Assessment Scale-cognitive subscale; BMI=body mass index; CDR-SOB=Clinical Dementia Rating scale-Sum of Boxes; CSSRS=Columbia Suicide Severity Rating Scale; CT=computed tomography; ECG=electrocardiogram; EOT=End of Treatment; FSH=follicle-stimulating hormone; HbA1c=haemoglobin A1c; IWRS=Interactive Web Response System; MMSE=Mini-Mental Status Examination; MRI=magnetic resonance imaging; NFM=nerve function

monitoring; NPI=Neuropsychiatric Inventory; NTB=Neuropsychological Test Batteries; NTSS=Neuropathy Total Symptom Score; RAVLT=Rey Auditory Verbal Learning Test; PD=pharmacodynamic; PK=pharmacokinetic; TCNS=Toronto Clinical Neuropathy Score.

1 Caregiver is required to be present at all visits (but not for all scales). For details see Section 9.4.1.

2 Subjects terminating the study early will, if possible, undergo all assessments planned for the EOT (Week 12) visit.

3 The NTSS-6 should be completed with the help of site staff, also taking into consideration input from the caregiver.

4 Vital signs must include but not be limited to the measurement of orthostatic changes in heart rate and blood pressure. For details see Section 12.6 Neurological examination will cover all aspects of the TCNS, which includes muscle strength/weakness in arms and legs, ataxia (gait, stance and finger-nose coordination), light touch (upper and lower extremity), pinprick (upper and lower extremity), position sense (toes and thumbs), reflexes (knee and ankle). The neurological examination can be conducted ± 3 days of the scheduled protocol visit (for details see Section 12.5).

5 NFM consists of sensory testing (vibration and thermal perception), motor and sensory nerve neurography (amplitude and conduction velocity) and clinician-rated outcome in TCNS. The NFM can be conducted ± 3 days of the scheduled protocol visit, except at the Screening visit where there is no limit and at the Baseline visit where it must be conducted within 3 days prior to the randomisation step. Note: Subject-related outcome measure, NTSS-6, is part of NFM but listed separately. For details see Section 12.7.

6 A brain MRI/CT scan is only needed if no historic scan is available from within 12 months prior to Screening. A wider window may be accepted but requires written approval from the ICON Medical Monitor.

7 One PK sample will be taken 3 to 5 hours post-dose at the Baseline (Week 0) visit and two PK samples will be taken (at arrival on site [pre-dose] and 3 to 5 hours post-dose) at the Interim visits (Week 4 and Week 8). One PK sample will be taken at the EOT (Week 12) visit. NB: The subject will not be dosed during the EOT visit. For details, see Section 9.4.1. The exact time-points of blood sampling for PK analysis and drug intake will be documented. Between visits, subjects will record the exact times of study drug intake in the Drug Intake Diary. The subject will be required to bring the diary to the Interim visits (Week 4 and Week 8) and EOT (Week 12) visit.

8 Taken from the blood sample at Baseline (Week 0), and EOT (Week 12) visits.

9 Women of childbearing potential only. A serum pregnancy test will be performed at Screening and a urine pregnancy test at all subsequent clinic visits.

10 Females only. To be taken only if there is clinical concern about the subject's menopausal status.

11 Urine collected for the urinalysis sample will also be used to test for the presence of benzodiazepines at the Screening visit. A second urine sample, prior to randomisation, will be needed if a benzodiazepine re-test is required.

12 This sample should be collected as soon as possible after the subject arrives at the study site (pre-dose). This could, if possible, be combined with other blood draws to minimise the burden for subjects. For optimal results, the sample for androstenedione analysis should be taken between 6 am and 10 am.

13 ECG at Baseline only required if Screening ECG was performed more than 2 weeks earlier.

14 Ad hoc telephone contact may occur at any time-point throughout the study, if deemed necessary by the investigator/study nurse, or if the subject wishes to report an AE. If an SAE occurs in a subject, the subject will return to the site for a PK sample. Additional procedures will be performed as indicated, for details see Section 12.1.1.3).

15 Cortisol will be measured using the existing PK blood samples taken at Baseline (Week 0), Week 4, Week 8, and Week 12.

Note: For each study visit, excluding the Screening visit, subjects will arrive at the study site having fasted for at least 10 hours. Subjects should aim to take study drug at the same time each morning with food (30 minutes after the start of a standard meal) at the study site, and after all pre-dose blood samples have been taken. It is recommended that the subject visit the study site in the morning so that the fasted period will have been overnight. The investigator will record time of arrival and the hours fasted. The investigator will take the appropriate blood samples from the subject, for various assessments, as indicated in the following sections. After the blood draws, the

subject will take food and a drink (to be provided either by the study site, or the subject). About 30 minutes after the start of the meal, subjects will be administered study drug in the presence of appropriate site staff. The exact time of dosing is to be recorded in the Drug Intake Diary.

9.4.1 Study Procedures and Assessments

For each study visit (except the Screening visit), subjects will arrive at the study site having fasted for at least 10 hours. It is recommended that the subject visit the study site in the morning so that the fasted period will have been overnight. The investigator will record the time of arrival and the hours fasted. The investigator will take the appropriate blood samples from the subject, for various assessments, as indicated in the following sections. After the blood draws for the Baseline visit, Interim visits (Week 4 and Week 8) and EOT (Week 12) visit, the subject will take food and a drink (to be provided either by the study site or the subject). About 30 minutes after the start of the meal, subjects will be administered study drug in the presence of the investigator. The exact time of dosing is to be recorded in the Drug Intake Diary (which forms part of the Subject Visit-by-Visit Guide).

9.4.1.1 Screening Visit (Weeks -1 to -4)

Subjects are to undergo a Screening visit at least 7 days, but no more than 28 days, prior to the planned Baseline visit (Week 0). Study sites may perform the Screening procedures at any time point within the Screening window. The subjects will spend approximately half a day at the study site. The screening period should be at least 1 week in duration to have a homogeneous sample regarding subject learning effects whilst performing the cognitive tests.

During the Screening visit, subjects will be screened at the study site to confirm their eligibility for participation in the study. The investigator or sub-investigator will discuss with each subject the nature of the study, its requirements, and its restrictions. Written informed consent must be obtained prior to the conduct of any protocol-specific procedures.

Subjects who do not randomise within 28 days of screening will be screen failed. The screening period may be extended to 31 days if the only outstanding eligibility criterion is the NFM assessment. Re-screening may be allowed once, after approval by the ICON MM. Subjects who are re-screened after 30 days (from date screen failure was confirmed), must be re-consented with a new screening number, and repeat the screening assessments. For subjects re-screened within 30 days (from date screen failure was confirmed), only assessments with results that would exclude the subject will need to be repeated.

Screening procedures and assessments are as follows:

The chronological order of the assessments below should be followed.

1. Obtain written informed consent from the subject and subject's caregiver in accordance with local regulations, including those for the sub-population PD assessment.
2. Register screening of the subject using the ICON Interactive Web Response System (IWRS).
3. Review subject eligibility (inclusion and exclusion criteria). Any questions regarding subject eligibility can be addressed to the ICON MM.
4. Document demographics.
5. Document medical history and prior and concomitant medications.

6. Complete screening scales (MMSE [subject only], CDR-SOB [subject and caregiver] and CSSRS [subject and caregiver]):
    - The neuropsychological testing (MMSE and CDR-SOB) should be performed during the same period of the day at the Screening, Baseline (Week 0) and EOT (Week 12) visits to minimise a confounding impact of fluctuations in vigilance.

Once the above assessments have been performed, the following can be performed in the order most convenient to the investigator/study site staff:

7. Physical examination (including height and weight), neurological examination and vital signs measurement (blood pressure, heart rate, respiration rate and oral temperature). The neurological examination shall cover all aspects of the TCNS:
    - Muscle strength/weakness in arms and legs
    - Ataxia (gait, stance and finger-nose coordination)
    - Light touch (upper and lower extremity)
    - Pinprick (upper and lower extremity)
    - Position sense (toes and thumbs)
    - Reflexes (knee and ankle)

    The thresholds for "Normal=0" for all Sensory Test Scores are set as follows: Subject can discriminate any of these qualities (pinprick, temperature, light touch, vibration, position sense) at least at the secondary (more proximal) region to test that quality (see Table 3 for primary and secondary skin-areas).
8. NTSS-6 (subject and caregiver): The six questions of NTSS-6 should be completed as part of the assessment of subjects' medical history, also asking for input from the caregiver to make sure no information is lost. Each item will also be graded for its frequency and intensity, adding up to a total score from "0" to "21.96" points. A total score of > 6 would exclude the subject from the study.
9. NFM: for details see Section 12.7. Two measures for each test will be obtained and averaged. The test must be undertaken and reviewed by suitably qualified and experienced personnel. The following tests will be performed:
    - Vibration detection threshold
    - Thermal (cold and warm) detection
    - Nerve conduction (velocity and amplitude)
        - Sensory nerve - Sural nerve or back-up nerves (Ulnar nerve or Median nerve) SNAP and NCV
        - Motor nerve - Peroneal nerve or back-up nerve (Tibial nerve) CMAP and NCV

    For quality control measures, the results of neurography of one subject per study site will be reviewed by a member of the DSMB Nerve Function Monitoring sub-committee. The

study site will complete a Neurography Screening Quality Control Form and send it to the ICON MM (STUDY-MA-DL-3580-0001@iconplc.com). The study site may, however, proceed with subject randomisation if all eligibility criteria are fulfilled.

10. Laboratory sampling:
    - A blood sample will be taken for haematology and biochemistry, pregnancy test (WOCBP only) and Vitamin B12. If there is clinical concern about a female subject's menopausal status, FSH will be measured.
    - Safety laboratory urine sampling. Note: the urine sample can be collected from the subject at any time whilst at the study site, whenever he/she visits the toilet.
11. Urine screen for benzodiazepines. This sample will be taken from the urine sample collected above.
12. ECG (local ECG equipment with ECG to be read locally by an appropriately qualified and experienced ECG reader at the study site).
13. Brain MRI or CT scan, if applicable. This is only needed if no historic scan is available from within 12 months prior to Screening.

Before the subject leaves the study site, the following final procedures should be completed:

14. Record AEs (including SAEs) that may have occurred after informed consent was obtained.
15. Remind the subject to attend the Baseline (Week 0) visit in a fasted state.
16. Schedule the Baseline (Week 0) visit.
17. Remind the caregiver that he/she is required to be present at all visits (but not for all scales).

9.4.1.2 Baseline Visit (Week 0)

Eligible subjects will return to the study site for the Baseline (Week 0) visit, in a fasted state. Subjects must continue to satisfy inclusion/exclusion criteria in order to be eligible for randomisation. The subjects will attend the study site from the morning until approximately mid-afternoon.

Baseline procedures and assessments should be conducted in chronological order as follows:

1. Re-review subject eligibility (inclusion and exclusion) criteria to ensure that the subject continues to be eligible for inclusion into the study.
2. Laboratory sampling:
    - A blood sample will be taken for haematology and biochemistry, including metabolic function testing (HbA1c, glucose and lipids).
    - Urine will be collected. Note: the urine sample can be collected from the subject at any time whilst at the study site, whenever he/she visits the toilet. A urine pregnancy test (WOCBP only) will be performed from this sample at the site.

- An additional blood sample will be taken **3 to 5 hours post-dose** for PK analysis. The exact times of sampling plus the exact time of study drug intake on this day must be documented.

For those subjects who have volunteered for the optional PD sub-study:

- An **optional** blood sample will be taken for PD analysis, i.e. ACTH, DHEAS, androstenedione and testosterone. This sample will be taken from approximately 50 subjects enrolled into the main study, who also volunteer to take part in this sub-study. For optimal results, the sample for androstenedione analysis should be taken between 6 am and 10 am.

3. Ensure the subject has breakfast after the laboratory sampling. The subject will take study drug 30 minutes after the start of breakfast and study site staff will document the exact time of study drug intake.
4. ECG (only required in case Screening was performed more than 2 weeks earlier). Confirm that the QTc is still acceptable for inclusion.
5. Perform physical and neurological examination and vital signs measurement (blood pressure, heart rate, respiration rate and oral temperature). The neurological examination can be conductedwithin 3 days prior to the scheduled protocol visit. Assess weight for calculation of BMI. Complete TCNS in the course of the neurological examination, as well as NTSS-6 (with input from the caregiver) to ensure the subject did not develop new signs or symptoms of neuropathy which would exclude him/her from further participation.
6. Review concomitant medication.
7. NFM: for details see Section 12.7. Perform the assessment at the area the subject could detect the sensory stimulus during the Screening visit. Two measures for each test will be obtained and averaged. Both extremities will be assessed. The test must be undertaken and reviewed by suitably qualified and experienced personnel. The NFM can be conducted within 3 days prior to the scheduled protocol visit, but must be prior to the randomisation step. Even in case Screening and Baseline are scheduled within 1 week, a second NFM assessment is required.

   Example: Subject was able to detect a vibration threshold at the medial malleolus at 2/8, perform the vibration threshold testing again at the medial malleolus. Where subjects can no longer detect vibration at the medial malleolus (but at patella with a threshold of 4/8), this would still reflect a worsening and may disqualify the subject from further participation.

