Actinogen Medical

Protocol Number: ACW0002

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)

STATISTICAL ANALYSIS PLAN

Version: Final V3.0

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REVISION HISTORY

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26Apr2016	Draft V0.1	Initial Draft	Sunoj Chacko Varughese
28FEB2017	Draft V0.2	Updated as per Amended protocol Amendment 2; 24-Nov-2016	Ramesh Vishwakarma
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05Jan2018	Final V2.1	Removed analysis on QTcB	Prasanth Sasidharan
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19Feb2019	Final V2.1	Section 7.11 (new) : adding subgroup analyses section	DukHyun Kim
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07Mar2019	Final V2.1	Added Section 7.12 Statistical Analysis Plan for Additional Analyses to be Conducted by McCloud Consulting Group After Database Lock	Prasanth Sasidharan
11Mar2019	Final V2.1	1.In section 7.3, update "major/minor" into" Key and Non-Key" per Peter's comments 2.In section 7.11, add "if at least 25% of subjects are in both groups" for Baseline CDR Global score (0.5 vs 1.0) per Peter's comments	Jing Luo
18Mar2019	Final V2.1	In section 7.7.1 (1)Update Repeat a) to g) for placebo group and combine both datasets into"Repeat a) to g) for placebo group and combine both datasets with the records from both groups with non-missing ADCOMs score at Week 12." (2)For resampling part, Update the SAS code. (3) Add "Under this approach we assume that patients with missing data in both treatment groups would have outcomes like a patient in the placebo group as soon they become missing." And "Under this approach we assume that patients with missing data in	Jing Luo

		each treatment groups would have outcomes like a patient in that treatment group as soon they become missing." Separately for the 2 multiple imputation part.	
21Mar2019	Final V2.1	In section 7.7.1, update the description of "imputing missing Week 12/EOT data based on multiple imputation using both the Xanamem and placebo group" per MCG suggestion.	Jing Luo
22Mar2019	Final V2.1	In the abbreviation section, revert back MAR and add MNAR.	Jing Luo
22Mar2019	Final V3.0	Updated the version as 3.0	Jing Luo

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LIST OF ABBREVIATIONS

Abbreviation	Term
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
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CDR	Clinical Dementia Rating Scale
CDR-SOB	Clinical Dementia Rating scale - Sum of Boxes
CFT	Category Fluency Test
CI	Confidence Interval
COWAT	Controlled Word Association Test
CSSRS	Columbia Suicide Severity Rating Scale
DHEAS	Dehydroepiandrosterone Sulfate
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EOT	End of Treatment
FAS	Full Analysis Set
HbA1c	Haemoglobin A1c
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
LS	Least Squares (means)
MAR	Missing at Random
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMSE	Mini-Mental Status Examination
MNAR	Missing not at Random
N, n	Number of subjects/subjects in a sample from a population or analysis group
NCV	Nerve Conduction Velocity
NPI	Neuropsychiatric Inventory
NTB	Neuropsychological Test Batteries
PLS	Partial Least Squares
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
QD	Once a day
QTcF	QT Time using the Fridericia's Correction
RAVLT	Rey Auditory Verbal Learning Test

LIST OF ABBREVIATIONS

Abbreviation	Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
UK	United Kingdom
USA	United States of America
VIP	Variable Importance of Projection
VLDL	Very Low-density lipoprotein
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

1.0 INTRODUCTION

The purpose of this document is to provide further details about the statistical analysis methods, data derivations and data summaries to be employed in the study protocol ACW0002 [Universal Trial Number: U1111-1177-5932]: 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). This statistical analysis plan (SAP) has been based on International Conference on Harmonisation (ICH) E3 and E9 guidelines and in reference to protocol final Protocol Amendment 4 16Oct2017 and Annotated Case Report Form version 1.0: date 10-March-2017. The SAP covers statistical analysis, tabulations and listings of all data including efficacy and safety data.

Any major deviations from the methods specified in this document and the protocol will be discussed and documented with revision history.

2.0 STUDY 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™ 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 (Controlled Word Association Test [COWAT] and Category Fluency Test [CFT]

3.0 STUDY DESIGN

3.1 Description of the Disease

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 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). 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 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.

3.2 Study Design

Study ACW0002 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.

A subject will be eligible for enrolment in the study if ALL of the inclusion and exclusion criteria met.

After obtaining informed consent, the screening procedures will be performed at the screening visit as per the schedule of activities (Appendix 1). Protocol section 9.4.1 has detail description about the study procedures and assessments. It is planned to randomise approximately 174 subjects at approximately 20 sites in the three countries (Australia, UK and USA), with the aim to enroll 7 to 10 subjects at each study site.

The overall study duration for an individual subject will be 17 to 20 weeks, including a screening period of one to four weeks, a double-blind treatment period of 12 weeks, and a follow-up period of four weeks. The total duration of the study is expected to be two years.

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. Subjects withdrawn from the study cannot be re-enrolled at a later time, regardless of the reason for withdrawal. This study may be terminated prematurely at any time by Actinogen Medical for medical, operational or ethical reasons at individual or all study sites. Study protocol will help to understand more about the study design.

3.3 Study Treatments and Assessments

One capsule of Xanamem™, or the matching placebo, will be administered orally with approximately 200 mL of preferably warm water once a day (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. One Follow-up visit is planned. Throughout the study, subjects will be assessed for the study objectives as outlined in the schedule of activities (Appendix 1). The visit window details are outlined in the Appendix 2.

3.4 Randomisation and Blinding

This study is randomised, double-blind, placebo-controlled Phase II proof-of-concept study. There is a well-defined randomisation plan for subject's randomisation and blinding. Detailed randomisation details will be document in the study randomisation plan. 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 whoever performs the PK and PD assessments, when the Pharmacokinetic (PK) and Pharmacodynamic (PD) data are analysed, as well as to the DSMB (Data Safety Monitoring Board). Randomisation codes will be generated in blocks stratified by site to ensure approximate balance between dose schemes (1:1) and balanced per site.

3.5 Sample Size

Study is planned to randomise approximately 174 subjects (87 per treatment group) at approximately 20 study sites in three countries (Australia, UK, and USA), with the aim to enroll 7 to 10 subjects at each study site.

4.0 ENDPOINTS AND VARIABLES

The primary as well as secondary and other endpoints and its variables are given below.

Primary Efficacy Endpoints

The primary efficacy endpoints of this study are:

- Change from Baseline (Week 0) to Week 12/EOT in the ADCOMs (a 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])
- Change from Baseline (Week 0) to Week 12/EOT in the ADAS-Cog v14 score

Primary Efficacy Endpoints variables

The following primary efficacy variables will be evaluated:

- ADCOMs: a composite score based on ADAS-Cog v14, CDR-SOB and MMSE.
- ADAS-Cog v14

Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study are:

- Change from Baseline (Week 0) to Week 12/EOT of RAVLT score
- Change from Baseline (Week 0) to Week 12/EOT of CDR-SOB score
- Change from Baseline (Week 0) to Week 12/EOT of MMSE score
- Change from Baseline (Week 0) to Week 12/EOT of NPI score
- Change from Baseline (Week 0) to Week 12/EOT of NTB – Executive Domain score (COWAT and CFT)

Secondary Efficacy Endpoints variables

The following secondary efficacy variables will be evaluated:

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

Safety Endpoints

The safety endpoints of this study are:

- Change in clinical safety laboratory values from Baseline (Week 0) to EOT (Week 12)
- Incidence of adverse events (AEs)
- Change in electrocardiogram (ECG)
- Change in Nerve Function monitoring (NFM) (including NTSS-6, TCNS and neurography (nerve conduction velocity and amplitude) of peripheral sensory and motor nerves)
- Change in Columbia suicide severity rating scale (CSSRS) and the incidence of CSSRS related event
- Abnormality in physical examination
- Change in vital signs