   The following tests will be performed:

   - Vibration detection threshold
   - Thermal (cold and warm) detection
   - Nerve conduction (velocity and amplitude)

- Sensory nerve - Sural nerve or back-up nerves (Ulnar nerve or Median nerve) SNAP and NCV
- Motor nerve - Peroneal nerve or back-up nerve (Tibial nerve) CMAP and NCV

If any of these NFM tests show a deterioration from the "Before Treatment" status (calculated as the average of the Screening visit and Baseline visit data), please contact the ICON MM (STUDY-MA-DL-3580-0001@iconplc.com) within 24 hours of becoming aware of the deterioration, to define follow-up activities and assess whether the subject must be withdrawn from study.

8. Randomise the subject visit using ICON IWRS, dispense study drug and provide the subject with a Subject Visit-by-Visit Guide (which also contains the Drug Intake Diary).

   Note: the first dose of study drug must be taken in the presence of the investigator/study site staff, to ensure compliance, and enable the subject to open the drug container and make an entry into the Drug Intake Diary.

9. Assess AEs.
10. Complete scales (MMSE [subject only] and CDR-SOB [subject and caregiver]).
11. Neuropsychological scales (ADAS-Cog v14 [subject only], RAVLT [subject only], NTB [subject only], and NPI [caregiver only]):
    - The neuropsychological testing should be performed during the same period of the day at the Screening, Baseline (Week 0) and EOT (Week 12) visits to minimise a confounding impact of fluctuations in vigilance.
12. Before leaving the study site, the 3 to 5 hour post-dose PK sample (as described in No. 2 above), should be drawn.
13. Remind the subject to document the time of study drug intake each day and to attend the Interim (Week 4) visit in a fasted state.
14. Schedule the Interim (Week 4) visit.

9.4.1.3 Interim Visit (Week 4)

Subjects will attend the study site for the Interim (Week 4 ± 4 days) visit, in a fasted state. The subjects will attend the study site from the morning until approximately mid-afternoon.

The proposed chronology of events for the interim procedures and assessments are as follows:

1. Laboratory sampling:
   - A blood sample will be taken for haematology and biochemistry.
   - Urine will be collected. Note: the urine sample can be collected from the subject at any time whilst at the study site, whenever he/she visits the toilet. A urine pregnancy test (WOCBP only) will be performed from this sample at the site.

- A blood sample will be taken pre-dose for PK analysis (only if the subject can provide the date and time of the last dose of study drug). A second blood sample will be taken 3 to 5 hours post-dose for PK analysis. The exact times of sampling plus the exact time of study drug intake on this day must be documented.

For those subjects who have volunteered for the optional PD sub-study:

- An **optional** blood sample will be taken for PD analysis, i.e. ACTH, DHEAS, androstenedione and testosterone. This sample will be taken from approximately 50 subjects enrolled into the main study, who also volunteer to take part in the sub-study. For optimal results, the sample for androstenedione analysis should be taken between 6 am and 10 am.

2. Register the subject visit using ICON IWRS and dispense study drug.
3. Allow the subject to have breakfast after the laboratory sampling. The subject will take study drug 30 minutes after the start of breakfast and study site staff will document the exact time of study drug intake.
4. Perform physical and neurological examination and vital signs measurement (blood pressure, heart rate, respiration rate, weight and oral temperature). The neurological examination can be conducted ± 3 days of the scheduled protocol visit. Complete TCNS in the course of the neurological examination, as well as NTSS-6 (with input from the caregiver) to ensure the subject did not develop new signs or symptoms of neuropathy.
5. Review concomitant medications.
6. CSSRS (subject and caregiver).
7. ECG (local ECG equipment with ECG to be read locally by an appropriately qualified and experienced ECG reader at the study site). The same equipment as for Baseline ECG should be used, to avoid errors in calculating QTc.
8. NFM - for details see Section 12.7. Peform the assessment at the area the subject could detect the sensory stimulus during the Baseline visit. Two measures for each test will be obtained and averaged. Both extremities will be assessed. The test must be undertaken and reviewed by suitably qualified and experienced personnel. The NFM can be conducted ± 3 days of the scheduled protocol visit. The following tests will be performed:
    - Vibration detection threshold
    - Thermal (cold and warm) detection
    - Nerve conduction (velocity and amplitude)
        - Sensory nerve - Sural nerve or back-up nerves (Ulnar nerve or Median nerve) SNAP and NCV
        - Motor nerve - Peroneal nerve or back-up nerve (Tibial nerve) CMAP and NCV

If any of these NFM tests show a deterioration from the "Before Treatment" status (calculated as the average of the Screening visit and Baseline visit data), please contact ICON MM (STUDY-MA-DL-3580-0001@iconplc.com) to define follow-up activities and assess whether the subject must be withdrawn from study.

9. Record AEs. AEs of special interest (AESIs) (worsening of NFM [calculated as the average of the Screening visit and Baseline visit data] or prolongation of QTc) must be treated as SAEs and notified to ICON Pharmacovigilance (PV) within 24 hours (see Section 12.1.1). ICON PV or ICON MM will then contact the study site to explain the required next steps for further evaluation.
10. Perform study drug accountability and review Drug Intake Diary for completion compliance.
11. Schedule the second Interim (Week 8) visit.
12. Remind the subject to document the time of study drug intake on each day and to attend the Interim (Week 8) visit in a fasted state.
13. Remind the caregiver that he/she is required to be present at all visits (but not for all scales).
14. Before leaving the study site, the second PK sample (3 to 5 hours post-dose; as described in No. 1 above), should be drawn.

9.4.1.4 Interim Visit (Week 8)

Subjects will attend the study site for the Interim (Week 8 ± 4 days) visit, in a fasted state. The subjects will attend the study site from the morning until approximately mid-afternoon.

The proposed chronology of events for the interim procedures and assessments are as follows:

1. Laboratory sampling:
    - A blood sample will be taken for haematology and biochemistry.
    - Urine will be collected. Note: the urine sample can be collected from the subject at any time whilst at the study site, whenever he/she visits the toilet. A urine pregnancy test (WOCBP only) will be performed from this sample at the site.
    - A blood sample will be taken pre-dose for PK analysis (only if the subject can provide the date and time of the last dose of study drug). A second blood sample will be taken 3 to 5 hours post-dose for PK analysis. The exact times of sampling plus the exact time of study drug intake on this day must be documented.

For those subjects who have volunteered for the optional PD sub-study:

- An **optional** blood sample will be taken for PD analysis, i.e. ACTH, DHEAS, androstenedione and testosterone. This sample will be taken from approximately 50 subjects enrolled into the main study, who also volunteer to take part in the sub-study. For optimal results, the sample for androstenedione analysis should be taken between 6 am and 10 am.

2. Register the subject visit using ICON IWRS and dispense study drug.
3. Allow the subject to have breakfast after the laboratory sampling. The subject will take study drug 30 minutes after the start of breakfast and study site staff will document the exact time of study drug intake.
4. Perform physical and neurological examination and vital signs measurement (blood pressure, heart rate, respiration rate, weight and oral temperature). The neurological examination can be conducted ± 3 days of the scheduled protocol visit. Complete TCNS in the course of the neurological examination, as well as NTSS-6 (with input from the caregiver) to ensure the subject did not develop new signs or symptoms of neuropathy.
5. Review concomitant medications.
6. CSSRS (subject and caregiver).
7. ECG (local ECG equipment with ECG to be read locally by an appropriately qualified and experienced ECG reader at the study site). The same equipment as for Baseline ECG should be used, to avoid errors in calculating QTc.
8. NFM - for details see Section 12.7. Perform the assessment at the area the subject could detect the sensory stimulus during the Week 4 visit. Two measures for each test will be obtained and averaged. Both extremities will be assessed. The test must be undertaken and reviewed by suitably qualified and experienced personnel. The NFM can be conducted ± 3 days of the scheduled protocol visit. The following tests will be performed:
    - Vibration detection threshold
    - Thermal (cold and warm) detection
    - Nerve conduction (velocity and amplitude)
        - Sensory nerve - Sural nerve or back-up nerves (Ulnar nerve or Median nerve) SNAP and NCV
        - Motor nerve - Peroneal nerve or back-up nerve (Tibial nerve) CMAP and NCV

    If any of these NFM tests show a deterioration from the "Before Treatment" status (calculated as the average of the Screening visit and Baseline visit data), please contact ICON MM (STUDY-MA-DL-3580-0001@iconplc.com) to define follow-up activities and assess whether the subject must be withdrawn from study.
9. Record AEs. AESIs (worsening of NFM [calculated as the average of the Screening visit and Baseline visit data] or prolongation of QTc) must be treated as SAEs and notified to ICON PV within 24 hours (see Section 12.1.1). ICON PV or ICON MM will then contact the study site to explain the required next steps for further evaluation.
10. Perform study drug accountability and review Drug Intake Diary for completion compliance.

11. Schedule the EOT (Week 12) visit.
12. Remind the subject to document the time of study drug intake on each day and to attend the EOT (Week 12) visit in a fasted state.
13. Remind the caregiver that he/she is required to be present at all visits (but not for all scales).
14. Before leaving the study site, the second PK sample (3 to 5 hours post-dose; as described in No. 1 above), should be drawn.

9.4.1.5 Telephone Contact (Ad Hoc)

Subjects can telephone the study sites at any time during the study in order to report an AE. At this contact, site staff will be required to:

1. Question the subject about any new/updates on AEs.
2. Question the subject to determine any changes to concomitant medications.
3. Complete NTSS-6 (with input from the caregiver) to ensure the subject did not develop new signs or symptoms of neuropathy.
4. Remind the subject of the date of next visit, if applicable.
5. Remind the subject to document the exact time of study drug intake each day.
6. Remind the caregiver that he/she is required to be present at all visits (but not for all scales).

9.4.1.6 End of Treatment Visit (Week 12)

Subjects will attend the study site for the EOT (Week 12 ± 4 days) visit, in a fasted state. The subjects will attend the study site from the morning until approximately mid-afternoon. This is also an early termination visit for subjects who withdraw prior to Week 12.

Proposed chronology of events for the EOT procedures and assessments are as follows:

1. Laboratory sampling:
    - A blood sample will be taken for haematology and biochemistry, including metabolic function testing (HbA1c, glucose and lipids).
    - Urine will be collected. Note: the urine sample can be collected from the subject at any time whilst at the study site, whenever he/she visits the toilet. A urine pregnancy test (WOCBP only) will be performed from this sample at the site.
    - A blood sample will be taken for PK analysis (only if the subject can provide the date and time of the last dose of study drug). The exact time of sampling must be documented.

For those subjects who have volunteered for the optional PD sub-study:

- An **optional** blood sample will be taken for PD analysis, i.e. ACTH, DHEAS, androstenedione and testosterone for PD analysis. This sample will be taken from approximately 50 subjects enrolled into the main study, who also volunteer to take

part in the sub-study. For optimal results, the sample for androstenedione analysis should be taken between 6 am and 10 am.

2. Allow the subject to have breakfast after the laboratory sampling.
3. Perform physical and neurological examination and vital signs measurement (blood pressure, heart rate, respiration rate, weight and oral temperature). The neurological examination can be conducted ± 3 days of the scheduled protocol visit. Complete TCNS in the course of the neurological examination, as well as NTSS-6 (with input from the caregiver) to ensure the subject did not develop new signs or symptoms of neuropathy.
4. NFM - for details see Section 12.7. Perform the assessment at the area the subject could detect the sensory stimulus during the Week 8 visit. Two measures for each test will be obtained and averaged. Both extremities will be assessed. The test must be undertaken and reviewed by suitably qualified and experienced personnel. The NFM can be conducted ± 3 days of the scheduled protocol visit. The following tests will be performed:
    - Vibration detection threshold
    - Thermal (cold and warm) detection
    - Nerve conduction (velocity and amplitude)
        - Sensory nerve - Sural nerve or back-up nerves (Ulnar nerve or Median nerve) SNAP and NCV
        - Motor nerve - Peroneal nerve or back-up nerve (Tibial nerve) CMAP and NCV

    If any of these tests show a deterioration from the "Before Treatment" status (calculated as the average of the Screening visit and Baseline visit data), please contact ICON MM (STUDY-MA-DL-3580-0001@iconplc.com) to define the follow-up activities and assess whether the subject must be withdrawn from study.
5. Review concomitant medications.
6. Neuropsychological scales (ADAS-Cog v14 [subject only], CDR-SOB [subject and caregiver], MMSE [subject only], RAVLT [subject only], NTB [subject only], NPI [caregiver only] and CSSRS [subject and caregiver]):
    - The neuropsychological testing should be performed during the same period of the day at the Screening, Baseline (Week 0) and EOT (Week 12) visits to minimise a confounding impact of fluctuations in vigilance
7. ECG (local ECG equipment with ECG to be read locally by an appropriately qualified and experienced ECG reader at study site). The same equipment as for Baseline ECG should be used, to avoid errors in calculating QTc.
8. Record AEs. AESIs (worsening of NFM [calculated as the average of the Screening visit and Baseline visit data] or prolongation of QTc) must be treated as SAEs and notified to

ICON PV within 24 hours (see Section 12.1.1). ICON PV or ICON MM will then contact the study site to explain the required next steps for further evaluation.

9. Perform study drug accountability and review Drug Intake Diary for completion compliance.

9.4.1.7 Follow-up Visit (4 Weeks Post Last Dose of Study Drug ± 4 Days)

Subjects who complete the 12-week double-blind treatment period, or subjects who terminated early, will attend a Follow-up (4 weeks post last dose of study drug ± 4 days) visit for safety purposes, in a fasted state. The subjects will spend the morning at the study site.

Follow-up procedures and assessments are as follows:

1. Laboratory sampling:
    - A blood sample will be taken for haematology and biochemistry.
    - Urine will be collected. Note: the urine sample can be collected from the subject at any time whilst at the study site, whenever he/she visits the toilet. A urine pregnancy test (WOCBP only) will be performed from this sample at the site.

For those subjects who have volunteered for the optional PD sub-study:

- An **optional** blood sample will be taken for PD analysis, i.e. ACTH, DHEAS, androstenedione and testosterone. This sample will be taken from approximately 50 subjects enrolled into the main study, who also volunteer to take part in the sub-study. For optimal results, the sample for androstenedione analysis should be taken between 6 am and 10 am.

2. Perform physical and neurological examination and vital signs measurement (blood pressure, heart rate, respiration rate, weight and oral temperature). The neurological examination can be conducted ± 3days of the scheduled protocol visit. Complete TCNS in the course of the neurological examination, as well as NTSS-6 (with input from the caregiver) to ensure the subject did not develop new signs or symptoms of neuropathy.
3. NFM - for details see Section 12.7. Perform the assessment at the area the subject could detect the sensory stimulus during the Week 12 visit. Two measures for each test will be obtained and averaged. Both extremities will be assessed. The test must be undertaken and reviewed by suitably qualified and experienced personnel. The NFM can be conducted ± 3 days of the scheduled protocol visit. The following tests will be performed:
    - Vibration detection threshold
    - Thermal (cold and warm) detection
    - Nerve conduction (velocity and amplitude)
        - Sensory nerve - Sural nerve or back-up nerves (Ulnar nerve or Median nerve) SNAP and NCV

- Motor nerve - Peroneal nerve or back-up nerve (Tibial nerve) CMAP and NCV

If any of these tests show a deterioration from the "Before Treatment" status (calculated as the average of the Screening visit and Baseline visit data), please contact ICON MM (STUDY-MA-DL-3580-0001@iconplc.com) to define the follow-up activities.

4. Review concomitant medications.
5. Complete the CSSRS (subject and caregiver).
6. ECG (local ECG equipment with ECG to be read locally by an appropriately qualified and experienced ECG reader at the study site). The same equipment as for Baseline ECG should be used, to avoid errors in calculating QTc.
7. Record AEs. AESIs (worsening of NFM [calculated as the average of the Screening visit and Baseline visit data] or prolongation of QTc) must be treated as SAEs and notified to ICON PV within 24 hours (see Section 12.1.1). ICON PV or ICON MM will then contact the study site to define follow-up activities and to assess whether the subject must be withdrawn from study.

9.4.1.8 Unscheduled Safety Visit

If an SAE occurs in a subject, the subject will return to the site for a PK sample, as close as possible to SAE onset. Procedures and assessments are as follows:

1. Review concomitant medications.
2. A blood sample will be taken for PK analysis. The exact date and time of sampling must be documented.
3. Review the Drug Intake Diary for completion compliance and for the date and time of the last dose of study drug prior to the PK sample.
4. Perform physical and neurological examination and vital signs measurement (blood pressure, heart rate, respiration rate, weight and oral temperature). The neurological examination can be conducted ± 1 day of the scheduled protocol visit. Complete TCNS in the course of the neurological examination, as well as NTSS-6 (with input from the caregiver) to ensure the subject did not develop new signs or symptoms of neuropathy.
5. Record AEs. AESIs (worsening of NFM [calculated as the average of the Screening visit and Baseline visit data] or prolongation of QTc) must be treated as SAEs and notified to ICON PV within 24 hours (see Section 12.1.1). ICON PV or ICON MM will then contact the study site to define follow-up activities and to assess whether the subject must be withdrawn from study.

9.5 Withdrawal of Subjects

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioural, or administrative reasons. The decision to withdraw consent and discontinue participation in the study will not prejudice the subject's future medical treatment in any way. If a subject

does not return for a scheduled visit, every effort will be made to contact the subject. In any circumstance, every effort will be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, and request the subject to return for the EOT (Week 12) visit, if applicable, and follow-up with the subject regarding any unresolved AEs (for details see Section 12.1.1.1). The investigator or sub-investigator will be responsible for reporting subject withdrawal to Actinogen Medical/ICON. Subjects withdrawn from the study cannot be re-enrolled at a later time, regardless of the reason for withdrawal.

If a subject consents to undertake additional and optional study procedures/assessments but withdraws consent for doing so at a later visit, he/she will be retained in the study for the routine study procedures/assessments. If a subject withdraws from the study, and also withdraws consent for disclosure of future information, no additional data should be collected. Actinogen Medical/ICON may retain and continue to use any data collected before such withdrawal of consent.

Subjects shall be withdrawn during the course of the study when subject well-being is at risk, including but not limited to:

- Subject needs to take a prohibited medication. In case medication from the list of drugs potentially prolonging QTc (Appendix III) is introduced, the most appropriate approach will be discussed upfront with the ICON MM since the subject may not need to be withdrawn in all cases, e.g. in situations where the new drug is only provided temporarily, or in low doses, or in situations where baseline QTc was in the lower range of normal.
- ECG indicates a QTc level above a threshold of 480 msec at the Interim (Week 4 and Week 8) visits or an increase in QTc from Baseline > 60 msec (for details see Section 12.3). In this case, it should be reported as an AESI, within 24 hours.
- Subject develops signs or symptoms of peripheral neuropathy in any two tests of NFM, confirmed by the DSMB Nerve Function Monitoring sub-committee.
- The subject is unable to tolerate their prescribed study drug per protocol.
- Subject has evidence of drug-induced liver injury or any other drug-induced injury (such as thrombocytopenia), detected in ongoing safety monitoring of laboratory results.
- Subject is confirmed to be pregnant.

9.6 Early Termination

This study may be terminated prematurely at any time by Actinogen Medical for medical, operational or ethical reasons at individual or all study sites.

If the study is prematurely terminated or discontinued, Actinogen Medical/ICON will promptly notify the investigator, institutions and all competent regulatory authorities in writing outlining the reasons for the termination. The investigator or Actinogen Medical/ICON will promptly inform the Independent Ethics Committee/Independent Regulatory Board (IEC/IRB). After notification, the investigator must contact all

participating subjects and the hospital pharmacies (if applicable) within a reasonable time period and inform them of the premature termination/discontinuation of the study.

As directed by Actinogen Medical/ICON, all study materials, except documents needed for archiving requirements, will be collected and all eCRFs completed to the greatest extent possible. The study monitor will ensure that any outstanding data clarification issues and queries are resolved, and that all study records at the study site are complete.

10 TREATMENT OF SUBJECTS

10.1 Identity of Study Treatments

10.1.1 Administration of Study Treatments

One capsule of Xanamem™, or the matching placebo, will be 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.

Subjects will attend the study site, in a fasted state, for a Baseline (Week 0) visit, Interim visits (Week 4 and Week 8) and EOT (Week 12) visit. Subjects should aim to take study drug at the same time each morning with food (30 minutes after the start of a standard meal) at the study site, and after all pre-dose blood samples have been taken.

Xanamem™ is formulated in green and cream-coloured size 3, Coni-Snap shaped gelatin capsules as an excipient blend at a dose of 10 mg (see Table 2). The dose of Xanamen™ will be 10 mg administered orally, QD.

Table 2 Ingredients of Xanamem™ and Matching Placebo Capsules, Using a Representative Dose of 10 mg (% w/w)

Component	Function	Placebo	10 mg
UE2343	Active pharmaceutical ingredient	0	5.26
Lactose	Diluent	95.0	89.74
Croscarmellose sodium	Disintegrant	4.0	4.00
Talc	Glidant	0.5	0.05
Magnesium stearate	Lubricant	0.5	0.05

Note: The formulations shown are based on % w/w with a nominal capsule fill weight of 190 mg.

10.2 Study Treatment Packaging and Labelling

10.2.1 Packaging

Xanamem™ will be provided in 35 mL high-density polyethylene bottles with child-resistant closure push down lids and an induction seal. Each bottle will contain 32 capsules and subjects will receive three bottles each (one bottle dispensed at the Baseline [Week 0] visit and one bottle dispensed at each of the Interim [Week 4 and Week 8] visits).

The drug product and matching placebo will be manufactured by Pharmaceutical Packaging Professionals Pty Ltd. All supplies will be provided in consistent packaging with consistent labelling to maintain the study blind. Further information relating to the study drug is available to the investigator(s) in the Investigator Brochure[20].

10.2.2 Labelling

Xanamem™ and placebo capsules will be packaged and labelled according to current ICH Good Manufacturing Practice and GCP guidelines and national legal requirements.

10.2.3 Shipment and Storage

The study drug will be supplied to study sites (initial and re-supply) by external providers on behalf of Actinogen Medical. The IWRS supports the study drug supply process. The recipient at the study site must check the study drug for completeness, correct bottle numbers, any loss or damage and confirm receipt. The study drug will be stored between 15 and 25ºC (59 to 77ºF), separately from normal hospital or practice inventories, in a locked facility with access limited to the investigator and authorised personnel. The investigator must ensure that the study drug is dispensed only to subjects enrolled in the study according to this study protocol.

Current stability data supports storage of the Xanamem™ and placebo capsules between 15 and 25ºC (59 to 77ºF). See drug label for further details.

10.2.4 Blinding and Randomisation of Study Treatment(s)

A double-blind design is employed so that both the investigators and the subjects will be unaware of the treatment assignment during the whole study.

After written informed consent is obtained from an eligible subject, a **6-digit subject number** will be assigned to this subject. The first digit will denote the country, followed by the study site number and a subject sequence number. This number will be created and allocated by the IWRS, when the subject first enters the system at Screening. The first subject screened at a study site will be assigned the number 001; the second will be assigned the number 002, and so on. For example, Subject 204001 will be the first subject screened at study Site 04 in Country 2. Subjects will be identified during the whole study only by their assigned subject number.

The randomisation codes will be computer-generated by ICON Biostatistics, and kept by a statistician independent from the project team. A copy will be provided to whomever performs the PK and PD assessments, when the PK and PD data are analysed, as well as to the DSMB. Randomisation codes will be generated in blocks stratified by site to ensure approximate balance between dose schemes (1:1) and balanced per site. Randomisation codes will be assigned sequentially as subjects become eligible for randomisation.

Subjects who are eligible for randomisation will be assigned a unique **3-digit randomisation number** at the Baseline (Week 0) visit by IWRS. This randomisation number identifies which treatment will be allocated to the subject. Subjects who withdraw after randomisation are not to be replaced and their randomisation number will not be re-used.

To ensure blinding, the study drug (Xanamem™ capsules) and the matching placebo have the same shape and size. Subjects will receive one capsule of Xanamem™ or one capsule of matching placebo capsule QD during the double-blind treatment period. 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.

The **4-digit bottle number** will identify study drug packs and will be detailed on the study drug label.

Dispensing of study drug will be coordinated by IWRS. The system will assign a bottle number corresponding to the randomisation arm.

10.3 Procedure for Breaking the Randomisation Code

The study site investigator and appropriate ICON project team members will be authorised to access the Emergency Unblinding functionality within the IWRS. The system will require the user to enter an authorisation key number to complete the emergency unblinding transaction. The exact description of the treatment assigned to the individual subject then will be accessible. Emergency unblinding can thus be made for any subject without affecting the double-blind nature of the study. Subject treatment information may only be accessed in the event of an emergency and out of necessity to know the identity of the allocated study drug in order to institute appropriate therapeutic management.

Should a situation arise where unblinding is urgently required (i.e. knowledge of treatment code is required to adequately manage a life-threatening situation), the investigator at that study site may perform immediate unblinding through IWRS. If time allows, the investigator may contact the ICON MM prior to unblinding the individual subject to discuss the rationale for emergency unblinding.

In the event that emergency unblinding is performed, the investigator can view and must print the blinded confirmation document from IWRS. The investigator must record on the confirmation document printout the reason for the emergency unblinding, and sign the document. The confirmation document must then to be kept in a safe place until the end of the study. Once a randomisation code has been broken for a subject, he/she must be withdrawn from the study. The investigator must inform the ICON MM (STUDY-MA-DL-3580-0001@iconplc.com) in writing within 24 hours.

10.4 Subject Compliance

After dispensing study drug (Xanamem™ or placebo) to subjects at Baseline (Week 0), investigators will follow up with subjects on their compliance to study drug. This first dose of study drug must be taken in the presence of the investigator/study site staff, to enable compliance and ensure the subject is capable to open the drug container and make an entry in the Drug Intake Diary.

Study drug accountability will be performed and documented by study site staff at the Interim visits (Week 4 and Week 8) and EOT (Week 12) visit. Subject compliance to treatment will be calculated as follows:

Treatment Compliance = (Number of study drug taken –number of study drug that should have been taken).

Any non-compliance will be documented, and explained in the source documents and the eCRF.

An 80% treatment compliance will still be acceptable as per protocol.

10.5 Study Treatment Accountability

Records will be maintained supporting the delivery of study drug(s) to the study sites, the inventory at the study sites, the use by each subject and the return to the study drug vendor or local on-site destruction.

These records will include dates, quantities, batch numbers, expiry dates and the unique code numbers assigned to the study drug and to the study subjects.