Safety Endpoint variables

The following safety variables will be evaluated:

- Clinical safety laboratory values for haematology, biochemistry and urinalysis
- AEs, serious adverse events (SAEs), and adverse events of special interest (AESIs)
- ECG
- NFM
- CSSRS
- Physical examination
- Vital signs

Pharmacokinetics (PK) /Pharmacodynamics (PD) endpoints

The following are the PK/ PD endpoints of this study:

- PK assessment
- Optional PD assessment

PK/PD Endpoints variables

The following PK/PD variables will be evaluated

- PK assessment : Xanamem™ concentration
- PD assessment: Adrenocorticotropic Hormone (ACTH), Dehydroepiandrosterone Sulfate (DHEAS), androstenedione and testosterone

Other Exploratory Endpoints

The other exploratory endpoints include:

- Metabolic function

Other Exploratory endpoints variables

The following other exploratory endpoints variables will be evaluated

- Metabolic function: lipids, blood pressure, glucose, hemoglobin A1c [HbA1c], body weight and body mass index [BMI]

5.0 STATISTICAL CONSIDERATIONS

5.1 General Considerations

Statistical analyses will be performed using SAS software, version 9.3 or higher. Formal hypothesis will be tested in this study and it will be explained in detail on following section.

Continuous data will be summarized using number (n), mean, standard deviation (SD), minimum value, median, maximum value and, if appropriate, number of missing values. Unless noted otherwise, summaries will be produced by visit (where applicable) and results will be presented overall and by treatment group. If more than one value is reported at a scheduled visit, the value collected closest to the intended visit date will be used. In the case of a tie, the latest version will be summarized. If there is more than one value reported at the same date, the average value of multiple values will be obtained. 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.

Categorical data will be summarized using number (n) and percentages. Percentages will be calculated based on the number of non-missing values (if result display by visit) otherwise it will be calculated based on the population count. The number of missing values will be presented as a separate category with no percentage, if one or more subjects have missing data for the summary. Otherwise, all categories will be presented (even if no subjects are counted in the category). Counts of zero in any category will be presented without percentage.

Precision of summary statistics:

- Integer – Sample size (n, N) and number of missing responses (if displayed).
- One additional decimal place than reported/collected on the electronic Case Report Form (eCRF) – mean and median
- Two additional decimal places than reported/collected on the eCRF – standard deviation.
- Same number of decimal places as reported/collected on the eCRF – minimum, maximum.
- Percentages, CV – one decimal place.
- P-values will be presented for three decimal points (i.e., 0.xxx).

Precision of output display:

- Report output will be generated using SAS (version 9.3 or higher) ODS RTF with no borders or framing around table elements.
- Font – Courier New font with minimum of eight point font size
- Margins – For USA, minimum of 3/4” bound edge margin and 3/8” other margins on 8.5”x11” paper.

All data will be presented on listings in order of treatment group, subject, site [wherever defined], assessment date/time and assessment (in order collected on eCRF, unless specified otherwise). Dates will be presented in the format DDMMMYYYY. Times will be displayed in 24-hour clock format. Numbering of tables, figures and listings will follow ICH E3 guidelines.

Unless noted otherwise, unscheduled measurements will be excluded from the descriptive statistical analysis. However, unscheduled measurements that were performed immediately after the scheduled measurement, in case of a previous measurement error (e.g. equipment failure), will not be excluded from the analysis. In these cases, the original erroneous measurement will be excluded from the analysis and the unscheduled visit substituted. All the unscheduled measurements will be included in the listing.

5.2 Specification of Baseline Values

For efficacy variables: Baseline value is defined as the latest Week 0 observation prior to or on the date of the first dose of study drug. The exception is MMSE which is defined as the latest Screening or Week 0 observation prior to or on the date of the first dose of study drug. When MMSE results are analysed as part of the ADCOMs analysis, use of screening results are not allowed, in order to ensure that all Baseline values contributing to the ADCOMs refer to the same point in time.For safety endpoints: Baseline value is defined as the observation prior to or on the date of the first dose of study drug.

5.3 Multiple Comparisons and Multiplicity

Multiplicity between both primary endpoints will be handled using an a priori hierarchical approach.

6.0 ANALYSIS POPULATION

The populations used for analysis will include Full Analysis Set (FAS), Per Protocol (PP) Analysis Set, Safety Analysis Set, PK Set and PD Set. The success of the primary efficacy endpoints will be evaluated based on the FAS; these primary efficacy endpoints will also be analyzed for the PP analysis set. The evaluation of secondary efficacy endpoints will be based on FAS and PP analysis set. The evaluation of safety endpoints will be based on safety analysis set. PK set and PD set will be used for PK and PD endpoints analysis.

6.1 Full Analysis Set (FAS)

The 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.

6.2 Per Protocol (PP) Analysis Set

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. A list of all protocol violations will be documented in a separate file.

6.3 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.

6.4 PK Set

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

6.5 PD Set

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

7.0 METHODS OF ANALYSES AND PRESENTATIONS

The following sub-sections would be considered for logical presentation of study data.

7.1 Subject Disposition

The number of subjects screened, screen failure, randomised, treated, subjects in each analysis set, on-going status, study completion status, Follow-up details will be summarized. Subjects who discontinued/withdrawn from the study will be summarized with reason and listed by their primary reason. Subject allocation by study site will also be summarized. Inclusion/exclusion criteria evaluation will be listed. The denominator which is used for the percentage calculation will be mentioned in the table footnote. This table will be summarized overall and by treatment group by using all subjects.

7.2 Demographic and Baseline Characteristics

Demographic data and subject characteristics at Baseline will be summarized overall and by treatment group using descriptive summary statistics for FAS. The demographic and Baseline characteristics include age [continuous summary and categorical summary as Age <65 years, Age >=65 years], gender, race, pregnancy test result. Also Baseline characteristics results of height, weight, BMI will be summarized overall and by treatment group. All demographic and Baseline characteristics will be listed in full.

7.3 Protocol Deviations

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. Deviations may result in study termination of an investigator or investigational site or discontinue subjects from study. Examples of deviations include, but are not limited to:

- Informed consent violation.
- Inclusion/exclusion criteria not met.
- Study procedures not followed.
- Missed visit.
- Visit outside study window.
- Others like procedural deviations such as incorrect storage of study drug, failure to update the Internal Consent Form (ICF) when new risks become known etc…

Protocol deviation will be identified by the project team prior to database lock. A summary of major protocol deviations will be provided overall and by treatment group. All protocol deviations (Key and Non-Key) will be listed. All randomised subjects will be included in the summary.

7.4 Medical History

All medical history will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). The incidence of medical history abnormalities will be summarized using descriptive statistics by system organ class (SOC) and preferred term (PT). Subjects are counted only once in each PT and SOC category. Summary table will be sorted in alphabetical order by SOC and in decreasing frequency of PT based on total number of incidence within each SOC. Safety analysis set will be used for the analysis with actual treatment received for the summary. Medical history will also be displayed in patient listing.

7.5 Prior and Concomitant Medication

Concomitant medication is defined as all medications still being taken by a subject at randomisation and which continue to be taken during the study.

Prior medication is defined as all medications taken by a subject within 1 month prior to randomisation into the study.

Prior and Concomitant medications will be classified using the latest version of World Health Organization Drug Dictionary (WHO drug). All prior/concomitant medication will be listed.

7.6 Study Drug Treatment Duration of Exposure and Compliance

Treatment exposure and compliance will be assessed by maintaining adequate study drug dispensing records. Duration of exposure to study medication (weeks) and compliance (%) will be summarized descriptively.

Duration of exposure = (Last treatment date – First treatment date) + 1.

Treatment Compliance = (Number of study drug taken / number of study drug that should have been taken) x 100.

Where, number of study drug taken = sum of (total number of capsule taken since last visit), and number of study drug that should have been taken= (date of last dose – date of first dose +1).