The investigator will be responsible for ensuring that the records adequately document that the subjects were provided the doses specified in the protocol and that all study drug received from the study drug vendor is reconciled. All study drug accountability records for study drug must be readily available for inspection by the study monitor and/or auditor, and open to regulatory inspection at any time.

10.6 Study Treatment Destruction

Any unused or partially used study drug or empty containers must not be destroyed until the study drug accountability documentation has been checked and specific permission for destruction has been given by the ICON study monitor. Any destruction of study drug must be documented and filed. Drug destruction may be performed on site, however, this must be discussed with the ICON study monitor before proceeding.

10.7 Concomitant Medications and Therapy

Medications that are considered necessary for the subject's safety and well-being may be given during the course of the study at the discretion of the investigator and must be recorded in the appropriate sections of the eCRF.

All medications taken by a subject within 1 month prior to Screening are regarded as **prior medication** and must be documented as such in the eCRF.

All medications still being taken by a subject at randomisation and which continue to be taken during the study are regarded as **concomitant medication** and must be documented as such in the eCRF.

10.8 Prohibited Medications

Details of prohibited medications are as follows (see Appendix III for a list of potential prohibited medications, including the brand names [please note this list is not exhaustive and serves as a guide to prohibited medications with brand names included and must be used in conjunction with the details of prohibited medications detailed below]):

- Initiating AChEIs or memantine during the study will not be permitted.
- Changes in medication or doses of psychotropics (or other medication that may have an impact on cognition such as anticholinergic medication) within 4 weeks prior to Screening and/or throughout the course of the study are not permitted.
- Regular intake of benzodiazepines may cause cognitive decline[24]. Use of sedative drugs (specifically benzodiazepines, barbiturates and other anxiolytics) more than twice in a week or three times in a month in the past 6 months prior to Screening, or positive at

Screening will result in a subject being excluded from the study. The subject will be asked by site staff about their use of benzodiazepines. If the subject responds with "No use", but subsequent benzodiazepine screening is positive, the subject will be excluded. If the subject responds with "Regularly", the subject will be excluded. If the subject responds with "Only rarely" (i.e. maximum of twice a week), the site staff should enquire when the last dose of benzodiazepines had been taken. One urine benzodiazepine screening re-test will be allowed in cases where the subject's intake of benzodiazepine is within the allowed dose and re-test is performed within 7 days of last benzodiazepine dose and prior to the Baseline visit. Positive re-test for urine benzodiazepines is exclusionary. If the re-test result is negative, the subject can remain in the study.

- Marked adrenal suppression occurs with high doses of inhaled corticosteroid above 1.5 mg/day (0.75 mg/day for fluticasone propionate)[25]. Thus, inhaled glucocorticosteroids (e.g. prednisone equivalent) > 1 g per day, and any oral steroid preparations, are prohibited within 2 weeks prior to Baseline (Week 0) and/or throughout the course of the study.
- Several studies have shown the potential for hypothalamic-pituitary-adrenal axis suppression from potent topical corticosteroids[26]. Thus, topical glucocorticosteroids > 50 g per week are prohibited during the study and within 2 weeks prior to Baseline (Week 0) and/or throughout the course of the study.
- Due to Xanamem™ being mainly metabolised by cytochrome P450 3A4 (CYP3A4), the following drugs which inhibit this isoenzyme must not be administered within 2 weeks prior to Baseline (Week 0) and/or throughout the course of the study: boceprevir, clarithromycin, erythromycine, indinavir, itraconazole, ketoconazole, nelfinavir, posaconazol, ritonavir, voriconazole, nefazodone.
- The following drugs strongly inducing CYP3A4 are prohibited within 2 weeks prior to Baseline (Week 0) and/or throughout the course of the study: carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, St Johns Wort.
- Drugs known to prolong the QTc interval (including quinidine and nuedexta) may be provided with caution after the Screening visit. In case such medication is introduced, the most appropriate approach will be discussed upfront with the ICON MM since the subject may not need to be withdrawn in all cases, e.g. in situations where the new drug is only provided temporarily, or in low doses, or in situations where baseline QTc was in the lower range of normal.
- Vitamin B12 and Omega 3 (including specifically Souvenaid) are allowed if at stable doses for 3 months prior to Baseline.
- Drugs that are known to cause peripheral neuropathy are not permitted within 6 months prior to Screening and/or throughout the course of the study. Known drugs included:
    - Arsenic, colchicine and gold
    - Cardiovascular drugs: amiodarone, hydralazine, perhexiline

- Anti-cancer drugs: cisplatin, docetaxel, paclitaxel, suramin, vincristine
- Anti-infectives: chloroquine, isoniazid, metronidazole, nitrofurantoin, thalidomide
- Autoimmune disease drugs: etanercept, infliximab, leflunomide
- Dermatologicals: dapsone
- Anti-convulsants: phenytoin
- Anti-alcohol drugs: disulfiram
- Anti-human immunodeficiency virus (HIV) drugs: didanosine, stavudine, zalcitabine

11 ASSESSMENT OF EFFICACY

11.1 Efficacy Variables

Efficacy variables include the following:

- ADAS-Cog v14
- RAVLT
- CDR-SOB
- MMSE
- NPI
- NTB – Executive Domain (COWAT and CFT)

11.1.1 Efficacy Assessments

Examples of all the scales used in this study and the NIA and AA criteria, together with instructions on how to use these scales are provided in the "XanADu Scale Binder" which includes the scale and scoring instructions. A short description of these scales and the rationale as to why these were selected are provided in the following sections.

11.1.1.1 Alzheimer's Disease COMposite Score (ADCOMs)

The FDA published draft guidance on developing drugs for early stage AD in 2013, called for outcome measures that assess both cognitive and functional domains that are clinically meaningful to individuals and caregivers[5]. The pre-dementia Clinical Outcome Assessments (pCOA) Team, in alliance with the Clinical Outcomes Working Group in Alzheimer's Disease Neuroimaging Initiative Private Partners Scientific Board, has worked over the past few years to harmonise industry efforts to develop composite outcome measures that would provide more sensitive clinical measures in the earlier, mild cognitive impairment, stages of the disease. After consideration of the various composites in development, the team selected the ADCOMs as the prototype clinical composite outcome assessment tool to be advanced through the regulatory qualification process. ADCOMs consists of a weighted combination of items from commonly used outcome scales; ADAS-Cog v14, MMSE and CDR-SOB have been identified through an unbiased statistical approach to be most sensitive in individuals with amnestic mild cognitive impairment and prodromal AD. In 2013, the Coalition Against Major Diseases submitted formal letters of intent to both the FDA and European Medicines Agency. Both agencies accepted the pCOA project into their qualification procedures; however, both stressed the need to demonstrate the clinical meaningfulness of the composite[21].

11.1.1.2 Rey Auditory Verbal Learning Test (RAVLT)

Originally developed in the 1940s, the RAVLT has evolved over the years, and several variations of the test have emerged. The standard RAVLT format starts with a list of 15 words, which an examiner reads aloud at the rate of one per second. The participant's task is to repeat all the words he or she can remember, in any order. This procedure is carried out

a total of five times which can be used for the evaluation of incremental practice effects. The examiner then presents a second list of 15 words, allowing the participant only one attempt at recall. Immediately following this, the participant is asked to remember as many words as possible from the first list. The RAVLT has proven useful in evaluating various functions of verbal learning and memory, including proactive and retroactive inhibition, retention, encoding versus retrieval, and the subjective organisation of learning material. Since the test is brief, straightforward, easy to understand, and appropriate for both children and adults (ages 7 through 89), it has gained widespread acceptance[27]. The enumerated functions represent various processes of auditory learning and (explicit) episodic (long-term) memory which are known to be associated with hippocampal functions and represent a core area of changes in early stages of AD.

11.1.1.3 Alzheimer's Disease Assessment Scale - Cognitive Behaviour Section (ADAS-Cog v14)

The ADAS-Cog was developed in the early 1980s in response to the then-perceived lack of appropriate instruments available to test the efficacy of AD drug treatments. It aims to assess the "severity of dysfunction and research in subjects with AD"[28]. Since its inception, the ADAS-Cog has been used in over 127 AD clinical studies and, although developed specifically for AD, it has frequently been used in non-AD populations, including mild cognitive impairment[29]. The original ADAS-Cog measures cognitive performance by combining ratings of 11 components (Word Recall, Word Recognition, Constructional Praxis, Orientation, Naming Objects and Fingers, Commands, Ideational Praxis, Remembering Test Instruction, Spoken Language, Word Finding, Comprehension) representing six broad areas of cognition: memory, language, ability to orientate oneself to time, place and person, construction of simple designs, and planning and performing simple behaviours in pursuit of a basic, predefined goal. The ADAS-Cog with 11 items is scored from 0 to 70. The ADAS-Cog v14 was designed to assess cognitive impairment in individuals with early AD. A version of the digit cancellation task was reliable and sensitive to a broad range of dementia severity. Performance on the word learning task with delayed recall and a subset of the mazes task were impaired even in mild AD. As such, these tasks were felt to be useful in studies involving mild or at-risk subjects, as they provide a useful addition to the 11-item version of the ADAS[30]. Three items (delayed word recall, attention/visual search task, and maze solution) have been added to the ADAS-Cog v11 to assess the participant's attention and concentration.

This 14-item instrument will be referred to as the ADAS-Cog v14. Total scores of ADAS-Cog 14 range from 0 to 90, with higher scores indicating greater disease severity.

11.1.1.4 Clinical Dementia Rating Scale - Sum of Boxes (CDR-SOB) and Global (CDR Global)

The Washington University CDR is a global assessment instrument that yields global and SOB scores, with the global score regularly used in clinical and research settings to stage dementia severity[31]. The CDR-SOB score has been considered a more detailed quantitative general index than the global score and provides more information than the global CDR score

in participants with mild dementia[32]. CDR Global results are relevant for subject eligibility and thus will also be performed at the Screening visit.

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 global CDR score is computed via an algorithm[33]. CDR Global score is calculated using the Washington University online algorithm[34].

The CDR-SOB is based on summing each of the domain box scores, with scores ranging from 0-18.

11.1.1.5 Mini-Mental Status Examination (MMSE)

The MMSE is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment[35] and is commonly used in medicine and allied health to screen for dementia. It is also used to estimate the severity and progression of cognitive impairment and to follow the course of cognitive changes in an individual over time; thus making it an effective way to document a participant's response to treatment. For this study, MMSE results are relevant for subject eligibility and thus will also be performed at the Screening visit.

11.1.1.6 Neuropsychiatric Inventory (NPI)

The NPI was constructed to survey neuropsychiatric disorders in demented patients[36]. Compared to many older scales, the NPI comprises a wide range of neuropsychiatric symptoms. Furthermore, the NPI uses screening and in-depth questions, which simulates a clinical interview, allowing it to be conducted relatively quickly and easily. An additional advantage of this instrument is that the same interview can optionally register emotional stress of caregivers[37]. The purpose of the interview and questionnaire are explained, one screening question per behaviour domain is asked, after which approximately seven in-depth questions are then possible. For each domain, the relatives assess the frequency of the behaviour (4-point scale), the severity of the symptom (3-point scale) and the emotional stress for the caregiver (6-point scale). The NPI total score is calculated by multiplying the frequency and severity rates per domain (maximum score per domain is 12) and then calculating the total of all domains (total NPI-score minimum is 0 and maximum 144). During this study, NPI will only be assessed at the Baseline (Week 0) and EOT visits (Week 12) to minimise burden for rater and subject and thus allowing more focus on primary parameters.

11.1.1.7 Neuropsychological Test Battery (NTB) - Executive Domain (COWAT and CFT)

The NTB is composed of a group of established cognitive performance tests that were chosen from existing, well known cognitive test batteries (e.g. Wechsler Memory Test) and known for their good reliability and sensitivity in early AD. The NTB measures various distinct

features of (episodic) memory and executive functions[38]. Since memory performance, especially features of episodic (long-term) memory, will already be assessed by other above-mentioned cognitive scales, only the NTB tests which are known measures of executive function features were selected for the current study. These include word association, category fluency tasks and digit span tasks; a combined cognitive (specifically executive function) performance score will be calculated through z-transformations of the raw scores obtained in the individual tests. The psychometric properties of the NTB suggest it to be particularly suitable for the evaluation of drug effects in participants with a mild severity of AD. During this study, NTB – Executive Domain will only be assessed at the Baseline (Week 0) and EOT visits (Week 12) to minimise burden for rater and subject and thus allowing more focus on primary parameters.

12 ASSESSMENT OF SAFETY

Safety variables include the following:

- Change in clinical safety laboratory values from Baseline (Week 0) to EOT (Week 12) (for details see Section 12.2)
- Incidence of AEs (for details see Section 12.1.1.1)
- ECG (for details see Section 12.3)
- NTSS-6 (for details see Section 12.8)
- Neurological examination: This will cover all aspects of the TCNS (for details see Section 12.5)
- NFM: This includes the abovementioned scales (NTSS-6 and TCNS), as well as neurography (nerve conduction velocity and amplitude) of peripheral sensory and motor nerves. The NFM should follow existing local standards and procedures and should be run in a consistent fashion. The test must be undertaken and reviewed by suitably qualified and experienced personnel. For details see Section 12.7.
- CSSRS (for details see Section 12.9)
- Physical examination (for details see Section 12.4)
- Vital signs (for details see Section 12.6)

Ad hoc telephone contact may occur at any time-point throughout the study, if deemed necessary by the investigator/study nurse, or if the subject wishes to report an AE. The timing and frequency of safety assessments are described in Section 9.4 and Section 9.4.1.

12.1 Adverse Events

12.1.1 Definitions

The definitions for AEs and SAEs are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The principal investigator is responsible for ensuring this.

Adverse Event

An AE is defined as any untoward medical occurrence in a subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not related to the IMP.

Adverse Event of Special Interest

An AESI is an AE of scientific and medical concern specific to the sponsor's product for which ongoing monitoring and rapid communication by the investigator to ICON could be appropriate. Such an event might require further investigation in order to characterize and understand it. These include worsening of NFM qualifying as a potential safety signal (see

Section 12.7), and prolongation of QTc above the threshold of 480 msec or a change from Baseline > 60 msec. An AESI will be reported similar to an SAE (see below). ICON PV or ICON MM will contact the study site reporting the AESI to discuss the required additional examinations of the affected subject.

Serious Adverse Event

An SAE is defined as, but is not limited to, one that:

- Results in death
- Is life-threatening
- Requires subject hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event*

*Important medical events that may not result in death, be life-threatening or require hospitalisation may be considered a serious adverse drug experience, when based on appropriate medical judgement. They may jeopardise the subject or the subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition. This also includes AESIs.

Where an SAE is reported, a PK sample should be collected, noting both the time at which the last dose of study drug was administered and the time at which the PK sample was collected (see Section 9.4.1.8).

12.1.1.1 Recording of Adverse Events

For the purposes of this study, any detrimental change in the subject's condition, after signing the informed consent form (ICF) and up to completion of the 4-week follow-up period after the last administration of study drug, should be considered an AE. At each study visit the investigator (or delegate) will determine whether any AEs have occurred. If known, the medical diagnosis of an AE should be recorded in preference to the listing of signs and symptoms. All AEs are to be recorded on the "adverse event" pages in the subjects' eCRF.

AEs and SAEs will be recorded from signing informed consent and at each study visit up to the end of the follow-up period at 4 weeks post last dose of study drug.

If, at any time after the Follow-up (4 weeks post last dose of study drug) visit, an investigator is made aware of an SAE that can be reasonably related to study drug, he/she should promptly notify Actinogen Medical/ICON.

The investigator will assess the intensity of AEs based on the following definitions:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 12.1.1.3.

An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

For an AE to be a suspected drug-related event, there should be at least a reasonable possibility of a causal relationship between the study drug and the AE.

12.1.1.2 Monitoring of Adverse Events

All ongoing AEs should be followed up for 30 days after the last administration of study drug, with the exception of any ongoing study drug-related AEs, which should be followed until resolution, unless in the investigator's opinion, the AE is unlikely to resolve due to the subject's underlying disease. Any new SAEs occurring up to 60 days after the last administration of study drug should be reported to Actinogen Medical/ICON according to Section 12.1.1.3.

Abnormal Laboratory Values/Vital Signs/Electrocardiograms

Laboratory/vital signs/ECG abnormalities should be reported as AEs if any one of the following criteria are met:

- Any criterion for an SAE is fulfilled
- The laboratory/vital signs/ECG abnormality causes the subject to discontinue from the study treatment
- The laboratory/vital signs/ECG abnormality causes the subject to interrupt the study treatment
- The laboratory/vital signs/ECG abnormality causes the subject to modify the dose of study treatment
- The investigator believes that the abnormality should be reported as an AE, especially when the investigator requested a confirmatory test which confirmed the initial value
- If laboratory/vital signs/ECG abnormality is associated with clinical signs and symptoms, the sign or symptom should be reported as an AE and the associated laboratory result or vital sign or ECG reading should be considered additional information that must be collected on the relevant eCRF

Deaths

Should a death occur within the study period or within 60 days after the last administration of study drug, both an AE form and an SAE form should be completed, detailing the AE that resulted in the death (note that death is an outcome, not an event). The SAE must be reported as detailed in Section 12.1.1.3. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

Overdose

There is no antidote available for Xanamem™. Any overdose needs to be managed according to standard of care and reported as an AE.

Pregnancy

In the very unlikely event that pregnancy occurs, the following should be noted: pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even after the subject has been withdrawn from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to Actinogen Medical/ICON on a pregnancy outcomes report form.

12.1.1.3 Reporting of Serious Adverse Events

Investigators and other study site personnel must inform the appropriate ICON representatives of any SAEs and AESIs that occur (whether or not attributable to the study drug) in the course of the study, within 24 hours of when he/she becomes aware of it.

When an SAE or AESI is discovered by the site or is identified by an ICON clinical research associate during site visits, SAEs or AESI will be entered by the site members into the eCRF, which contains specific questions for events regarded as serious. ICON PV will receive the alert through automated e-mail notification.

In case of technical problems in transmitting the SAE through the eCRF within the 24-hour timeline, the investigator/site representative shall complete the SAE form and fax or e-mail to:

For Australia:

Fax No.: +6565657939

Tel No.: +6568960378 (business hours)

+6565339503 (out of hours)

E-mail: icon-safety-centralreceipt@iconplc.com

For the UK:

Fax No.: +44 (0)208 100 5005

Tel No.: +44 (0)1628 496 300

E-mail: icon-safety-centralreceipt@iconplc.com

For the USA:

Fax No.: +1 215 616 3096

Tel No.: +1 888 723 9952

E-mail: icon-mads@iconplc.com

If the site staff calls ICON PV to report an SAE, the caller will be prompted to provide the following information, as available:

- Study name, sponsor name, protocol number
- Reporter's name, investigator's name and telephone number
- Site number, subject's study number and subject's initials
- SAE term, start and stop dates of the event
- Relationship to each IMP, action taken in regard to IMP, and subject outcome

The ICON representative will work with the investigator to compile all the necessary information and ensure that the appropriate sponsor representative receives a report within 1 day (24 hours) for all fatal and life-threatening cases and within 5 days for all other SAEs and AESIs.

Follow-up information on SAEs and AESIs must also be reported by the investigator by entering this updated information into the eCRF within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to ICON within 24 hours as described above. The following variables will be recorded for each AE: verbatim/AE description, time and date for AE start and stop, maximum intensity, seriousness, causality rating, whether or not the AE caused the subject to discontinue, and the outcome.

All SAEs and AESIs must be reported, whether or not considered causally related to the study drug or to the study procedure(s). All SAEs and AESIs will be recorded in the eCRF. Prompt notification of SAEs to ICON PV, as described above, is essential so that regulatory requirements and ethical obligations to the subjects involved in the study can be met. The investigator is responsible for informing the Ethics Committee of the SAE as per local requirements.

12.2 Laboratory Assessments

Information on the volume of blood to be sampled during the study for assessing laboratory parameters will be available in the laboratory manual. All blood samples will be collected, prepared and transferred according to the instructions provided by the central laboratory. The central laboratory will provide the study sites with the appropriate material prior to the study start.

Blood and urine samples will be collected for protocol clinical laboratory evaluations according to Table 1. The laboratory evaluations performed during the study are presented in Appendix II.

Additional laboratory safety evaluations will be performed at other times, if judged to be clinically appropriate, or if the ongoing review of the data suggests a more detailed assessment of laboratory safety evaluations is required. Any changes to the scheduled times of laboratory safety tests will be agreed with ICON/Actinogen Medical and documented. The investigator will perform a clinical assessment of all laboratory safety data.

Further details of the required activities and schedule for laboratory assessments can be found in the separate study specific laboratory manuals (or equivalent).

12.3 Electrocardiogram Assessments

Local equipment will be used. Subjects must be resting quietly in a supine position or in the most recumbent position possible for at least 5 minutes before the ECG is obtained. Where available, an auto-created assessment report should be printed and added to the source documents, otherwise, a manual assessment of the ECG must be documented. The following ECG parameters will be recorded: heart rate, RR, PR, QRS, and QT (uncorrected) and QTc (corrected) intervals. QTc will be calculated based on locally available algorithms. QTc will be calculated using the Fridericia correction. Bazett's correction overcorrects at elevated heart rates and under corrects at heart rates below 60 bpm. Fridericia's correction is more accurate than Bazett's correction in subjects with such altered heart rates. If the study site has no access to the Fridericia correction, the raw data will be shared with the ICON MM (STUDY-MA-DL-3580-0001@iconplc.com) and Data Management to calculate QTc accordingly. The investigator or designee is responsible for reviewing the ECGs to assess whether they are normal or abnormal. ECG assessment will include physician interpretation of the tracings, e.g. rhythm, presence of arrhythmia or conduction defects, morphology, any evidence of myocardial infarction, or ST segment, T-wave, and U-wave abnormalities, and over-reading of any incorrect machine interpretations. Abnormal ECGs will be assessed for clinical significance. A single repeat evaluation will be allowed if the investigator or designee has reason to believe the reading is faulty or to help assess the clinical significance of an abnormality. Any other ECG abnormality that is seen as exclusionary will first be discussed with the ICON MM (e.g. a marked prolongation of QT/QTc interval after repeated demonstration of a QTc interval > 450 ms, history of additional risk factors for Torsade Des Pointes, use of concomitant medications that prolong the QT/QTc interval).

For any ECG that the investigator considers clinically significant, the investigator will:

- Repeat the ECG
- Perform follow-up ECG(s) if any significant abnormalities are detected to document resolution and as clinically indicated
- Record as an AE any ECG that (1) is confirmed and the investigator considers clinically significant, or (2) requires a subject to be discontinued from the study, or (3) requires a subject to receive treatment.

12.4 Physical Examination

A standard physical examination is sufficient, assessing all core body functions.

12.5 Neurological Examination, Including Toronto Clinical Neuropathy Score

A basic, manual neurological examination will include all items of TCNS:

- Muscle strength/weakness in arms and legs
- Ataxia (gait, stance and finger-nose coordination)

- Light touch (upper and lower extremity)
- Pinprick (upper and lower extremity)
- Position sense (toes and thumbs)
- Reflexes (knee and ankle)

The thresholds for "Normal=0" for all Sensory Test Scores are set as follows: Subject can discriminate any of these qualities (pinprick, temperature, light touch, vibration, position sense) at least at the secondary (more proximal) region to test that quality (see**Error! Reference source not found.** Table 3 for primary and secondary skin-areas).

Table 3 Primary and Secondary Skin Area to Test the Sensory Quality

Sensory quality	Distal (primary) area	Proximal (secondary) area
1. Pinprick	Plantar area of foot	Ankle
2. Temperature	Plantar area of foot	None
3. Light touch	Plantar area of foot	Ankle
4. Vibration	Medial malleolus	Patella
5. Position	Big toe	Thumb

12.6 Vital Signs

The following vital signs will be recorded during this study (this must include but not be limited to the measurement of orthostatic changes in heart rate and blood pressure):

- Heart rate (beats per minute [bpm])
- Blood pressure (supine, according to Riva-Rocci's method, plus orthostatic change in blood pressure; pathologic orthostatic changes are defined as: Decrease of ≥ 15 mmHg diastolic last supine to first standing or decrease ≥ 20 mmHg systolic last supine to first standing or increase of pulse ≥ 20 bpm)
- Body temperature (Celsius or Fahrenheit)
- Height (Baseline only; feet or cm)
- Weight (pounds or kg)

12.7 Nerve Function Monitoring

NFM consists of sensory testing (vibration and thermal perception), motor and sensory nerve neurography (amplitude and conduction velocity) and clinician-rated outcome in TCNS. Subject-related outcome measure, NTSS-6, is part of NFM, and is discussed in Section 12.8. The aim is to detect intra-subject worsening from before treatment as an indicator for neurotoxicity. Subject total "Before Treatment" status is calculated as the average of the Screening visit and Baseline visit data. The tests will follow existing local standards and procedures, but should be run in a consistent fashion within a given site and subject to minimise intra-subject variability, e.g. constant skin temperature of the feet of at least

32ºC/90ºF, same assessor, same procedures, same chronological order of assessments, same time of day. Measurements will be taken twice for each assessed nerve in both the left and right extremity. The NFM can be conducted ± 3 days of the scheduled protocol visit, except at the Baseline visit, where it must be conducted within 3 days prior to the randomisation step.

The following tests will be performed:

- Vibration detection threshold: Note that vibration is also part of the TCNS. This test will be performed with a Rydel–Seiffer graded tuning fork (64 Hz, 8/8 scale) that is placed over a bony prominence (medial malleolus) of each foot and left there until the subject can no longer feel any vibration. Threshold will be determined as a disappearance threshold with two stimuli repetitions of each foot.

  Subjects with the ability to define a threshold within two assessments (even if at 1/8) will be graded "Normal=0" in TCNS. If the subject cannot discriminate such a threshold at the medial malleolus (most distal point to measure), the same exercise will be repeated with the tuning fork placed over the patella.

- Thermal (cold and warm) detection (qualitative) at both legs, at the lateral mid-dorsum of the feet; using the Minnesota Thermal Discs with Copper (C; felt as colder) and polyvinyl (P; felt as warmer than copper) at room termperature. Sites open to enrolment under this amendment that do not have access to Minnesota Thermal Discs, will continue to conduct thermal detection via cold and warm vials, as per the following: Thermal (cold and warm) detection (qualitative) at both legs, using one vial filled with ice water and one filled with warm water. This assessment will also be included in the scoring of TCNS. The subject will be asked (with eyes closed) whether it feels warm or cold when one of these vials is touching his/her feet. The number of correct answers out of 10 attempts (five with warm and five with cold in a random order) will define the threshold. Where subjects have less than five correct answers, the same test will be repeated in an area in the middle of the lower leg, up to the knee. If the subject can detect at least 6/10 correctly, the subject will be scored "0" (normal) in TCNS.