Descriptive summary statistics will be used to summarize treatment duration of exposure and compliance. Also the compliance will be summarized categorically as number of subjects with a compliance < 80%, between 80% and 120% and > 120%. Safety analysis set will be used for the analysis with actual treatment received and presented by treatment group and overall. All study drug accountability data will be listed.

7.7 Efficacy Endpoints and Analyses

The primary efficacy analysis will be based on both FAS and PP population. Sensitivity analyses with primary efficacy endpoints will be based on FAS population. The secondary efficacy analysis will be analysed in a descriptive summary statistics based on FAS and PP population. Descriptive summary statistics mentioned in section 5.1 will be performed for all data used

within the context of the efficacy analysis models. Summaries will be presented by visit and by treatment group. Comprehensive listings of all data will be presented.

7.7.1 Primary Efficacy Endpoints and Analyses

The objective 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 (Week 0) to Week 12/EOT. The two primary efficacy endpoints 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.

7.7.1.1 ADCOMs/ADAS-Cog v14 score

ADCOMs, composite score (0 - 1.97) is derived from ADAS-Cog v14, CDR-SOB, and MMSE.ADAS-Cog v14 score is sum of all 14 items of ADAS-Cog v14. Scoring details for ADCOMs and ADAS-Cog v 14 score are given in Appendix 3.

For analysis of the primary efficacy variables, 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. The ANCOVA model will include treatment group as fixed effects and the Baseline value as a covariate.

The primary efficacy hypothesis is:

H_o: $\mu_P \leq \mu_X$

H_1: $\mu_P > \mu_X$,

where μ_P and μ_X denote the change from Baseline (Week 0) 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, based on the least squares means (LS means) for 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.

Unless otherwise specified, the ANCOVA will have the following characteristics:

- All subjects in the FAS will be included in the primary efficacy analysis as long as there are both Baseline and valid post-Baseline measurements at Week 12/EOT available.
- The response variable will be the change in ADCOMs score from Baseline (Week 0) to Week 12/EOT visit. Only post-Baseline measurements collected on the EOT will be considered response values.
- The following covariate will be used in the models:
    - Baseline ADCOMs score

- Treatment group

- The following SAS statements will be employed:

proc mixed data=xxxx ;

class <treatment group>;

model < change ADCOMs score> = <baseline ADCOMs score> <treatment group> ;

lsmeans <treatment group>/ diff cl alpha=0.05;

lsmeans <treatment group>/ diff cl alpha=0.10;

ods output lsmean=xxx diffs=xxx;

run;

Baseline ADCOMs score, as well as observed and change from Baseline values at post-Baseline visits, will be summarized descriptively.

The analysis described above will be repeated for ADAS-Cog v14. Also analysis will be repeated on PP analysis set for supportive evidence.

Whilst the European Medicines Agency discussion paper[5] 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 (Week 0) and Week 12/EOT.

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

1) An additional ANCOVA, imputing missing Week 12/EOT data based on resampling from the placebo subjects, taking Baseline values into account

Process

a) Select records from placebo group with non-missing ADCOMs score at Week 12

b) Select records from Xanamem group with missing ADCOMs score at Week 12

c) Merge datasets from a) and b)

   (Total number of records in merged dataset = number of records in dataset a) * number of records in dataset b))

d) Using Baseline (placebo) and Baseline (Xanamem), calculate DIFF variable to find record in placebo group which has smallest in difference with Baseline in test group

   DIFF = abs (Baseline (Xanamem) – Baseline (placebo))

e) Calculate RANDNO variable with RANUNI function and select the smallest randno

f) Select 1 record for each missing case in Xanamem group and impute ADCOMs score at Week 12 based on ADCOMs score at Week 12 in placebo group

g) Calculate change from Baseline based on imputed ADCOMs score at Week 12 for Xanamem group

h) Repeat a) to g) for placebo group and combine both datasets with the records from both groups with non-missing ADCOMs score at Week 12.

i) Run proc ANCOVA specified above

The following SAS statements will be employed:

For Xanamem group:

```
data placebo;
set indata;
if <treatment group> = Placebo and <VISIT> = Week 12 and AVAL <> missing;
rename CHG=CHG_P BASE=BASE_P ID=ID_P AVAL=AVAL_P;
run;

data test;
set indata;
if <treatment group> = Test and <VISIT> = Week 12 and AVAL = missing;
run;

proc sql;
create table outdata as
select *from test, placebo ;
quit;
```

```
proc sort data=outdata;
by id id_p;
run;

data outdata1;
set outdata;
diff=abs(BASE – BASE_P);
seed_no=ID * ID_P;
randno=ranuni(seed_no);
AVAL = AVAL_P;
CHG=AVAL – BASE;
run;

proc sort data=outdata1 out=outdata2;
by id diff randno;
run;

proc sort data=outdata2 nodupkey;
by id;
run;

data outdata3;
set outdata2;
keep ID <treatment group> BASE AVAL CHG;
run;
```

For placebo group, follow above process and keep the imputed data in *outdata4.*

```
data nomissing;
set indata;
if aval^=missing;
run;
```

data FINAL;

set outdata3 outdata4 nomissing;

run;

where CHG= Change ADCOMs score from Baseline, BASE=baseline ADCOMs score and AVAL=ADCOMs score at Week 12/EOT.

Run PROC MIXED procedure specified above with FINAL dataset.

2) An additional ANCOVA, adding site as a factor. Sites will be pooled by country if randomized subjects will be less than or equal to 10.The following SAS statements will be employed:

proc mixed data=xxxx ;

class <treatment group> <site>;

model < change ADCOMs score> = <baseline ADCOMs score> <treatment group> <site>;

lsmeans <treatment group>/ diff cl alpha=0.05;

ods output lsmean=xxx diffs=xxx;

run;

3) An additional ANCOVA, imputing missing Week 12/EOT data based on placebo-based multiple imputation with missing not at random (MNAR) assumption.

Process

Missing data at Week 12/EOT will be imputed using a regression model based on placebo-based imputation model. The imputation model will include the Baseline values and Week 12/EOT values. The imputation model for the missing observations in both the Xanamem group and the placebo group will be constructed from the observed data in the placebo group only. Under this approach we assume that patients with missing data in both treatment groups would have outcomes like a patient in the placebo group as soon they become missing. The imputation will be performed for 100 times and imputed datasets will be analysed using an ANCOVA model. Approximately 100 imputed datasets will be created and results from the analysis of each imputed dataset will be combined using Rubin's method.

- The following SAS statements will be employed:

proc mi data=xxxx nimpute=100 seed=3489876 out=yyyy;

class < treatment group>;

monotone reg (<ADCOMs score at week 12/EOT>);

mnar model(<ADCOMs score at week 12/EOT> /modelobs=(<treatment group>='Placebo'));

var <baseline ADCOMs score> < ADCOMs score at week 12/EOT>;

run;

data zzzz;

set yyyy;

<change ADCOMs score> = <ADCOMSs score at week 12/EOT> –< baseline ADCOMs score>;

run;

** For 95% Confidence Interval;*

proc mixed data=zzzz;

by _imputation_;

class <treatment group>;

model <change ADCOMs score>=<baseline ADCOMs score> <treatment group>;

lsmeans <treatment group>/ diff cl alpha=0.05;

ods output lsmeans=aaaa diffs=bbbb;

run;

*** LSmeans;*

proc mianalyze parms(classvar=full)=aaaa;

class <treatment group>;

modelefficts <treatment group>;

ods output parameterestimates=cccc;

run;

*** Differences;*

proc mianalyze parms(classvar=full)=bbbb;

class <treatment group>;

modeleffects <treatment group>;

ods output parameterestimates=dddd;

run;

** For 90% Confidence Interval;*

proc mixed data=zzzz;

by _imputation_;

class <treatment group>;

model <change ADCOMs score>=<baseline ADCOMs score> <treatment group>;

lsmeans <treatment group>/ diff cl alpha=0.10;

ods output lsmeans=aaaa2 diffs=bbbb2;

run;

*** Differences;*

proc mianalyze params(classvar=full)=bbbb2;

class <treatment group>;

modeleffects <treatment group>;

ods output parameterestimates=dddd2;

run;

The analysis described above will be repeated for ADAS-Cog v14.