  This assessment will also be included in the scoring of TCNS. Each disc is placed in random order for about 2 seconds over the lateral dorsum of each foot. The subject will be asked (with eyes closed) whether a disc feels warmer or colder (realtive to each other). The two discs will be positioned in random order (C then P; or P then C) 10 times at each foot. After testing the first foot, the same procedure will be performed on the other side.

  1. If 9 or 10 pair tests at each side are identified correctly: the subject is eligible.
  2. If 8 or less pairs are correctly named as "warmer" or "colder" at any foot: exclude the subject.

  If the subject can detect at least 9 of /10 pairs correctly, the subject will be scored "0" (normal) in TCNS.

- Nerve conduction: Local equipment, procedures and normal values will be used. The measures will be obtained twice for each assessed nerve. For the second measure, all

electrodes need to be placed again. Preferably, surface electrodes will be used. It is recommended to measure in the following order: Sural No 1 – Peroneal No 1 – Sural No 2 – Peroneal No 2, to ensure independent measures.

- Sensory - Sural nerve: In case the Sural nerve is not measurable for SNAP, the Ulnar nerve or Median nerve will be used for sensory neurography as "back-up" nerves. SNAP amplitude will be assessed Baseline-to-peak. The number of repetitions will be according to local standards. NCV will be calculated according to local standards.
- Motor - Peroneal nerve: Only if the Peroneal nerve is not measurable for CMAP, the Tibial nerve motor component will be used as back-up. CMAP amplitude will be measured peak-to-peak. The number of repetitions will be according to local standards. NCV will be calculated according to local standards.

The NFM should follow existing local standards and procedures and should be run in a consistent fashion. Please see Table 4 for a summary of the NFM assessments and personnel involved:

Table 4 NFM Requirements

Outcome	Test	Conducted by	Frequency	Protocol reference
Clinician-rated	Toronto Clinical Neuropathy Score (TCNS)	Certified neurologist or a physician who has received appropriate training from a neurologist	Every visit, except ad hoc or unscheduled safety visits, i.e. maximum 6 times	Section 12.5
Sensory testing	Vibration detection threshold			Section 12.7
	Thermal detection			
Neurography	Motor and sensory nerve (amplitude and conduction velocity)	Individual trained in these techniques, which may include (but is not limited to) a neurologist, neurophysiologist or neurophysiology assistant		
Subject-rated	Neuropathy Total Symptom Score-6 (NTSS-6)	Health care professional, e.g. study nurse, study coordinator	Every visit, including ad hoc and unscheduled safety visits, i.e. approximately 6 times	Sections 12.7 and 12.8

12.7.1 Reporting Abnormal Nerve Function Monitoring

If the investigator observes any worsening of NFM assessments compared to the subject's status prior to administration of study drug (subject total Before Treatment status is calculated as the average of the Screening visit and Baseline visit data), they will complete a checklist with a set of additional standard questions that may explain the observation, and inform the ICON MM (STUDY-MA-DL-3580-0001@iconplc.com). The subject will continue to receive study drug.

The ICON MM will review the data for this subject within 1 business day and decide whether the event fulfils the criteria of a potential nerve safety signal (i.e. at least two related NFM parameters affected AND no other plausible explanation available). If classified as a potential nerve safety signal, this will be escalated to the DSMB Nerve Function Monitoring sub-committee, as per communication flow and according to timelines detailed in the DSMB Charter. If the event does not fulfil the criteria, the site is informed and the case is closed.

One member of the DSMB Nerve Function Monitoring sub-committee will review the package (in an unblinded fashion) and conclude within two business days whether the finding is:

- a) Confirmed: If Confirmed, the ICON MM is informed and will initiate a stop of dosing of the subject. The case is also escalated to the full DSMB to decide whether the study can progress as planned.
- b) Not confirmed: If Not confirmed, the DSMB Nerve Function Monitoring sub-committee needs to instruct the site, in a blinded manner (via the ICON MM), what additional measures are needed, e.g. to repeat the neurography, include other nerves in the assessment, etc.
- c) Artefact/existing event: If classified as an artefact/existing event, the case is closed and the subject will continue in the study as planned.

12.8 Neuropathy Total Symptom Score-6

The six questions of NTSS-6 should be completed as part of the assessment of subjects' medical history, also asking for input from the caregiver to make sure no information is lost. Each item will also be graded for its frequency and intensity, adding up to a total score from "0" to "21.96" points. A total score of > 6 would exclude the subject from the study.

12.9 Columbia Suicide Severity Rating Scale

The CSSRS was initially designed to assess suicidal ideation and behaviour in clinical studies[39]. Psychometric analysis of data on adolescents indicated that a lifetime history of worst-point suicidal ideation including either suicidal intent or intent with a plan, predicts a future risk of an actual attempt that is four times as great as the risk associated with a history of current suicidal ideation including a desire to be dead or increased general ratings of depression. The CSSRS demonstrated good convergent and divergent validity with other multi-informant suicidal ideation and behaviour scales and had high sensitivity and specificity for suicidal behaviour classifications compared with another behaviour scale and an independent suicide evaluation board.

The CSSRS is frequently asked for or recommended by various international agencies such as the FDA or World Health Organisation. The CSSRS has been administered numerous times and has exhibited excellent feasibility – no mental health training is required to administer it.

13 PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENT

PK and PD assessments will include:

- **PK assessment.** PK results are blinded and will not be provided to the sites or the subjects.
  - Each participating subject will provide one blood sample between 3 to 5 hours post-dose at the Baseline (Week 0) visit and two blood samples (pre- and post-dose) at each of the Interim visits (Week 4 and Week 8) and one sample at the EOT (Week 12) visit. The first sample is a trough sample and will be taken on arrival at the study site, from subjects in a fasted state, before dosing. The second sample will be taken between 3 to 5 hours post-dose, around the time anticipated peak concentrations occur. The exact time of sampling, plus the exact time of study drug intake on that day and the previous day, and the time of food intake must be documented.
  - The study site shall remind participating study subjects to write down the exact time-point when study drug was taken each day, in the Drug Intake Diary, between all study visits up to the EOT (Week 12) visit.
  - Subjects who cannot provide a documented time-point for study drug intake for the 24 hours prior to the visit will not undergo PK sampling. They will be reminded to properly document the time of study drug intake for the next visit. Another attempt for PK sampling will then be made.
  - PK blood samples will be analysed for concentrations of Xanamem™ by a validated liquid chromatography–mass spectrometry method. Data collection and standard curve regression will be performed using Analyst® software from AB Sciex. Only active treatment samples will be analysed. It should be noted that the randomisation code will be provided to ICON Bioanalytical Laboratory to exclude placebo samples for PK analysis. In no case will this code list be made known to the study investigators or the monitors. Xanamem™ concentrations will not be disclosed to the study site due to the unblinding potential. After the database lock and unblinding of the study, the PK data will be delivered within ICON for PK analysis.
  - PK blood samples will be analysed for cortisol levels by the secondary clinical laboratory in a blinded fashion.
- **Optional PD assessment.** Samples for the determination of ACTH, DHEAS, androstenedione and testosterone will be taken from a sub-population of approximately 50 subjects enrolled into the main study, who also volunteer to take part in the PD sub-study, unless a higher number is defined as a result of the analysis of the data from those subjects, by the DSMB. Subjects who cannot provide a PK sample will not undergo PD sampling. Another attempt for PD sampling will be made at the next visit. The objective of this is to assess the impact of Xanamen™ on the hypothalamic-pituitary-adrenal axis. The sample must be taken pre-dose (as early as possible in the morning). For optimal results, the sample for androstenedione analysis

should be taken between 6 am and 10 am. PD results are blinded and will not be provided to the sites or the subjects; results will not be disclosed to study sites to avoid unintended subject treatment unblinding.

14 OTHER EXPLORATORY ASSESSMENTS

Other exploratory assessments will include:

- **Metabolic function** (lipids, blood pressure, glucose, HbA1c, body weight and BMI) analysis will be performed on all enrolled subjects.

The timing and frequency of this assessment is described in Section 9.4 and Section 9.4.1.

15 STATISTICAL EVALUATION

15.1 Sample Size and Power

The sample size calculation is based on ADAS-Cog v14 rather than ADCOMs as prior information on the treatment effect to be anticipated in the ADCOMs scale is very limited. The sample size at a one-sided type I error rate of 5% and a power of 80% for detecting a difference of 2 points in the change from Baseline between the treatment groups is 78 subjects per arm, if the standard deviation of the change from Baseline is 5 points. It is planned to include ADAS-Cog v14 into the confirmatory testing stream by the use of a hierarchical testing procedure, such that no adjustment of the type 1 error rate is necessary.

As a drop-out rate of approximately 10% is assumed, the number of subjects randomised should be increased to approximately 174 (87 per treatment group).

Regarding NFM, the sample size of 156 subjects (approximately 78 subjects per treatment group) is sufficient to ensure that any untoward effects with a true proportion of at least 3% are observed in at least one subject within a treatment group with a probability of approximately 90%. An untoward effect with a true proportion of 5% or higher will be detected with a probability of > 98% in a sample of 78 subjects.

The study is planned to enrol 7 to 10 subjects at each study site.

15.2 Statistical Methods

15.2.1 Statistical Analysis Sets

Safety Analysis Set

The safety analysis set will consist of all subjects who received at least one dose of study drug. Subjects will be analysed according to the treatment they actually received.

The safety analysis set will be the primary analysis set for safety analyses.

Full Analysis Set

The full analysis set (FAS) will consist of all subjects randomised who received at least one dose of study drug. Subjects will be analysed in the treatment group they were randomised to even if they received incorrect study drug. Where changes from Baseline are analysed, subjects will be included only if both a Baseline and at least one valid post-Baseline measurement are available.

The FAS will be the primary analysis set for efficacy analyses.

Per Protocol Analysis Set

The per protocol (PP) analysis set is a subset of the FAS, and will consist of all randomised subjects for whom no key protocol violation is documented (refer to the applicable ICON standard operating procedure [SOP]). The PP analysis set will provide supportive data for the efficacy analyses.

Allocation of subjects to the PP analysis set will be performed before unblinding of the study.

PK Set

The PK set will consist of all subjects in the safety population who have at least one post-dose PK assessment. PK analyses will be performed using the PK set.

PD Set

The PD set will consist of all subjects in the safety population who have at least one post-dose PD assessment. PD analyses will be performed using the PD set.

15.2.2 Efficacy and Safety Variables

15.2.2.1 Primary Efficacy Variables

The primary objective of this study will be evaluated using two primary efficacy variables.

The first primary efficacy variable is the change from Baseline (Week 0) to Week 12/EOT in the ADCOMs, a composite score based on ADAS-Cog v14, CDR-SOB and MMSE.

The second primary efficacy variable is the change from Baseline (Week 0) to Week 12/EOT in the ADAS-Cog v14.

Multiplicity between both primary endpoints will be handled using an a priori hierarchical approach, such that the results for the ADAS-Cog v14 will only be interpreted in a confirmatory fashion if results for the ADCOMs allowed a rejection of the null hypothesis.

15.2.2.2 Secondary Efficacy Variables

The following secondary efficacy variables will be evaluated:

- RAVLT
- CDR -SOB
- MMSE
- NPI
- NTB – Executive Domain (COWAT and CFT)

15.2.2.3 Safety Variables

The following safety variables will be evaluated:

- Clinical safety laboratory values
- AEs, SAEs and AESIs
- ECG
- NFM:
    - NTSS-6
    - TCNS
    - NCV and amplitude of peripheral motor and sensory nerves
- CSSRS

- Physical examination
- Vital signs

15.2.2.4 PK and PD Variables

- PK assessment
- PD assessment: ACTH, DHEAS, androstenedione and testosterone

15.2.2.5 Other Exploratory Variables

- Metabolic function: lipids, blood pressure, glucose, HbA1c, body weight and BMI

15.2.3 Methods of Statistical Analyses

15.2.3.1 General Principles

The aim of the primary efficacy analysis is the evaluation of the performance of Xanamem™ as compared to placebo for the change in the primary efficacy endpoints ADCOMs and ADAS-Cog v14 from Baseline to Week 12/EOT. The two primary efficacy variables will be evaluated in an a priori hierarchical fashion, where the results of the ADAS-Cog v14 analysis will only be interpreted as confirmatory if superiority of Xanamem™ over placebo can be shown for the ADCOMs.

The aim of the secondary efficacy analyses is to provide general results regarding the performance of Xanamem™ as compared to placebo in subjects with mild dementia due to AD.

A statistical analysis plan (SAP) will be prepared and finalised before study data are unblinded. A separate Modelling and Simulation Analysis Plan will be prepared for PK data.

15.2.3.2 Missing Data

For efficacy variables where the change from baseline is analysed, no imputation for missing values will be performed, i.e. the analysis will be based on “Observed Cases”, except where otherwise specified.

Treatment of missing items for the individual scores will be described in the SAP.

Missing Baseline data for the MMSE may be replaced by the Screening results only for the analysis of MMSE alone. When MMSE results are analysed as part of the ADCOMs analysis, such a replacement is not allowed, in order to ensure that all Baseline values contributing to the ADCOMs refer to the same point in time.

Other replacement of missing values is not foreseen.

15.2.3.3 Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be analysed in a descriptive fashion and results will be presented overall and by treatment group.

15.2.3.4 Subject Disposition

The following will be summarised (overall and by treatment group where applicable):

- Subjects screened
- Subjects randomised
- Subjects treated
- Subjects in each analysis set
- Subjects completing the study/withdrawing early (including withdrawal reason)
- Subject allocation by study site

15.2.3.5 Evaluation of Primary Efficacy Variables

For analysis of the primary efficacy variables, an analysis of covariance (ANCOVA) model will be used to assess the change in ADCOMs/ADAS-Cog v14 score from Baseline (Week 0) to Week 12/EOT. Treatment group will be used as fixed effect and the baseline value as a covariate. For both primary efficacy variables, the following hypotheses will be tested:

$$H_0: \mu_P \leq \mu_X \text{ vs. } H_1: \mu_P > \mu_X,$$

where μ_P and μ_X denote the change from Baseline to Week 12/EOT in ADCOMs and ADAS-Cog v14 for the placebo and Xanamem™ treatment groups, respectively. Both tests will be performed at a type I error rate of 0.05 one-sided, with a priori hierarchical handling of multiplicity, as described above, based on the least squares means (LS means) for the change from Baseline to Week 12/EOT. LS means from the ANCOVA will be used to derive 90% and 95% confidence intervals. The primary efficacy analysis will not replace missing Week 12/EOT.

The analysis described above will be repeated on the PP set for supportive evidence.

Sensitivity analyses aim at assessing the robustness of the primary efficacy analysis. The following two analyses will be performed:

- An additional ANCOVA, imputing missing Week 12/EOT data based on resampling from the placebo subjects, taking baseline values into account
- An additional ANCOVA, adding site as a factor. Sites contributing few subjects may be pooled. Any decision on pooling sites will be undertaken before unblinding.

Whilst the European Medicines Agency discussion paper[40] foresees the use of the linear models for sensitivity analyses, complementing different methods of primary analyses, the type and order of analyses in this study – ANCOVA as primary efficacy analysis and placebo-based imputation as sensitivity analysis – are chosen in a different fashion due to the following reasons:

- The development stage this study is associated with, where the primary aim is to explore a possible therapeutic effect of Xanamem™; in conjunction with
- The relatively short study duration which can be expected to reduce the number of missing values in either treatment group and
- The fact that the primary efficacy variables will only be assessed at Baseline and Week 12/EOT.

15.2.3.6 Evaluation of Secondary Efficacy Variables

Secondary efficacy variables will be analysed in a descriptive manner. Summary statistics will be presented overall and by treatment group, and an exploratory comparison will be performed between the two treatment groups.

RAVLT: Results will be described for each visit as actual values and change from Baseline. An exploratory ANCOVA will be performed on the change from Baseline to Week 12/EOT for comparison between the treatment groups, including treatment group as fixed effect, and the baseline value as a covariate.

CDR-SOB: Results will be described for each visit as actual values and change from Baseline. An exploratory ANCOVA will be performed on the change from Baseline to Week 12/EOT for comparison between the treatment groups, including treatment group as fixed effect and the baseline value as a covariate.

MMSE: Results will be described for each visit as actual values and change from Baseline. An exploratory ANCOVA will be performed on the change from Baseline to Week 12/EOT for comparison between the treatment groups, including treatment group as fixed effect and the baseline value as a covariate.

NPI: Results will be described by domain for Baseline and last visit. An exploratory ANCOVA will be performed on the change from Baseline to Week 12/EOT for comparison between the treatment groups, including treatment group as fixed effect. Sub-group analyses will be performed for subjects with (score > 1) and without (score 0 to 1) symptoms at Baseline if warranted by the number of subjects in each treatment group and sub-group.

NTB – Executive Domain (COWAT and CFT): Results will be described for Baseline and last visit. An exploratory ANCOVA will be performed on the change from Baseline to Week 12/EOT for comparison between the treatment groups, including treatment group as fixed effect, and the baseline value as a covariate. In addition to the composite score, independent components will be analysed.

15.2.3.7 Evaluation of Safety Variables

Clinical safety laboratory data: clinical safety laboratory data will be presented by treatment group and overall. For each visit, the actual result and the change from Baseline will be presented. Count and shift tables for values outside the normal ranges will be presented as appropriate. In addition, individual listings will be provided for subjects with at least one value outside the normal range for a given laboratory parameter.

AEs: TEAEs will be described using descriptive statistics, and coded according to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and MedDRA preferred term, by treatment group and overall for the following categories:

- All TEAEs
- Treatment-emergent AESI
- Treatment-emergent SAEs

- TEAEs by severity
- Drug-related TEAEs
- TEAEs leading to temporary or permanent discontinuation of study drug
- TEAEs leading to study discontinuation

ECG: The results for the ECG will be presented by treatment group and overall. For each visit, the actual results and the change from Baseline will be presented.

CSSRS: Suicidal ideation, suicidal behaviour and self-injurious behaviour without suicidal intent, as well as suicide-related TEAEs based on the CSSRS during treatment, will be tabulated by treatment group and overall. Shift tables by treatment group will be prepared for changes in CSSRS categories from Baseline to during treatment, as well as for the maximum suicidal ideation score. In addition, individual listings will be provided for subjects with at least one occurrence of suicidal ideation, suicidal behaviour or self-injurious behaviour without suicidal intent at any time under treatment.

Vital signs: The results for vital signs will be presented by treatment group and overall. For each visit, the actual results and the change from Baseline will be presented.

Physical examination: Abnormal results will be presented by individual listings.

NFM data will be analysed in the safety data set. Variables will be presented using summary statistics according to each variable's scale and treatment groups will be compared in an exploratory fashion. Special attention will be directed at intra-subject changes over the course of the study. Count tables will be provided by treatment group and overall for subjects with a) an NTSS-6 > 6 and b) abnormal results for any sensory test from the TCNS. For each visit, the actual results and the change from status before study drug treatment will be presented.

15.2.3.8 PK/PD Modelling

Nonlinear mixed effects modelling will be utilised to develop a population PK model for Xanamem™ plasma concentrations. From this, exposure metrics will be derived which may be used subsequently to explore exposure-response relationships with selected exposure and efficacy/safety endpoints.

A separate Modelling and Simulation Analysis Plan will be prepared and results from the PK/PD modelling will be reported separately from the clinical study report.

15.2.3.9 Evaluation of Exploratory Variables

Exploratory variables will be analysed by treatment group and overall using descriptive statistics for categorical and continuous data, as applicable. For continuous data, the change from Baseline will be analysed in addition to the actual visit values; for categorical data, shift tables will be presented as appropriate.

15.2.3.10 Compliance and Exposure

Exposure will be analysed by calculating the number of days with exposure to study drug. Results will be presented overall and by treatment group.

Compliance will be analysed by calculating the ratio between the actual intake of study drug as documented by dispensed and returned study drug and the expected intake of study drug according to the treatment schedule. The percentage compliance will be described overall and by treatment group, and the number of subjects with a compliance < 80%, between 80% and 120% and > 120% will be presented by treatment group and overall.

15.2.3.11 Interim Analysis

There is one planned interim analysis after 50 completed subjects. The following endpoints will be analysed in this interim analysis:

Efficacy:

- ADAS-Cog
- MMSE
- CDR-SOB
- ADCOMS
- RAVLT
- NPI
- NTB – Executive domain (COWAT and CFT)

Safety:

- Laboratory values
- Incidence of AEs
- NFM

PK/PD:

- Plasma concentrations of Xanamem™

Evaluation of efficacy evaluables will be conducted as described in Sections 15.2.3.5 and 15.2.3.6. For control of the type I error rate, the Haybittle-Peto approach will be used, thus setting the stopping boundary for the primary efficacy variables at a one-sided 0.001, leaving the full type I error rate of a one-sided 0.05 for the final analysis. Full details of the interim efficacy analysis will be specified in the SAP.

This interim efficacy analysis aims at providing additional information on the efficacy parameters to the DSMB, including both descriptive and inferential statistics. No study adaptations are planned based on these analyses. Should there be evidence of an overwhelming effect, the DSMB may recommend stopping early for success. Further details will be available in the DSMB Charter.

15.2.4 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 make recommendations for the remaining part of the study (further details will be provided in the DSMB Charter). The DSMB may recommend to continue with the study as planned, stop the study for early safety reasons, or judge if the dose is in any way problematic for this subject population and determine if dose modification is needed.

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.

The DSMB will also review unblinded PD data, available at the time of the interim analysis, of the subjects enrolled into the main study, who also volunteer to take part in the sub-study, to determine whether enough samples were collected from subjects on active drug. The PD sampling in this study will complement the previously reported Phase I data, in which most of the subjects were male and only a small number of subjects were aged 50 years or older.

The interim efficacy analysis aims at providing additional information on the efficacy parameters to the DSMB. No study adaptations are planned based on these analyses. Should there be evidence of an overwhelming effect, the DSMB may recommend stopping early for success. For control of the type I error rate, the Haybittle-Peto approach will be used, thus setting the stopping boundary at a one-sided 0.001, leaving the full type I error rate of a one-sided 0.05 for the final analysis.

The DSMB will act according to its own written SOP described in a charter and will prepare written minutes of its meetings. The Charter of the DSMB will be stored in the Trial Master File. The DSMB will maintain records of its meetings and these will become part of the study file when the study is complete.

In order not to disseminate unblinded data and to ensure that all staff involved in the conduct and final analysis of the study remain blind to the data, only the members of the DSMB, the DSMB Nerve Function Monitoring sub-committee and the unblinded DSMB statistician will have access to these data.

15.2.4.1 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. Further details will be provided in the DSMB Charter.

For quality control measures, the results of neurography of one subject per study site will be reviewed by a member of the DSMB Nerve Function Monitoring sub-committee. The study site will complete a Neurography Screening Quality Control Form and send it to the ICON MM. The study site may, however, proceed with subject randomisation if all eligibility criteria are fulfilled.

16 DIRECT ACCESS TO SOURCE DATA/NOTES

The investigator/study site will provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review and regulatory inspection.

17 QUALITY CONTROL AND QUALITY ASSURANCE

17.1 Conduct of the Study

ICON shall implement and maintain quality control and quality assurance procedures with written SOPs to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP and applicable regulatory requirements.

This study will be conducted in accordance with the provisions of the Declaration of Helsinki (October 1996), and in accordance with USA FDA regulations (CFR, Sections 312.50 and 312.56), with ICH GCP (CPMP/ICH 135/95) (applicable to clinical studies run in the European Union and Australia) and the National Statement on Ethical Conduct in Human Research (2007) - Updated May 2015 (applicable to clinical studies run in Australia).

The investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IEC/IRB, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve(s) only logistical or administrative aspects of the study. In the event of such deviations from the protocol, the implemented deviation or change and the reason(s) for it, should be submitted to:

- Actinogen Medical/ICON for agreement
- The IEC/IRB for review and approval or favourable opinion (if required)
- The applicable competent regulatory authority (if required)

At the earliest opportunity, the investigator (or delegate) must inform Actinogen Medical/ICON about any notable protocol deviations and explain any deviation from the approved study protocol in the eCRF and/or in the Protocol Deviation Log, if applicable.

Any deviations may result in the subject being withdrawn from the study and render that subject non-evaluable.

17.2 Study Initiation and Monitoring

Before the start of the study, the ICON study monitor will visit the study site to ensure adequacy of the facilities and to discuss responsibilities regarding study protocol adherence with the investigator and other personnel involved in the study.

The investigator may not recruit subjects into the study until such time that a visit has been made by an ICON study monitor to conduct a detailed review of the protocol, eCRF and study supplies (Site Initiation Visit). In addition, the investigator may not enrol any subjects into the study before written approval or a favourable opinion from the IEC/IRB for conducting the study has been received.

The investigator will permit the ICON study monitor access to review study data as frequently as deemed necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactory (on-site monitoring visits). These data include records of tests performed as a requirement for participating in the study as well as other medical records required to confirm subject eligibility for the study and to confirm information contained in the eCRF. During on-site monitoring visits, the ICON study

monitor will require access to the Investigator Site File to ensure completeness and correctness of all documentation required for the study. The date on which the ICON study monitor (or delegate) visits the study site will be recorded in the Site Visit Log (or equivalent). During monitoring visits, the study site's coordinator (if applicable) and the investigator should be available, the source documentation should be accessible, and a suitable environment should be provided for the ICON study monitor to review study-related documentation.

The investigator, as part of his/her responsibilities, is expected to co-operate with the sponsor and ICON in ensuring that the study adheres to ICH GCP requirements and applicable regulatory requirements. The investigator (or delegate) should record all data generated in the eCRF in a timely manner, so that the data is available for off-site monitoring and review.

18 ETHICS

18.1 Independent Ethics Committee/Institutional Review Board

Prior to the start of the study, the investigator is responsible for ensuring that the protocol and consent form have been reviewed and approved by a relevant regulatory authorities and IEC/IRB. The IEC/IRB shall be appropriately constituted and perform its functions in accordance with the FDA, ICH GCP and local requirements, as applicable.