4) An additional ANCOVA, imputing missing Week 12/EOT data based on multiple imputation using both the Xanamem and placebo group with the missing at random (MAR) assumption.

Process

Missing data at Week 12/EOT will be imputed using a regression based imputation model. The imputation model will include Treatment Group, Baseline values and Week 12/EOT values. The imputation model for the missing observations in both the Xanamem group and the placebo group will be constructed from the complete-case observed data for patients in both the Xanamem group and the placebo group. Under this approach we assume that patients with

missing data in each treatment group would have outcomes like a complete-case patient in that treatment group, where a complete-case patient is one with no missing values for any of the variables in the imputation model. This is known as the complete-case missing values (CCMV) approach. By study design, all patients will have non-missing data for Baseline and Treatment Group. Therefore Week 12/EOT is the only variable in the imputation model which can possibly have missing values. Since there is only one possible missing data pattern for the ADCOMs analysis, an imputation model based on complete-case patients only (CCMV) is equivalent to an imputation model based on patients with any missing data pattern. For this reason, although CCMV is usually a MNAR approach, for the specific case of the ADCOMs analysis (and ADAS-Cog v14 analysis), it is equivalent to a MAR approach.

The imputation will be performed 100 times and imputed datasets will be analysed using an ANCOVA model. Approximately 100 imputed datasets will be created and results from the analysis of each imputed dataset will be combined using Rubin's method.

- The following SAS statements will be employed:

proc mi data=xxxx nimpute=100 seed=3489876 out=yyyy;

class < treatment group>;

monotone reg (<ADCOMs score at week 12/EOT>);

mnar model(<ADCOMs score at week 12/EOT>/modelobs=ccmv);

var <treatment group> <baseline ADCOMs score> < ADCOMs score at week 12/EOT>;

run;

data zzzz;

set yyyy;

<change ADCOMs score> = <ADCOMSs score at week 12/EOT> – <baseline ADCOMs score>;

run;

** For 95% Confidence Interval;*

proc mixed data=yyyy;

by _imputation_;

class <treatment group>;

model<change ADCOMs score>=<baseline ADCOMs score> <treatment group>;

lsmeans <treatment group>/ diff cl alpha=0.05;

ods output lsmeans=aaaa diffs=bbbb;

run;

*** LSmeans;*

proc mianalyze parms(classvar=full)=aaaa;

class <treatment group>;

modelefficts <treatment group>;

ods output parameterestimates=cccc;

run;

*** Differences;*

proc mianalyze parms(classvar=full)=bbbb;

class <treatment group>;

modeleffects <treatment group>;

ods output parameterestimates=dddd;

run;

** For 90% Confidence Interval;*

proc mixed data=yyyy;

by _imputation_;

class <treatment group>;

model<change ADCOMs score>=<baseline ADCOMs score> <treatment group>;

lsmeans <treatment group>/ diff cl alpha=0.1;

ods output lsmeans=aaaa2 diffs=bbbb2;

run;

*** Differences;*

proc mianalyze parms(classvar=full)=bbbb2;

class <treatment group>;

modeleffects <treatment group>;

ods output parameterestimates=dddd2;

run;

The analysis described above will be repeated for ADAS-Cog v14.

7.7.2 Secondary Efficacy Endpoints and Analyses

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. Analysis will be done for FAS and PP analysis set.

7.7.2.1 Rey Auditory Verbal Learning Test (RAVLT) Score

RAVLT results of Recall List A [Total number of correct words], Recall List B [Number of correct words] and Final recall of List A scores [Number of correct words] will be analysed for each visit as actual values and change from Baseline. An exploratory ANCOVA will be performed on the change from Baseline (Week 0) to Week 12/EOT for comparison between the treatment groups, including treatment group as fixed effect, and the Baseline value as a covariate. The analysis described for primary efficacy analysis will be used for RAVLT data. Scoring details are given in Appendix 3.

7.7.2.2 Clinical Dementia Rating scale - Sum of Boxes (CDR-SOB) Score

CDR-SOB score (0 – 18) is a sum of all six items of CDR-SOB. CDR-SOB score will be analysed for each visit as actual values and change from Baseline. An exploratory ANCOVA will be performed on the change from Baseline (Week 0) to Week 12/EOT for comparison between the treatment groups, including treatment group as fixed effect, and the Baseline value as a covariate. The analysis described for primary efficacy analysis will be used for CDR-SOB data. Scoring details are given in Appendix 3.

7.7.2.3 Mini-Mental Status Examination (MMSE) Score

MMSE total score (0 - 30) is a sum of all 30 point questionnaire of MMSE. MMSE will be analysed for each visit as actual values and change from Baseline. An exploratory ANCOVA will be performed on the change from Baseline (Week 0) to Week 12/EOT for comparison between the treatment groups, including treatment group as fixed effect, and the Baseline value as a covariate. The analysis described for primary efficacy analysis will be used for MMSE data. Scoring details are given in Appendix 3.

7.7.2.4 Neuropsychiatric Inventory (NPI)

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). Total distress score (0 – 60) will summarized descriptively. Scoring details are given in Appendix 3.

Total NPI score, score by domain and total distress score will be analysed for baseline and last visit including change from Baseline. An exploratory ANCOVA will be performed on the change from Baseline (Week 0) to Week 12/EOT in the total NPI score for comparison between the treatment groups, including treatment group as fixed effect. Subgroup 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. The analysis described for primary efficacy analysis will be used for NPI data.

7.7.2.5 Neuropsychological Test Batteries (NTB) – Executive Domain

Total NTB score is the sum of 'Total correct response' of Category Fluency Test (CFT) and 'Total number of correct words' of Controlled Oral Word Association – Test (COWAT). Each score ('Total correct response' of CFT and 'Total number of correct word' of COWAT) will also be analysed. Those results will be analysed for Baseline and last visit including change from Baseline. An exploratory ANCOVA will be performed on the change from Baseline (Week 0) to Week 12/EOT in the NTB total score 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, the change from Baseline (Week 0) to Week 12/EOT in independent components will be analysed with ANCOVA for COWAT and CFT - total correct responses score. The analysis described for primary efficacy analysis will be used for NTB- executive domain data. Sensitivity analysis with adding sites as covariate will be performed in FAS population. Site will be pooled as same to the primary efficacy endpoint. Scoring details are given in Appendix 3.

7.8 Safety Endpoints and Analyses

All safety endpoints will be summarized for safety analysis set with actual treatment group received. The following are the safety endpoint variables that will be summarized.

- Clinical safety laboratory values for haematology, biochemistry and urinalysis
- AEs, SAEs, and AESIs
- ECG
- NFM
    - NTSS-6
    - TCNS

    - NCV and amplitude of peripheral motor and sensory nerves
- CSSRS
- Physical examination
- Vital signs

7.8.1 Adverse Events

Any detrimental change in the subject's condition collected from after signing the ICF and up to completion of the 4-week Follow-up period after the last administration of study drug, should be considered an AE. Any new SAEs occurring up to 60 days after the last administration of study drug should be reported.

Treatment-emergent adverse events (TEAEs) are those AEs which worsen in severity on or after date of first administration of study drug or with onset date on or after first administration of study drug.

AEs with missing start dates, but with stop dates either overlapping into the treatment period or missing, will be considered TEAEs. A TEAE with missing drug-relationship will be considered as related.

All AEs will be coded by SOC and PT using the latest version of MedDRA. Incidences of TEAEs will be tabulated by SOC and PT. Incidences of TEAEs will also be presented by maximum severity, seriousness, AESI and drug-related. Subjects who are temporary or permanently discontinued from treatment and discontinued from study will be summarized by SOC and PT in a separate table. Subjects are counted only once in each SOC, and only once in each PT category.

The following tables will be developed for summarizing AEs.

- Overall summary of TEAEs: it includes number of TEAEs, subjects with any TEAE, subjects with any SAE, subjects with any severe TEAEs, subjects with any drug-related TEAEs, subjects with any AESI, subjects with TEAEs leading to temporary or permanently treatment discontinuation, subjects with TEAEs leading to study discontinuation.
- Summary of TEAEs by SOC and PT
- Summary of serious TEAEs by system organ class and preferred terms
- Summary of TEAEs by system organ class, preferred terms and maximum severity
- Summary of drug-related TEAEs by system organ class, preferred terms
- Summary of Treatment-emergent AESI by system organ class and preferred terms

- Summary of TEAEs leading to temporary or permanent discontinuation of study drug by system organ class, preferred terms
- Summary of TEAEs leading to study discontinuation by system organ class, preferred terms

All AEs, AESI, SAEs and deaths will be listed.

7.8.2 Clinical Safety Laboratory Parameters

Descriptive statistics for absolute value and absolute change from Baseline [only for continuous results parameters, otherwise display percentage change from Baseline] for protocol specified laboratory parameters of biochemistry, haematology and urinalysis will be presented for Baseline (Week 0) to EOT (Week 12) by treatment group and overall. International System of Units (SI units) will be used for the analysis. The abnormality in laboratory parameters will be summarized by treatment group.

Values outside the normal range (N) will be categorized as H (above the normal range) or L (below the normal range) based on the reference range of the Safety Laboratories. Shift tables will be presented showing the number of subjects per treatment group with N, H or L at the Baseline (Week 0) to EOT (Week 12). Laboratory test results will be listed by including laboratory blood tests, which are to only be performed at screening and abnormal values outside normal ranges will be flagged.

The following laboratory test parameters will be summarized:

Laboratory Test	**Parameters**
Haematology	Haemoglobin, Haematocrit, Platelet count, Red blood cell count, White blood cell count and differential, Basophils, Eosinophils, Monocytes, Neutrophils and Lymphocytes
Biochemistry	Alkaline Phosphatase, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Gamma-glutamyl transpeptidase, Phosphorous, Potassium, Uric acid, Bilirubin (total), Protein (total), Creatinine, Follicle-stimulating hormone [Females only. To be taken only if there is clinical concern about the subject's menopausal status], Human chorionic gonadotrophin [Pregnancy test on women of childbearing potential only]
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 [Performed only if required, based on urinalysis results]

Metabolic indicators	Glucose, fasting, Cholesterol, Triglycerides, High-density lipoprotein-cholesterol, Low-density lipoprotein-cholesterol, HbA1c, Very Low-density lipoprotein (VLDL) Cholesterol

7.8.3 Electrocardiogram

Descriptive statistics for absolute value and absolute change from Baseline for protocol specified laboratory parameters of heart rate, RR, PR, QRS, and QT (uncorrected) and QTc (corrected) interval, QTcF will be presented for scheduled visits by treatment group and overall.

Shift tables will be presented for overall ECG result showing the number of subjects per treatment group with Normal, Abnormal without Clinical Significance, and Abnormal with Clinical Significance at the Baseline to post-dose scheduled visits.

ECG data will be listed.

7.8.4 Nerve Function Monitoring (NFM)

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 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 and approximate same time of day. Measurements will be taken twice for each assessed nerve in both the left and right extremity. Two measures for each test will be obtained and averaged.

7.8.4.1 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 (maximum score per symptom is 3.66). A total score of > 6 would exclude the subject from the study.

Descriptive statistics for absolute value and absolute change from Baseline for total NTSS-6 score and each score per symptom will be presented for screening, Baseline (Week 0), Interim (Week 4), Interim (Week 8) EOT (Week 12) and Follow-up (4 weeks post last dose of study drug) visits by treatment group and overall. The subjects with total NTSS-6 score> 6 will also be summarized by treatment group and overall for screening, Baseline (Week 0), Interim (Week 4), Interim (Week 8) EOT (Week 12) and Follow-up (4 weeks post last dose of study drug) visits. NTSS-6 data will be listed.

7.8.4.2 Toronto Clinical Neuropathy Score (TCNS)

The neurological examination will cover all aspects of the Toronto Clinical Neuropathy Score (TCNS). Following TCNS data[15] will be collected.

Symptom scores (0-6)	Reflex scores (0-8)	Sensory test scores (0-5)
Foot	Knee reflex	Pinprick
Pain	Ankle reflex	Temperature
Numbness		Light touch
Tingling		Vibration
Weakness		Positioin
Ataxia		
Upper-limb symptoms		
Symptom scores: present=1; absent=0.		
Reflex scores: absent=2; reduced=1, normal=0 for each side (right and left)		
Sensory test scores: abnormal (for any side, left or right)=1, normal=0		

The total TCNS score (0 – 19) is sum of all items of TCNS[15].

Descriptive statistics for absolute value and absolute change from Baseline for total TCNS score will be presented for screening, Baseline, Interim (Week 4), Interim (Week 8) EOT (Week 12) and Follow-up (4 weeks post last dose of study drug) visits by treatment group and overall. The abnormal results for any sensory test from the TCNS will also be summarized by treatment group and overall for screening, Baseline (Week 0), Interim (Week 4), Interim (Week 8) EOT (Week 12) and Follow-up (4 weeks post last dose of study drug) visits. TCNS data will be listed.

7.8.4.3 Neurography (SNAP, CMAP and NCV)

Neurography (nerve conduction velocity and amplitude) of peripheral sensory and motor nerves will be tested. Measurements will be taken twice for each assessed nerve in both the left and right extremity. Two measures for each test will be obtained and averaged. Descriptive statistics for absolute value and absolute change from Baseline for neurography (SNAP, CMAP and NCV – sensory nerve and motor nerve assessment) data will be presented for screening, Baseline (Week 0), Interim (Week 4), Interim (Week 8), EOT (Week 12), Follow-up (4 weeks post last dose of study drug) by treatment group and overall. Neurography data will be listed.

7.8.5 Columbia Suicide Severity Rating Scale (CSSRS)

The CSSRS is a measure of suicidal ideation and behaviour. The below mentioned endpoints will be summarized descriptively by visit [wherever applicable]. Total score for past 6 months [screening visit] will be the Baseline value[14].

CSSRS Endpoints

1. Suicidal Ideation Score (1 – 5): The maximum suicidal ideation category present at the assessment. Assign a score of 0 if no ideation is present.
2. Suicidal ideation (yes, no): A "yes" answer at any time during treatment to any one of the suicidal ideation questions on the CSSRS.
3. Suicidal behaviour (yes, no): A "yes" answer at any time during treatment to any one of the suicidal behaviour questions on the CSSRS.
4. Suicidal ideation or behaviour (yes, no): A "yes" answer at any time during treatment to any one of the suicidal ideation and behaviour questions on the CSSRS.
5. Treatment-emergent suicidal ideation compared to recent history (yes, no): An increase in the maximum suicidal ideation score during treatment from the maximum suicidal ideation category during a specific pre-treatment period (CSSRS scales taken during the specified pre-treatment period; excludes "lifetime" scores from the Baseline CSSRS scale or Baseline/Screening CSSRS scale).
6. Treatment-emergent serious suicidal ideation compared to recent history (yes, no): An increase in the maximum suicidal ideation score to 4 or 5 on the CSSRS during treatment from not having serious suicidal ideation (scores of 0-3) during a specified pre-treatment period (CSSRS scales taken during the specified pre-treatment period; excludes "lifetime" scores from the Baseline CSSRS scale or Baseline/Screening CSSRS scale).
7. Emergence of serious suicidal ideation compared to recent history (yes, no): An increase in the maximum suicidal ideation score to 4 or 5 on the CSSRS during treatment from no suicidal ideation (scores of 0) during a specified pre-treatment period (CSSRS scales taken during the specified pre-treatment period; excludes "lifetime" scores from the Baseline CSSRS scale or Baseline/Screening CSSRS scale).
8. Improvement in suicidal ideation at a time point of interest compared to Baseline (yes, no): An improvement in this endpoint can be considered as a decrease in suicidal ideation score at the time point of interest (e.g., the last measurement during treatment) from the Baseline measurement (e.g., the measurement taken just prior to treatment).
9. Emergence of suicidal behaviour compared to all prior history (yes, no): The occurrence of suicidal behaviour during treatment from not having suicidal behaviour prior to treatment (includes "lifetime" and/or "screening" scores from the Baseline CSSRS scale, Screening CSSRS scale, or Baseline/Screening CSSRS scale, and any "Since Last Visit" from the Since Last Visit CSSRS scales taken prior to treatment.

Numbers of subjects with "yes" answer to each question for suicidal ideation and suicidal behaviour, and CSSRS endpoint 2 – 4 (Suicidal ideation, Suicidal behaviour, and Suicidal ideation or behaviour) will be summarized by treatment group and overall.

Number of subjects with events per CSSRS endpoint 5-9 (Treatment-emergent suicidal ideation compared to recent history, Treatment-emergent serious suicidal ideation compared to recent history, Emergence of serious suicidal ideation compared to recent history, Improvement in suicidal ideation at a time point of interest compared to Baseline and Emergence of suicidal behaviour compared to all prior history) will be summarized by treatment group and overall.

Shift tables will be presented showing the number of subjects per treatment group with 'No suicidal ideation or behaviour', 'Suicidal ideation' or 'Suicidal behaviour' at the Baseline to post-treatment. Subjects with both 'Suicidal ideation' and 'Suicidal behaviour' are included in the 'Suicidal behaviour' category.

Shift tables will be presented for Suicidal Ideation Score (CSSRS endpoint 1) showing the number of subjects per treatment group with maximum score 0 - 5 at the Baseline to post-treatment.

CSSRS data will be listed.

7.8.6 Other Safety Endpoints and Analyses

Other safety endpoints of vital signs and physical examination data will be summarized or listed. Safety analysis set will be used for the analyses.

Vital Signs

Descriptive statistics for absolute value and absolute change from Baseline for protocol specified vital sign parameters of blood pressure, heart rate, respiratory rate and oral temperature will be presented for scheduled visits by treatment group and overall. Vital signs data will be listed.

Physical Examination

Physical examination data will be listed.

7.9 Pharmacokinetics (PK) /Pharmacodynamics (PD) Endpoints Analyses

PK plasma and PD parameters will be assessed using the PK/ PD set, respectively.

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.

Xanamem™ concentrations will be summarized descriptively by treatment group, visit and time point.

PD parameters of ACTH, DHEAS, androstenedione and testosterone will be summarized for absolute values, change from baseline and % change from baseline.

Sub-group analysis will be performed by gender for PK/PD data. PK/PD data sampling details will be listed.

7.10 Other Exploratory Endpoints Analyses

The other exploratory endpoints will be summarized for safety analysis set with actual treatment group received. The following other endpoints will be summarized.

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

7.10.1 Metabolic Function

Descriptive statistics for absolute value and absolute change from Baseline for protocol specified laboratory parameters of lipids [cholesterol, triglycerides, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol], supine systolic and diastolic blood pressure, glucose, HbA1c, body weight, BMI will be presented for scheduled visits by treatment group and overall. International System of Units (SI units) will be used for the analysis.

7.11 Subgroup Analyses

To explore the homogeneity of the treatment effect across relevant patient subsets, following subgroup analysis will be performed for efficacy endpoints as specified.

- Baseline CDRGlobal score (0.5 vs 1.0) : all primary and secondary efficacy endpoints if at least 25% of subjects are in both groups.
- Baseline HbA1c (lower 30% vs upper 30%) : co-primary efficacy endpoints
- Baseline Glucose level (lower 30% vs upper 30%) : co-primary efficacy endpoints

7.12 Statistical Analysis Plan for Additional Analyses to be Conducted by McCloud Consulting Group After Database Lock

Any additional analyses conducted after database lock performed by McCloud Consulting Group (MCG) will be specified in the document 'MCG ACW002 XanADu Statistical Analysis Plan for Additional Analyses Conducted After Database Lock'. The analyses to be conducted by MCG may include, but are not limited to, analyses of cortisol data which will not be available until after the date of database lock, and additional subgroup analyses planned after reviewing the final unblinded study results.

8.0 HANDLING OF MISSING VALUES

In general, for all variables only the observed data from the patients will be used in the analysis.

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.

No imputation of values for other missing data will be performed, unless specified, for e.g. sensitivity analysis for primary efficacy endpoints.

Adverse events with missing causal drug relationship will be summarized as related.

Missing safety data will not be replaced, except for AE and Concomitant Medication dates as described below.

Adverse Event:

If due to partial dates or times it is not possible to definitively conclude that an AE is not treatment emergent, then a conservative approach will be taken into account whereby it will be classified as a TEAE, e.g. if the first dose date is "13May" and the AE starts in "May", then that AE will be classified as a TEAE, unless the AE stop date precludes this (i.e. the AE stop date is definitively prior to the first dose date).

Some more imputation scenarios:

If onset date is missing or partial, but stop date is prior to first dose date, then onset date is set to January 1st on the same year of stop date.

If onset date is completely missing, onset date is set to date of first dose.

If (year is present and month and day are missing) or (year and day are present and month is missing):

If year = year of first dose, then set month and day to month and day of first dose

If year < year of first dose, then set month and day to December 31st unless the calculation results in a negative time duration.

If year > year of first dose, then set month and day to January 1st.

If month and year are present and day is missing:

If year = year of first dose and

month = month of first dose then set day to day of first dose date

month < month of first dose then set day to last day of month

month > month of first dose then set day to first day of month

If year < year of first dose then set day to last day of month

If year > year of first dose then set day to first day of month

For all other cases, set onset date to date of first dose.

Concomitant Medication Dates:

Missing or partially missing medication date and prior or concomitant medication determination:

If due to partial dates it is not possible to categorize a medication as prior or concomitant, then a conservative approach will be taken into account whereby it will be classified as such, e.g. if the first dose date is "13May" and another medication is started in "May", then that medication will be classified as both prior and concomitant, unless the medication stop date precludes one of these classifications.

Some more imputation scenarios:

If start date is completely missing, start date will not be imputed.

If (year is present and month and day are missing) or (year and day are present and month is missing), set month and day to January 1.

If year and month are present and day is missing, set day to 1st day of month.

If end date is completely missing, end date will not be imputed.

If (year is present and month and day are missing) or (year and day are present and month is missing), set month and day to December 31.

If year and month are present and day is missing, set day to last day of the month.

9.0 INTERIM ANALYSIS

9.1 Introduction

One interim analysis is planned to be performed when approximately 50 subjects corresponding to FAS completed the study to make a decision on early discontinuation with efficacy on the basis of an analysis of covariance (ANCOVA) for the change in ADCOMs/ADAS-Cog v14 score from Baseline (Week 0) to Week 12/EOT. To adjust the overall probability of type I errors to 0.05, 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. 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.

9.2 Data Safety Monitoring Board (DSMB)

A DSMB must be established to independently monitor safety and efficacy data as well as operation of the study. After each meeting, the DSMB will provide advice on whether the study should be continued, modified, or discontinued on the basis of the toxicities observed. The DSMB will also review the results of the interim analysis and determine whether these data meet the criteria for stopping the study early for efficacy. Detailed tasks of the DSMB will be described in a separate DSMB charter.

9.3 Analysis Population for Interim Analysis

For efficacy endpoints, the FAS will be used for the interim analysis.

For safety endpoints, the Safety Analysis Set will be used for the interim analysis.

Each analysis set is defined in the section 6.0.

9.4 Cutoff Data for Interim Analysis

Cutoff date will be the time point when approximately 50 subjects corresponding to FAS completed the study with the primary efficacy assessments at Week 12/EOT. All data available at the cutoff will be included in the interim analysis.

9.5 Endpoint for Interim Analysis

The following endpoints will be analysed in this interim analysis:

Efficacy;

Primary efficacy endpoints:

- ADCOMS
- ADAS-Cog

Secondary efficacy endpoints:

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

Safety;

- Laboratory values
- Incidence of AEs
- NFM

PK/PD;

- Plasma concentrations of Xanamem™

The details of analysis on efficacy, safety and PK/PD endpoints are presented under SAP section 7.7 efficacy endpoints and analysis, 7.8 safety endpoints and analysis and 7.9 PK/PD endpoint analyses.

10.0 CHANGES FROM ANALYSIS METHODS PLANNED IN THE PROTOCOL

Not Applicable

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12.0 APPENDIX

Appendix 1: Schedule of Activities

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						
PK blood sample [7]		X	X	X		X		X
Safety laboratory sample (biochemistry, haematology and urine examination)	X	X	X	X		X	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**	
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 of protocol

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 of protocol. 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 of protocol.).

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 of protocol.

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 of protocol. 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.

15 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 of protocol).

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.

Appendix 2: Classification of Visits Window

Timing of assessment (days relative to Treatment [a])	Visit	Visit Name to display for Analysis	Study Day (Relative Day) [a]
Weeks -1 to -4	Screening	Screening	-28 ~ -1
Week 0*	Baseline	Baseline (Week 0)	1
Week 4 (± 4 days)	Interim	Interim (Week 4)	29 (25 – 33)
Week 8 (± 4 days)	Interim	Interim (Week 8)	57 (53 – 61)
Week 12 (± 4 days)	EOT	EOT (Week 12)	85 (81 - 89)
4 Weeks Post Last Dose of Study Drug (± 4 days)	Follow-up	Follow-up (4 weeks post last dose of study drug)	28 (24 ~ 32) days after last dose of study drug [b]

* It also depends on Baseline definition of each variable.

a. Day 1 is the day of first dose of treatment.

b. calculate study day (relative day) based on last dose of study drug

Appendix 3: Scoring Details of Efficacy Variables

Alzheimer's Disease COMposite Score (ADCOMs)

ADCOMs score is composite score derived from ADAS-Cog v14, CDR-SOB, and MMSE.

The resultant composite score, ADCOMS, is a weighted linear combination of the remaining individual scale items in the final fitted PLS model using the corresponding PLS coefficients as weighting factors see the table. The range of ADCOMS is between 0 and 1.97. Items making contributions to ADCOMS include 4 items of the ADAS-cog; two items of the MMSE, and all six items of the CDR-SOB.

Items selected in the Wold's PLS model and their corresponding PLS coefficients [7]

Scale	Item name	PLS coefficients
ADAS-cog	Delayed word recall	0.008
	Orientation	0.017
	Word recognition	0.004
	Word finding difficulty	0.016
MMSE	Orientation time	0.042
	Drawing	0.038
CDR-SB	Personal care	0.054
	Community affairs	0.109
	Home and hobbies	0.089
	Judgment and problem solving	0.069
	Memory	0.059
	Orientation	0.078

ADAS-cog: Alzheimer's Disease Assessment Scale–cognitive subscale; CDR-SB: Clinical Dementia Rating, sum of boxes; MMSE: Mini-Mental State Exam; PLS: partial least squares.

The ADCOMs score, which is rescaled decline, will be derived based on the coefficients and corresponding items selected from PLS regression in above table:

$$\begin{aligned}\text{ADCOMs score} &= 0.008 * Delayed\ word\ recall\ (ADAS-cog) + 0.017 \\ &* Orientation(ADAS-cog) + 0.004 * Word\ recognition(ADAS-cog) \\ &+ 0.016 * Word\ finding\ difficulty(ADAS-cog) + 0.042 \\ &* Orientation\ time(MMSE) + 0.038 * Drawing(MMSE) + 0.054 \\ &* Personal\ care\ (CDR-SB) + 0.109 * Community\ affairs(CDR-SB) \\ &+ 0.089 * Home\ and\ hobbies(CDR-SB) + 0.069 \\ &* Judgement\ and\ problem\ solving(CDR-SB) + 0.059 \\ &* Memory\ (CDR-SB) + 0.078 * Orientation(CDR-SB)\end{aligned}$$

It is careful to use the reversed score with regard to MMSE (maximum score for each item – MMSE score of each item). It means that for the derivation of ADCOMS score, (5- MMSE score of ‘Orientation time’) will be used for ‘Orientation time’ and (1-MMSE score for ‘Drawing’) will be used for ‘Drawing’.

Rey Auditory Verbal Learning Test (RAVLT)

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. Then the examiner 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[8].

The RAVLT test and its score details are given below:

RAVLT	**Scoring**
Recall List A	Total number of correct words
Recall List B	Number of correct words
Final recall of List A	Number of correct words

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

The ADAS-cog v14[9] includes the following 14 items, with a Total scoring range of 0 – 90.

ADAS Cog Item	Scoring Details
Item 1 - Word Recall Task	On this task, the participant is given three trials to learn a list of ten high-frequency, high imagery nouns. The ten words are printed in block letters on white cards. **Scoring:** The participant's score is the mean number of words not recalled across the three trials (maximum score = 10). The score should be calculated to two decimal places. If any of the three trials is not completed for any reason, then the task is considered incomplete and a missing data code must be assigned to the item score.
Item 2 - Naming Objects and Fingers	For this task, the participant is asked to name 12 randomly presented real objects, with high (flower, bed, whistle, pencil), medium (rattle, mask, scissors, comb) and low (wallet, harmonica, stethoscope, tongs) frequency values. The participant is also asked to name the fingers of his/her dominant hand. **Scoring:** 0 = 0-2 items (objects and fingers) named incorrectly 1 = 3-5 items (objects and fingers) named incorrectly 2 = 6-8 items (objects and fingers) named incorrectly 3 = 9-11 items (objects and fingers) named incorrectly 4 = 12-14 items (objects and fingers) named incorrectly 5 = 15-17 items (objects and fingers) named incorrectly
Item 3 - Commands	This task is designed to assess receptive speech. The participant is asked to carry out five separate commands with 1 to 5 steps per command. **Scoring:** 0 = all commands correct 1 = 1 command incorrect 2 = 2 commands incorrect 3 = 3 commands incorrect 4 = 4 commands incorrect 5 = all 5 commands incorrect
Item 4 - Constructional Praxis	This test assesses the participant's ability to copy four geometric forms ranging from a very simple one (circle) to a fairly difficult one (cube). **Scoring:** 0 = all 4 drawings correct 1 = 1 form drawn incorrectly 2 = 2 forms drawn incorrectly 3 = 3 forms drawn incorrectly 4 = 4 forms drawn incorrectly (but one or more side/section of at least one shape drawn) 5 = No figures drawn, no recognizable attempt at drawing any side/section of any figure
Item 5 - Ideational Praxis	This task is designed to determine whether the participant can perform a familiar but complex sequence of actions. **Scoring:** 0 = all components performed correctly 1 = failure to perform 1 component

ADAS Cog Item	Scoring Details
	2 = failure to perform 2 components 3 = failure to perform 3 components 4 = failure to perform 4 components 5 = failure to perform 5 components
Item 6 - Orientation	In this task, the participant is asked 8 questions regarding his or her orientation to person, place and time. **Scoring:** One point is given for each incorrect response (maximum = 8).
Item 7 - Word Recognition Task	On this task the participant is given one trial to learn a list of 12 words. **Scoring:** There are 24 opportunities for error in the one trial of recognition, including the 12 learning (target) words and 12 distractor words. The participant could incorrectly identify a distracter word as one of the learning words they were just shown, or they could incorrectly say they were not shown a learning word. While all incorrect responses should be noted on the form by the tester (there are 0-24 errors possible in the trial), the maximum error score is 12. If the participant makes 13-24 errors, the score for the trial remains at 12. Dr. Mohs has stated that the maximum error score is 12 per trial as this is the average number of errors that would be made by a person guessing randomly.
Item 8 - Language	This item is a global rating of the quality of speech, i.e., lack of clarity, difficulty in making oneself understood with words. **Scoring:** 0 = participant speaks clearly and/or is understandable 1 = very mild: one instance of lack of understandability 2 = mild: participant has difficulty less than 25% of the time 3 = moderate: participant has difficulty 25-50% of the time 4 = moderately severe: participant has difficulty more than 50% of the time 5 = severe: one or two word utterances; fluent, but empty speech; mute
Item 9 - Comprehension of spoken language	This item evaluates the participant's ability to understand spoken language. **Scoring:** 0 = None: participant understands. 1 = Very Mild: one or two instances of misunderstanding. 2 = Mild: 3–5 instances of misunderstanding. 3 = Moderate: requires several repetitions and rephrasings. 4 = Moderately Severe: participant only occasionally responds correctly; i.e., yes-or-no questions. 5 = Severe: participant rarely responds to questions appropriately; not due to poverty of speech.
Item 10 - word finding difficulty	Along with Spoken Language Ability, this item rates impairment in expressive speech, but it rates only word finding difficulty, whereas Spoken Language Ability is a more global rating of the extent to which the participant can communicate verbally. **Scoring:** 0=no evidence of word finding difficulty in spontaneous speech 1=very mild: 1 or 2 instances, not clinically significant 2=mild: noticeable circumlocution or synonym substitution 3=moderate: loss of words without compensation on occasion

ADAS Cog Item	Scoring Details
	4=moderately severe: frequent loss of words without compensation 5=severe: nearly total loss of content of words; speech sounds empty; 1-2 word utterances
Item 11 - Remembering Test Instructions	This item evaluates the participant's ability to remember the instructions given for the Word Recognition task only. The score is based on the number of instruction repetitions only after the first two words. No other tasks or aspects of the ADAS-cog are considered when scoring this item. **Scoring:** 0 = No reminders given in Word Recognition 1 = very mild: reminded once 2 = mild: reminded 2 times 3 = moderate: reminded 3 or 4 times 4 = moderately severe: reminded 5 or 6 times 5 = severe: reminded 7 or more times
Item 12 - Maze	In this task, the participant is asked to find his or her way through a maze with a pencil, without hitting a dead end. The participant is told he or she may pause to make a decision. The task is halted after the participant makes two errors or 240 seconds has elapsed. An example maze is given for practice before the participant attempts the test maze. **Scoring:** The score is the time to completion or the time at which the participant made the second error (maximum time = 240 seconds). The score from the practice task is not included. The score is calculated only from the timed performance task.
Item 13 - Number Cancellation	In this task, the participant is asked to cross off as many target digits as possible in 45 seconds. **Scoring:** The score is the number of target items correctly crossed off in 45 seconds, minus the number of incorrectly crossed off items, and minus the number of reminders given. The score from the practice task is not included. The score is calculated only from the timed performance task.
Item 14 - Delayed Recall	If added, this item adds 10 points to the possible total ADAS-cog score. In this task, the participant is asked to recall the 10 words presented during the Word Recall task. There is one trial of recall. This task is administered following completion of the COMMANDS and CONSTRUCTIONAL PRAXIS items. **Scoring:** The score is the number of words not recalled (Maximum score = 10).
Final	Sum score of 14 items

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

The CDR-SOB includes the following six items, with a Total scoring range of 0 – 18. Only caregiver/ informant details are to be collected [10].

CDR	**Scoring**
Domain 1: Memory Questions	Scoring (0, 0.5, 1, 2, 3) for replies of Informant
Domain 2: Orientation	Scoring (0, 0.5, 1, 2, 3) for replies of Informant
Domain 3: Judgment and Problem Solving	Scoring (0, 0.5, 1, 2, 3) for replies of Informant
Domain 4: Community Affairs	Scoring (0, 0.5, 1, 2, 3) for replies of Informant
Domain 5: Home and Hobbies	Scoring (0, 0.5, 1, 2, 3) for replies of Informant
Domain 6: Personal Care	Scoring (0, 1, 2, 3) for replies of Informant
	Total score = Sum of the Boxes

Mini-Mental Status Examination (MMSE)

The MMSE is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment11 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. The total score range is 0 – 30.

Neuropsychiatric Inventory (NPI)

The NPI was constructed to survey neuropsychiatric disorders in demented patients[12]. NPI having 12 domains and 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 10 domains [domain A to L]. (total NPI-score minimum is 0 and maximum 144). The 12 item score is being used. Total distress is sum of distress of 12 items of the NPI distress questions [13].

NPI	Scoring
Domain A: Delusions	Score of Frequency (1 - 4), Score of Severity (1 - 3), Distress (0-5)
Domain B: Hallucinations	Score of Frequency (1 - 4), Score of Severity (1 - 3), Distress (0-5)
Domain C: Agitation / Aggression	Score of Frequency (1 - 4), Score of Severity (1 - 3), Distress (0-5)
Domain D: Depression/Dysphoria	Score of Frequency (1 - 4), Score of Severity (1 - 3), Distress (0-5)
Domain E: Anxiety	Score of Frequency (1 - 4), Score of Severity (1 - 3), Distress (0-5)
Domain F: Elation/Euphoria	Score of Frequency (1 - 4), Score of Severity (1 - 3), Distress (0-5)
Domain G: Apathy / Indifference	Score of Frequency (1 - 4), Score of Severity (1 - 3), Distress (0-5)
Domain H: Disinhibition	Score of Frequency (1 - 4), Score of Severity (1 - 3), Distress (0-5)
Domain I: Irritability / Lability	Score of Frequency (1 - 4), Score of Severity (1 - 3), Distress (0-5)
Domain J: Aberrant Motor Behavior	Score of Frequency (1 - 4), Score of Severity (1 - 3), Distress (0-5)
Domain K: Sleep	Score of Frequency (1 - 4), Score of Severity (1 - 3), Distress (0-5)
Domain L: Appetite and eating disorders	Score of Frequency (1 - 4), Score of Severity (1 - 3), Distress (0-5)

Frequency is rated as: 1 - Occasionally - less than once per week; 2 - Often - about once per week; 3 - Frequently - several times per week but less than every day; 4 - Very frequently - daily or essentially continuously present.
Severity is rated as: 1 - Mild - produces little distress in the patient; 2 - Moderate - more disturbing to the patient but can be redirected by the caregiver; 3 - Severe - very disturbing to the patient and difficult to redirect.
Distress is scored as: 0 - no distress; 1- minimal; 2 – mild; 3 – moderate; 4 - moderately severe; 5 - very severe or extreme

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

NTB score is the sum of correct response of Category Fluency Test (CFT) and Controlled Oral Word Association – Test (COWAT). The following scoring table will explain it very clearly.

NTB (COWAT and CFT)	Scoring
COWAT	Total number of correct words
CFT	Total correct responses
	Total incorrect responses
	Total intrusions
Total	COWAT + CFT(Correct response)