The applicable regulatory authorities and IEC/IRB shall approve all protocol amendments (except for logistical or administrative changes), written informed consent documents and document updates, subject recruitment procedures (e.g. advertisements), written information to be provided to the subjects, Investigator Brochure, available safety information, information about payment and compensation available to subjects, the investigator's curriculum vitae and/or other evidence of qualifications and any other documents requested by the IEC/IRB and Regulatory Authority (Competent Authority), as applicable.

18.2 Written Informed Consent

A Subject Information Sheet and ICF will be prepared by Actinogen Medical/ICON in accordance with the provisions of ICH GCP and local legal requirements. The subject caregiver information sheet and ICF will be prepared by ICON in accordance with the provisions of ICH GCP and local legal requirements. This may be included in the study Subject Information Sheet and ICF or be a separate document as determined by local requirements and is referred to as the Caregiver Information and Consent form for the purpose of this protocol. The caregiver must separately give informed consent for his/her own participation in the study.

Before undergoing Screening procedures for possible enrolment into the study, the subject and subject's caregiver must be informed about the nature, scope, and possible consequences of the study. This information must be given orally to the subject and subject's caregiver by a physician or medically qualified person (according to applicable regulatory requirements) who is well informed about the nature, scope, and possible consequences of the study. Written information about the study will also be provided in the Subject Information Sheet and Caregiver Information and Consent form. The date on which this oral and written information on the study was provided to the subject and subject's caregiver, and by whom it was provided, must be documented in the subject's medical records.

The subject and subject's caregiver must be given ample time and opportunity to inquire about details of the study and to consider participation in the study. If, after reading the Subject Information Sheet, ICF and Caregiver Information and Consent form, consent is given to participate in the study, then the ICF must be signed and personally dated by the subject and the person conducting the informed consent discussion. If the subject cannot provide written informed consent, the subject's legal guardian or other representative, accordingly to local regulations as appropriate, must provide written informed consent prior to beginning screening activities. Even if unable to provide written informed consent, the subject must assent verbally to participating in the study and the subject's medical records

should note this assent (according to local regulations as appropriate). The subject and subject's caregiver will be provided with a copy of the signed ICF. The original signed ICF will be filed with the subject's records.

The Subject Information Sheet, ICF and Caregiver Information and Consent form must be approved by the IEC/IRB before they can be used in the study.

The Subject Information Sheet, ICF and Caregiver Information and Consent form must be revised whenever important new information becomes available that may be relevant to the subject's and subject's caregiver consent. Any revision of these documents must be approved by the IEC/IRB before they can be used in the study. The subject and subject's caregiver must be informed in a timely manner if new information becomes available that may be relevant to their willingness to continue participation in the study. The communication of this information should be documented appropriately.

Subjects will sign a separate section of the ICF or a separate ICF (depending on local legal requirements) for the optional assessment of PD sampling. Subjects who do not sign the respective ICF or section of ICF, will still be able to take part in the main study.

19 DATA HANDLING AND RECORD KEEPING

19.1 Case Report Forms/Source Data Handling

The investigator shall be provided with standardised eCRFs and shall ensure that all data from subject visits are promptly entered into the eCRFs in accordance with the specific instructions given. The investigator must electronically sign subjects' eCRF to verify the integrity of the data recorded.

The investigator must maintain source documents, such as laboratory reports, ECGs, consultation reports, and complete medical history and physical examination reports.

19.2 Retention of Essential Documents

The investigator/institution should maintain the study documents as specified in the ICH guidelines on GCP and as required by the applicable regulatory requirements. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Actinogen Medical. It is the responsibility of Actinogen Medical to inform the investigator/institution as to when these documents no longer need to be retained.

20 FINANCING AND INSURANCE

Clinical Trial Insurance will be addressed in a separate agreement and will be maintained by Actinogen Medical.

21 PUBLICATION POLICY

Actinogen Medical shall retain the ownership of all data. Actinogen Medical/ICON will provide the relevant study protocol information in a public database (ClinicalTrials.gov) at commencement of the study. When the study is complete, ICON shall arrange the analysis and tabulation of data. A clinical study report shall then be prepared by ICON, which may be used by Actinogen Medical for publication, presentation at scientific meetings, or submission to IEC/IRB and regulatory authorities in accordance with applicable requirements, or as otherwise required. All proposed publications based on this study are subject to approval by Actinogen Medical.

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23 APPENDICES

Appendix I World Medical Association Declaration of Helsinki, version of 1996 (the version referenced by FDA and European Commission)

October 1996 17.C
Original: English

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964

and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
and the
48th General Assembly,Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

    Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

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Appendix II Per Protocol Laboratory Evaluations

Haematology:	
Haemoglobin	Basophils
Haematocrit	Eosinophils
Platelet count	Monocytes
Red blood cell count	Neutrophils
White blood cell count and differential	Lymphocytes
Biochemistry:	
Alkaline phosphatase	Cholesterol
Aspartate aminotransferase	Triglycerides
Alanine aminotransferase	High-density lipoprotein-cholesterol
Gamma-glutamyl transpeptidase	Low-density lipoprotein-cholesterol
Phosphorous	Protein (total)
Potassium	Creatinine & Creatinine Clearance
Glucose, fasting	Follicle-stimulating hormone [1]
Uric acid	Human chorionic gonadotrophin [2]
Bilirubin (total)	
Urinalysis:	
Urate crystals, phosphate crystals, bilirubin crystals, blood, clarity, colour, glucose, ketones, leukocytes, protein, squamous epithelial cells, trans. epithelial cells, triple phosphate crystals	
Microscopic examination [3]	
Other:	
HbA1c	DHEAS
VLDL Cholesterol	Total testosterone
ACTH	Vitamin B12
Androstenedione	Cortisol [4]
Xanamem™	
Drugs of abuse screen:	
Urine benzodiazepines (Screening visit, unless a re-test is required. If a re-test is required this must be performed prior to randomisation.)	

1. Females only. To be taken only if there is clinical concern about the subject's menopausal status.
2. Pregnancy test on women of childbearing potential only.
3. Performed only if required, based on urinalysis results.
4. Performed using the PK blood samples.

Appendix III Prohibited Medication - Brand Names per Country

Appendix III Prohibited Medication

6 months prior to Screening (and throughout the study)

Sedative drugs (specifically benzodiazepines, barbiturates and other anxiolytics) more than twice in 1 week or 3 times in 1 month.

This also includes sedative (anticholinergic) anti-incontinence drugs:

Oxybutynin	Ditropan, Gelnique, Oxytrol, Cystrin, Kentera, Lyrinel, Oxytrol
probantheline/propantheline	Pro-Banthine
solifenacin	Vesicare, Vesomni
trospium	Sanctura, Flotros, Regurin, Uraplex

Sedative (and anticholinergic) Antihistamines:

chlorpheniramine/chlorphenamine maleate	Chlor-trimeton, Efidac, Kloromin, Phenetron, Teldrin, Piriton
cyproheptadine	Periactin
diphenhydramine	Benadryl, Beldin, Belix, Benylin, Nytol
hydroxyzine	Atarax, Vistaril, Orgatrax, Ucerax

Sedative (anticholinergic) antidepressants are not allowed at any dose. NOTE: Major Depression is an Exclusion criterion:

Amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, paroxetine

Medicines that are known to cause peripheral neuropathy:

	Arsenic , Colchicine, Gold
Cardiovascular drugs	Amiodarone, Hydralazine, Perhexiline
Anti-cancer drugs	Cisplatin, Docetaxel, Paclitaxel, Suramin, Vincristine
Anti-infectives	Chloroquine, Isoniazid, Metronidazole, Nitrofurantoin, Thalidomide
Anti-human immunodeficiency virus (HIV) drugs	Didanosine, Stavudine, Zalcitabine
Autoimmune disease drugs	Etanercept, Infliximab, Leflunomide
Dermatologicals	Dapsone
Anti-convulsants	Phenytoin
Anti-alcohol drugs	Disulfiram

4 weeks prior to Screening

Changes in medication or doses of psychotropics (antidementive drugs)

2 weeks prior to Baseline (and throughout the study)

Inhaledglucocorticosteroids (e.g. prednisone equivalent) > 1 g per day, topical glucocorticosteroids > 50 g per week, and any oral steroid preparations

Inhaled glucocorticosteroids

budesonide	Budelin, Easyhaler, Pulmicort, Symbicort
flunisolide	Aerobid, Aerospan
fluticasone	Advair, Flovent, Flixotide, Seretide, Breo Ellipta
ciclesonide	Alvesco
mometasone	Asmanex
beclomethasone	Beclovent, Qvar, Fostair, Vanceril

Topical glucocorticosteroids

Hydrocortisone	Dermacort, Epicort, Egocort, Sigmacort
Triamcinolone	Kenacort
Fluticasone	Cutivate
Clobetasol	Dermovate, Clobex, ClobaDerm, Temovate
Betamethasone	Betnovate, Diprosone, Diprolene, Celestone
Halobetasol	Ultravate

Drugs known to inhibit or induce CYP3A4 as listed below:

Erythromycin	E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone MY-E, Pediamycin, Zineryt, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth
Clarithromycin	Biaxin, Prevpac, Clarac, Clarithro, Kalixocin, Klacid
Indinavir	Crixivan
Itraconazole	Lozanoc, Sporanox, Onmel,
Ketoconazole	Ketozole, Daktarin, Nizoral, Extina, Xolegel
Ritonavir	Kaletra, Norvir, Technivie, Viekira Pak
Rifampicin	Rifadin, Rifater, Rifinah, Rimactane, Rimstar, Rimycin, Rifamate
St. John's Wort	Various, including OTC
Vandetanib	Caprelsa
Voriconazole	Vfend, Vttack

Further listed in protocol but either rarely used or anyway not relevant since the underlying disease (e.g. epilepsy) is usually an exclusion criterion: boceprevir, nelfinavir, posaconazol, nefazodone, carbamazepine, phenytoin, primidone.

Prohibited during to the study

Initiating AChEIs or memantine

Changes in medication or doses of psychotropics (or other medication that may have an impact on cognition), such as any anticholinergic drug, including antidepressants (see above), and antipsychotics (chlorpromazine, clozapine, olanzapine, thioridazine).

NOTE that psychiatric diseases that may impact cognition and memory are an Exclusion Criterion.

Allowed when stable 3 months prior to Baseline prior and during to the study

Vitamin B12 and Omega 3 (including specifically Souvenaid)

Allowed during to the study, but requiring upfront discussion with ICON Medical Monitor

Drugs that may prolong QTc

Antiarrhythmics

Amiodarone	Cordarone, Pacerone, Nexterone, Aratac , Rithmik
Disopyramide	Norpace, Rythmodan
Dofetilide	Tikosyn
Dronedarone	Multaq
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flecaine, Flecatab
Ibutilide	Corvert
Procainamide	Pronestyl, Procan
Quinidine	Quinaglute Duraquin, Quinact, Quinidex, Cin-Quin, Quinora, Nuedexta
Sotalol	Betapace, Sotalex, Sotacor, Cardol, Solavert, Sotab

Anesthetic

Propofol	Diprivan, Propoven, Anesia, Fresefol , Provive
Sevoflurane	Ulane, Sojourn, Sevorane

Antibiotic

Azithromycin	Zithromax, Zmax, Azith, Zitrocin
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin, C-Flox, Ciprol, CIFRAN , Ciproxin, Loxip, Roflo
Grepafloxacin	Raxar
Levofloxacin	Levaquin, Tavanic
Moxifloxacin	Avelox, Avalox, Avelon

Antidepressants

Citalopram	Celexa, Cipramil, Celapram, Celica, Ciazil, Cipramil, Citadrl, Dralopram, Lopacit, Talam
Escitalopram	Cipralex, Lexapro, Nexito, Seroplex, Elicea, Lexamil, Lexam, Esitalo, Cilopam-S escilupin, escital, escitalup, Escicor, Esipram, Loxalate

Antifungal

Fluconazole	Diflucan, Trican, Dizole, Fluzole, Ozole
Pentamidine	Pentam

Phosphodiesterase 3 inhibitor

Anagrelide	Agrylin, Xagrid
Cilostazol	Pletal

Appendix IV Contraception

Appendix IV - Contraception

1. Definitions

Definition of women of childbearing potential and of fertile men

For the purpose of this study, a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

For the purpose of this study, a man is considered fertile after puberty unless permanently sterile by bilateral orchiectomy.

2. Birth control methods

Birth control methods which may be considered as highly effective

For the purpose of this study, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen- and progesterone-containing) hormonal contraception associated with inhibition of ovulation[1]:
  - oral
  - intravaginal
  - transdermal
- progesterone-only hormonal contraception associated with inhibition of ovulation[1]:
  - oral
  - injectable
  - implantable[2]
- intrauterine device (IUD)[2]
- intrauterine hormone-releasing system (IUS)[2]
- bilateral tubal occlusion[2]
- vasectomized partner[2,3]
- sexual abstinence[4]

Birth control methods which may not be considered as highly effective

Birth control methods that result in a failure rate of more than 1% per year include:

- progesterone-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide[5]
- cap, diaphragm or sponge with spermicide[5]

Birth control methods which are considered unacceptable in clinical trials

- Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

Footnotes:

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

[2] Contraception methods that in the context of this study are considered to have low user dependency.

[3] Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[4] In the context of this study, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

[5] A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods