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European Prevention of Alzheimer's Dementia Consortium

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D2.11 -Master Statistical Analysis Plan for the EPAD Platform Proof-of-Concept Trial

WP2 – Statistical/Methodology Engine Room

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Final

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DEFINITIONS

- Partners of the EPAD Consortium are referred to herein according to the following codes:
  - **Janssen**. Janssen Pharmaceutica NV (Belgium)
  - **UEDIN**. The University of Edinburgh (United Kingdom)
  - **UOXF.** Masters and Scholars of the University of Oxford (United Kingdom)
  - **BBRC.** BarcelonaBeta Brain Research Center (Spain)
  - **SYNAPSE.** Synapse Research Management Partners S.L (Spain)
  - **KI.** Karolinska Institutet (Sweden)
  - **VUMC.** Stichting VUmc (Netherlands)
  - **UCAM.** Masters and Scholars of the University of Cambridge (United Kingdom)
  - **MRC.** Medical Research Council (United Kingdom)
  - **BERRY.** Berry Consultants LLP (United Kingdom)
  - **UNIGE.** Université de Genève (Switzerland)
  - **RUMC.** Stichting Katholieke Universiteit (Netherlands)
  - **CU.** Cardiff University (United Kingdom)
  - **CHUT.** Centre Hospitalier Universitaire de Toulouse (France)
  - **IQVIA.** IQVIA, Ltd (United Kingdom)
  - **AE.** Alzheimer Europe (Luxemburg)
  - **EMC.** Erasmus Universitair Medisch Centrum Rotterdam (Netherlands)
  - **APHP.** Hôpital de la Salpêtrière (France)
  - **INSERM.** Institut National de la Santé et de la Recherche Médicale (France)
  - **ULEIC.** University of Leicester (United Kingdom)
  - **IXICO.** IXICO Technologies Ltd (United Kingdom)
  - **ARACLON.** Araclon Biotech S.L (Spain)
  - **FRAUNHOFER.** Fraunhofer-Gesellschaft zur Förderung der angewandten Forschung e.V. (Germany)
  - **Eisai.** Eisai Inc (United States)
  - **SARD.** Sanofi-Aventis Recherche & Développement (France)
  - **NOV.** Novartis Pharma AG (Switzerland)
  - **BI.** Boehringer Ingelheim International GmbH (Germany)
  - **Eli Lilly.** Eli Lilly and Company Ltd (United Kingdom)
  - **HLU.** H. Lundbeck A/S (Denmark)
  - **Takeda EU.** Takeda Development Centre Europe Ltd (United Kingdom)
  - **AC Immune.** AC Immune SA (Switzerland)
  - **Biogen**. Biogen Idec Limited (United Kingdom)
  - **Amgen.** Amgen NV (Belgium)
  - **Pfizer.** Pfizer Limited (United Kingdom)
  - **UCB.** UCB Biopharma SPRL (Belgium)
  - **ARIDHIA**. Aridhia Informatics Ltd (United Kingdom)
  - **ROCHE**. F. Hoffmann - La Roche (Switzerland)
  - **UKK**. University Hospital of Cologne (Germany)
  - **MSD**. Merck Sharp & Dohme (United States)

- **Grant Agreement.** The agreement signed between the beneficiaries and the IMI JU for the undertaking of the EPAD project (115736).
- **Project.** The sum of all activities carried out in the framework of the Grant Agreement.
- **Work plan.** Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Annex I to the Grant Agreement.
- **Consortium.** The EPAD Consortium, comprising the above-mentioned legal entities.
- **Project Agreement.** Agreement concluded amongst EPAD participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

EXECUTIVE SUMMARY

The purpose of the EPAD Proof-of-concept (PoC) Platform Trial Protocol is to study multiple interventions for the secondary prevention of Alzheimer's dementia in people with prodromal or preclinical Alzheimer's disease. This document is the corresponding Statistical Analysis Plan (SAP). As the PoC Platform Trial was not initiated, the SAP has not been finalized. The role of this document is to make the material available for future use. Consequently, it has not been a priority to make the document have a finished appearance. In other words, the document includes unfinished parts.

As a master SAP, a key point is to describe the data sharing between the Intervention-specific trials and the consequences of this sharing. A second point is to describe the common methods, in particular, the interim analyses used to decide on whether the trials stop or continue. Each Intervention Specific Trial will have a dedicated SAP.

Each intervention specific trial will have interim analyses for efficacy made every 3 months, after 50 research participants have reached 12 months of follow-up. The primary endpoint is RBANS total score. The dataset for the analysis consists of all available data for the research participants in the intervention specific trial supplemented with placebo data from the other intervention specific trials within the relevant strata. The model is a Bayesian disease progression model, where the placebo group has an arbitrary development over time, in each of the up to four strata recruiting to the trial. The active treatment group is assumed to show a change from baseline multiplied by a common factor (CPRR: Cognitive Progression Rate Ratio), so a value below 1 means that the disease progression is delayed. If an interim analysis shows that the posterior probability of CPRR<0.90 is greater than 0.85, the intervention meets the success criterion. If the posterior probability of CPRR<0.90 is less than 0.05, the intervention is declared futile.

1. List of Abbreviations and Definitions of Terms

AE	Adverse Event
AESI	Adverse Event of Special Interest
Amsterdam-IADL	Amsterdam-Instrumental Activity of Daily Living
AR	Adverse Reaction
CDR-GS	Clinical Dementia Rating Scale Global Score
CDR-SB	Clinical Dementia Rating Scale- Sum of Boxes
CSF	Cerebro-Spinal Fluid
C-SSRS	Columbia–Suicide Severity Rating Scale
DSMB	Data Safety Monitoring Board
EPAD	European Prevention of Alzheimer's Disease
FSFV	First Subject First Visit (baseline) of the relevant IST
GDS	Geriatric Depression Scale
IDMC	Independent Data Monitoring Committee
ISA	Intervention Specific Appendix
ISA-POC	Intervention-specific Appendix Statistical Analysis Plan
IST	Intervention Specific Trial
LCS	Longitudinal Cohort Study
LSFV	Last Subject First Visit (baseline) of the relevant IST
MRI	Magnetic Resonance Imaging
NIH-EXAMINER	National Institutes of Health-Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research
PoC	Proof of Concept
PSC	PoC Steering Committee
PSQI	Pittsburgh Sleep Quality Index
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RP	Research Participant
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
STAI	State-Trait Anxiety Inventory
TIA	Cerebrovascular accident (stroke and/or transient ischemic attack
WML	White Matter Lesion

2. INTRODUCTION

EPAD (European Prevention of Alzheimer's Disease) is a project to develop an environment for studying Alzheimer's disease and then test multiple different interventions for the secondary prevention of Alzheimer's dementia in people with prodromal or preclinical Alzheimer's disease. The EPAD project is running across Europe with multiple partners from academia and the commercial sector.

The project is designed as a perpetual platform trial. This implies that there is a single Master Protocol dictating the conduct of the trial. The specific protocol for each intervention or combination of interventions that enters the platform trial is summarized by an Intervention Specific Appendix (ISA) to the Master Protocol. Each intervention specific trial is inferentially separate, meaning that conclusions and reports are done separately even though some placebo treated research participants may contribute to several such reports. Thus, there will not be considerations of type I error across intervention specific trials.

The overarching statistical analysis considerations of the trial are dictated in a single Master Statistical Analysis Plan (SAP) – this document. The specific SAP for each intervention specific trial is summarized by an appendix to the master SAP. In case of conflicting information between the Master SAP and the ISA, the ISA should be heeded.

An overview of the terminology is given in the table below

Generic name	Name in full trial	Name in substudy
Clinical trial	POC Platform trial	Intervention specific trial (IST) (Master protocol calls this Intervention-specific Appendix)
Protocol	Master protocol	Intervention-specific Appendix (ISA)
Statistical Analysis Plan	Master SAP (SAP)	Intervention-specific Appendix Statistical Analysis Plan (ISA-SAP)
Subject	Research Participant (RP)	Intervention specific trial participant
Population	Trial population	Intervention specific trial population (Master protocol calls this Intervention Cohort)
Interim analysis	- (not applicable)	Interim analysis (Master protocol calls this evolution analysis)

Three kinds of analyses will be performed: Interim analyses for the Independent Data Monitoring Committee (IDMC), interim analyses for the Data Safety Monitoring Board (DSMB) and final analyses. The below is trying to cover all three kinds. No calculations will involve unblinded data from active treatments from several ISTs unless agreed by all owners of compounds involved in the calculation. Interim analyses will be done every three months; at the same time for all ongoing ISTs but as said above there will be separate analyses for each IST; involving all research participants from the relevant substudy and selected placebo research participants from other ISTs (details described in Section 7). For each IST, there will be one final analysis, which is done, when all Intervention specific trial participants have reached the safety follow-up visit. As concurrent placebo research participants may continue to participate after end of an IST, the exact cut-off date will be decided in each case.

3. Responsibilities

Final analysis: IQVIA

Interim analyses for IDMC: IQVIA using software provided by Berry Consultants. There is one IDMC handling the master trial.

Interim analyses for DSMB: IQVIA. There is one DSMB handling the master trial.

4. Objectives

The ISA may add objectives referring to the IST.

4.1. Primary objective(s)

The primary objective of this clinical trial is to assess the efficacy and safety of multiple interventions compared to placebo, in research participants showing evidence of preclinical to prodromal Alzheimer's disease for the secondary prevention of Alzheimer's dementia. The interventions can be tested simultaneously, with the potential for new interventions to be added sequentially, and perpetually. The primary objective of the trial is to evaluate the potential for a reduction in the rate of clinical decline as measured by the primary cognitive clinical endpoint.

4.2. Secondary objective(s)

The secondary objectives of the trial are to evaluate the potential for a reduction in decline or improvement in the specific cognitive domains as measured by the secondary cognitive outcomes (RBANS domains and other cognitive endpoints) as well as reduction in decline or improvement in the biological and other clinical endpoints.

4.3. Exploratory objective(s)

The exploratory objectives of the trial are to evaluate the potential for a reduction in decline or improvement in the specific cognitive domains as measured by the exploratory cognitive outcomes as well as reduction in decline or improvement in the biological and other clinical endpoints.

4.4. Safety objectives(s)

The safety of an intervention will be monitored throughout the trial.

5. Study Design

This is a multi-centre, multi-national, double-blind, randomized, placebo-controlled, adaptive, perpetual platform clinical trial to investigate the efficacy and safety of multiple drugs simultaneously or sequentially.

There will be multiple interventions, where the research participants on an intervention and its specific blinded placebo are labelled as the intervention specific trial population. Intervention specific trial populations may start at different time points in the course of the trial. Therefore, the double-blind will be maintained within an intervention specific trial population between the different arms in that cohort. Research participants will not be blinded to which intervention specific trial they participate in. For an intervention specific trial, the number of intervention arms versus placebo will be defined in the Intervention Specific Appendix. The randomization ratio within each intervention specific trial is 3:1 (total active arms: placebo). Each intervention arm within an intervention specific trial is labelled as a subarm.

This adaptive platform design will utilise common control research participants from multiple intervention specific trials and common minimum success and futility criteria evaluated at the interim analyses. The ISA may describe further adaptive features, referring to the IST, such as changes in allocation ratios for the active arms, when there are multiple active arms

Research participants who have been enrolled in the LCS for the below minimum time points will be invited to participate in the PoC trials (note that the criteria referring to CSF may have been assessed at an earlier time point):

1. For prodromal research participants they have completed Visit 2/Month 6 procedures in the EPAD LCS.

2. For preclinical research participants they have completed Visit 3/Month 12 procedures in the EPAD LCS.

The allocation procedure is illustrated in Figure 1. Research participants who provide consent at the transition visit will have an eligibility check done and then be randomly allocated to one of the ongoing Intervention-specific Trials in the EPAD PoC trial for which they are eligible. The participant will be informed of this allocation and provided with written information specific to the IST, then subject to consent they will begin screening procedures for the IST.

If eligibility criteria are fulfilled, they will then be randomized on a 3:1 ratio to the intervention active arm or placebo. If there are subarms for an intervention (doses, frequency) then a further randomization would determine the subarm.

In case of a screening failure, participants can be re-randomized as follows:

- Participants who fail to meet eligibility criteria for the Master Protocol will have the possibility to continue to be followed in the LCS until they are eligible for the PoC Platform Clinical Trial Master Protocol

- Participants who fail to meet eligibility criteria during the screening of an intervention will have the possibility to be re-assigned to another intervention for which they are eligible (except see below)

- Participants assigned to an intervention but who withdraw consent for personal reasons (eg, inconvenience of the intervention, mode of administration, etc.) will not be re-assigned to another intervention for 12 months. If a second withdrawal of consent after randomization to the Master Protocol occurs, the subject will be permanently discontinued from the EPAD studies including LCS.

The duration of treatment for each intervention, the follow-up period and the end of the intervention-specific trial will be described in the Intervention Specific Appendix. On the participant level, the trial duration can be up to four years.

At minimum, on-site visits will occur every 3 months during the first year and every 6 months for the remaining years of the trial.

The primary and secondary clinical outcomes will be assessed for all interventions every 6 months. More frequent assessments are discouraged because of the potential learning effects, which could lead to discrepancies between different assessments and therefore a potential bias in the results.

Evolution analyses will take place quarterly within the platform trial. At each of these evolution analyses a set of possible evolutions or adaptions that an intervention is eligible for will be checked.

1. An intervention can be found to be successful at modifying the progression of cognitive disease, which will be termed graduation. In this case the sponsor or responsible party will be informed of the successful graduation of the intervention. Upon meeting the criteria for success, no further subjects will be randomized in that IST, but subjects already in that IST may continue for the full, prespecified duration of treatment, if the ISA dictates continuing exposure. The ISA may also specify that exposure is halted upon success.

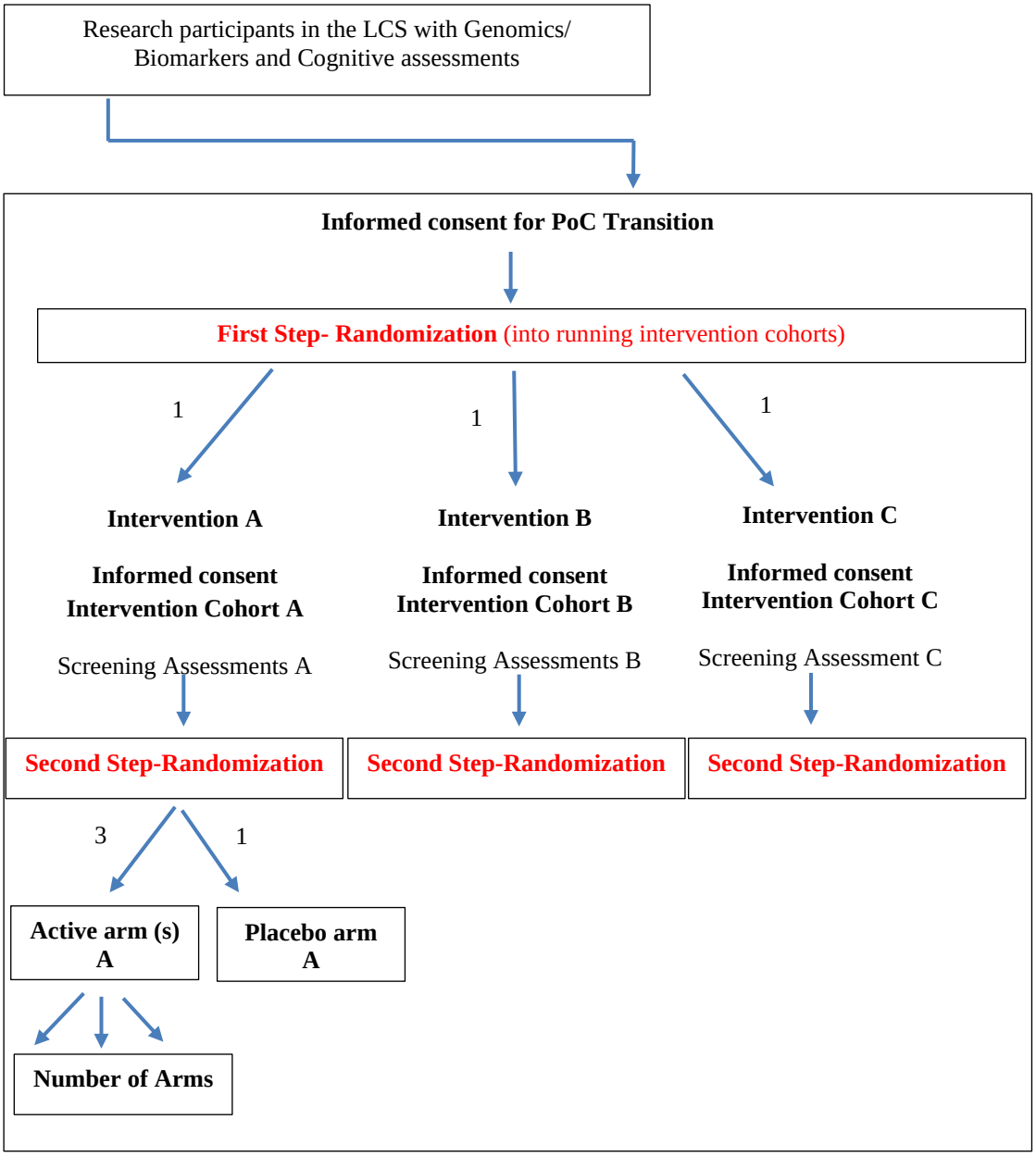
2. An intervention can be found to have failed to modify the progression of disease and be deemed futile. Upon meeting the criteria for futility, enrolment in that IST would be discontinued for that and all research participants in that IST (including placebo) would discontinue intervention use. Subjects may return to EPAD-LCS or after washout to another intervention if eligible.

3. Maximum exposure may be reached for an intervention. This implies the maximum time of follow-up for all research participants in an arm has been reached. In this case this is the end of the study for that intervention and all research participants in the respective IST would have completed treatment.

If an IST has multiple subarms then adaptive rules dictating the behaviour of these arms can be conducted. This can include stopping subarms, evolving subarms, and changing randomization probabilities among subarms. This will be detailed in the Intervention Specific Appendix.

Patients who are withdrawn from treatment will be followed-up; Visit 13 (see Master protocol) should be performed for all research participants who permanently discontinue the IST or complete their treatment period.

Figure 1. *Scheme of randomisation process.*



6. Definitions

Baseline: unless otherwise specified in the ISA, the value captured at Visit 2 (Day 1), before first dose.

Screening period 1: Screening period for the PoC trial Master Protocol. The research participants in the LCS eligible for the PoC trial will be contacted to enter the trial based on eligibility criteria of the Master Trial Protocol. The research participants should be enrolled in the LCS for at least 6 months prior to the screening visit (Visit 1). Screening period 1 starts at Visit 1 and ends at Visit 2.

Screening period 2: Screening period for an Intervention Specific Trial. At Visit 1, the research participant and the study partner will have to consent to participate to one specific intervention for which the research participant is eligible. Screening period 2 starts at Visit 1 and ends at Visit 2.

Treatment period: active treatment period for the intervention specific trial. Starts at Visit 2. The duration of the treatment period will be specified in the ISA.

Follow-up period: safety follow-up period for the intervention specific trial. The duration of the safety follow-up period will be specified in the ISA.

Withdrawal: A patient who withdraws from the study during the treatment period. Patients that complete the treatment period are considered completers.

7. Trial Endpoints

An intervention specific Appendix may choose to upgrade secondary or exploratory endpoints. This will have to be described in the Intervention Specific Appendix and approved by the Appendix Steering Committee.

7.1. Primary Endpoint(s)

The primary endpoint is the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)™ Total Scale Index Score .

The RBANS™ Total Scale Index Score is comprised of the total mean score of the following 5 indexes themselves comprised of 12 subtests:

1. Immediate Memory – List Learning and Story Memory
2. Visuospatial/Constructional – Figure Copy and Line Orientation
3. Language – Picture naming and Semantic Fluency
4. Attention – Digit Span and Coding
5. Delayed Memory – List Recall, List Recognition, Story Memory, and Figure Recall

The rate of decline during the treatment period of the intervention will be compared to placebo using the proportional disease progression model.

If the intervention owner requires an additional endpoint for decision making for an intervention, it will be specified in the Intervention Specific Appendix. This will not change the primary endpoint required in the Master Protocol and the Master SAP.

7.2. Intermediate Biomarker Primary Endpoint

Pharmacological interventions will be required to have already demonstrated target engagement, or if this has not been done, target engagement will have to be demonstrated during the course of the study. Failure to do so as determined by pre-specified criteria will lead to that particular Intervention Specific Appendix (ISA) being discontinued. If not demonstrated before participation into EPAD, the Intervention Specific Appendix will create rules to demonstrate target engagement on biomarker relevant to the proposed mechanism of action. Therefore, this endpoint can be optional if target of engagement has been already demonstrated.

7.3. Secondary endpoint(s)

7.3.1. Cognitive endpoints:

- The 5 RBANS™ indices and the 12 subtests comprising the RBANS™.
- The Following 5 cognitive domains
- RBANS index Attention/Executive Functioning: Digit Span & Coding
- RBANS index Verbal Episodic Memory: List Learning & Story Memory
- RBANS index Delayed Memory: List Recall, List Recognition, Story Recall & Figure recall
- RBANS index Visuospatial/Constructional: Figure Copy & Line Orientation
- RBANS index Language: Picture Naming & Semantic Fluency

- Dot Counting (NIH EXAMINER)
- Flanker (NIH EXAMINER)
- Favourites (University of California, San Francisco)

7.4. Exploratory endpoint(s)

7.4.1. Cognitive endpoints:

- Four Mountains Task (Cambridge Cognitive Neurosciences)
- Supermarket Trolley (University College London)

7.4.2. Other clinical endpoints:

- 30-item Geriatric Depression Scale (GDS-30 items)

- State-Trait Anxiety Inventory (STAI)
- Pittsburgh Sleep Quality Index (PSQI)
- Amsterdam Instrumental Activities of Daily Living Questionnaire (Amsterdam-IADL)
- Clinical Dementia Rating Scale- Global Scale (CDR-GS) and Sum of Boxes (CDR-SB)

7.4.3. Exploratory biomarker endpoints:

- Cerebrospinal fluid (CSF) biomarkers: beta-amyloid, t-tau, p-tau
- Neuroimaging parameters (Magnetic Resonance Imaging [MRI]): hippocampal and whole brain volume; vascular burden (white matter lesions [WML], infarcts, lacunes, microbleeds, superficial siderosis)

7.5. Safety endpoint(s)

Details of any specific safety assessments required for the trial drug will be reported in the Intervention Specific Appendix

7.5.1. Physical examination

A physical examination will be carried out as described in the Master Protocol Flow Chart section.

The physical examination will include, but not be limited to, general appearance, skin, neck, eyes, ears, nose, throat, breast, lungs, heart, abdomen, back, lymph nodes, extremities, and nervous system will be performed.

1. Body weight in kg (to the nearest 0.1 kg) will be measured at the visits indicated in the Flow Chart and the same scale will be used for all measurements

2. The height is measured at Visit 1 (screening) only. Height will be measured to the nearest cm. Height data obtained from the LCS can be used for this measure.

7.5.2. Vital Signs

Vital signs, including, but not limited to, systolic/diastolic blood pressure (including orthostatic measurement) and supine pulse rate (after 5 minutes rest) will be recorded at all the study visits, including the early End of Treatment Visit and the Follow-up-Visit, as indicated in the Master Protocol Flow Chart section.

Blood pressure and pulse rate including orthostatic measurements will be assessed supine and standing.

Clinically relevant abnormal findings that become apparent following baseline assessments will be reported as (S)AEs. 'Seriousness' will be defined, when required, in the Intervention Specific Appendix.

7.5.3. Safety laboratory parameters

The following comprises a minimum laboratory parameter set to be assessed for all interventions (as indicated in the Master Protocol Flow Chart section).

- Haematology: haematocrit, haemoglobin, erythrocyte count, white blood cell count (total and differential: lymphocytes, monocytes, neutrophils, eosinophils, basophiles), platelet count
- Serum chemistry: urea, uric acid, creatinine, creatinine clearance, protein total, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), alkaline phosphatase, total bilirubin, sodium, potassium, chloride, glucose, total cholesterol, triglycerides, bicarbonate
- Urinalysis: protein, glucose, urobilinogen, blood
- Drug abuse screen test in urine (planned at screening Visits only). The following drugs will be tested: marijuana, cocaine, opiates, methamphetamine, amphetamines, Phencyclidine, benzodiazepine, barbiturates, methadone, ecstasy, and oxycodone.

7.5.4. Electrocardiogram

ECG-recordings will be made at the time points indicated in the Master Protocol Flow Chart section. Additional, intervention specific ECG-recordings (including time points) may be detailed in the intervention specific appendix flow chart.

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 – V6) will be recorded using equipment provided by a central ECG vendor. The ECG record should include a minimum of 5 heart cycles (beats). The electronic record will be forwarded to a central ECG facility for evaluation. A report must be filed in the subject's records. The ECG provider will transfer the data to the Sponsor or designee. Electrode placement will be performed according to the method of Einthoven/Goldberger (ankles and wrists). At all timepoints, indicated in the Flow Chart, single ECGs will be recorded. ECG recordings at planned time points may be repeated for quality reasons like alternating current artefacts, muscle movements and electrode dislocation.

7.5.5. Suicidal risk assessed by the C-SSRS

Suicidal risk will be assessed in terms of suicidal behaviour and suicidal ideation using the Columbia–Suicide Severity Rating Scale (C-SSRS®).

Potential research participants will be assessed at the screening visit with the aim of excluding those with active moderate or severe symptomatology prior to the Screen Visit, or recent (or current) suicidal or suicide attempt according to the C-SSRS® (baseline/screening version). Potential research participants presenting with any suicidal behaviour or suicidal ideation will be excluded from participation in EPAD.

Subsequently, the C-SSRS® will be performed at every visit after baseline and as shown in the Flow Chart. If there is a positive response of suicide attempt or suicidal ideation by the research participant during the administration of the C-SSRS® during the treatment period, the appropriately qualified

clinician will immediately interview the research participant during the clinic visit and determine if the research participant will be discontinued from the trial. Appropriate actions for the research participant's safety will be initiated by the investigator. For assessment of the C-SSRS®, paper forms will be used and results will be transcribed into the e-CRF.

7.5.6. Medical history

Full medical history will be taken for the research participants, including but not limited to:

• Cerebrovascular accident (stroke and/or transient ischemic attack [TIA])

• Seizures (including febrile seizures in childhood) or epilepsy

• Thrombotic conditions, including deep venous thrombosis or pulmonary embolus

• Confirmed myocardial infarction and symptoms of angina

• Congestive heart failure

• Other dementias (e.g., vascular dementia, Dementia with Lewy bodies, and frontotemporal lobar dementia)

• Other central nervous system conditions that may cause progressive deficits in memory and cognition (eg, cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, and brain tumor)

• Systemic conditions known to cause dementia (eg, hypothyroidism, Vitamin B12, folic acid deficiency, neurosyphilis, or HIV infection)

• Substance use and abuse

• Major psychiatric illness , not limited to, major depressive disorder, bipolar disorder, anxiety disorder, schizophrenia, and delirium

• Hypertension

• Diabetes

• Medication related side effects: drowsiness, confusion and anorexia

• Falls and syncopes

• Concussion(s) and/or traumatic brain injuries

• Incontinence

• Infections

• Pulmonary disease

• Kidney disease

• Osteoarthritic conditions

• Vision loss

• Hearing loss

• Pregnancies.

7.5.7. Adverse events

This includes adverse events covering AE, SAE, AR (adverse reactions), AESI (adverse events special interest), and TLAE (adverse events that are treatment limiting or lead to early discontinuation). See Section 15 for further details on adverse events. The exact safety assessments required for a specific substudy will be outlined in the ISA.

8. Analysis set(s)

Analysis sets will be given a two or three-level name. The first level concerns whether patients were randomized, treated and whether they have valid measurements on the primary outcome (ASRS/ASTS/FAS). The second level concerns which type of control patients are included (ISA-controls/Concurrent-controls/All-controls). For the third level, a qualifier "controls-only" may be added to select only control patients. All sets refer to a single IST but this is not part of the naming. All sets are restricted to subjects within the strata (pre-clinical/pro-dromal; APOe-status) covered by the IST. Other inclusion/exclusion criteria are by default not accounted for, as they may not be assessed in all ISTs. However, an ISA-SAP may specify further restrictions.

The primary efficacy analysis is performed on the set FAS-concurrent controls, with sensitivity analysis on other analysis sets. Poolability of controls is done on the set FAS-concurrent controls-controls only. Safety analyses are done on the set ASTS-concurrent controls.

8.1. First level

ASRS: All Subjects randomized set.

ASTS: All Subjects treated set. All subjects in ASRS, who have received at least one administration of IMP.

FAS: Full Analysis set. All subjects in the ASTS, who have a baseline assessment and at least one assessment of the primary outcome (RBANS) after first administration of IMP. If an IST has a key outcome different from the RBANS, the ISA-SAP may make use of a definition covering at least one assessment of the primary outcome (RBANS) or the key outcome, after first administration of IMP.

8.2. Second level

IST controls: All subjects in all treatment arms in the IST.

Concurrent controls: All subjects in all treatment arms in the IST supplemented with control subjects from other ISTs, defined as follows: The present IST has a First Subject First Visit (FSFV) and Last Subject First Visit (LSFV), and a specified intended study duration. The dates refer to the baseline visit. The placebo subjects contributing from other ISTs are all subjects with a Visit 2 (baseline) date between the dates of the first subject first visit (FSFV) and the last subject first visit (LSFV) in the focus IST(both

dates included). Here FSFV and LSFV refer to the baseline visits. Only data from research participants from the strata included in the focus IST are shared. Individual data will be used until the minimum of the study durations of the relevant study and the other study. So, if the actual IST runs over 2 years and the other study over 4 years, only data up to 2 years will be shared. On the other side if the actual IST runs over 4 years and the other study over 2 years, still only data up to 2 years will be shared as further data are not available.

All controls: Defined similar to the concurrent controls, but without the condition of start in PoC between FSFV (inclusive) and LSFV (inclusive). Before unblinding, a cut-off will need to be set regarding the last enrolment day to include. The cut-off date should allow for including data from the Month 6 visit. Research participants who cannot have experienced their Month 6 visit are not included.

8.3. Third level

Without qualifier: Subjects as restricted by the first and second level.

With qualifier “controls-only”. Subjects as restricted by the first and second level and included in the control arms of the studies.

8.4. General

Additional analysis sets can be defined in the ISA. The ISA will also outline a strategy with respect to estimands as the intercurrent events and strategy may depend on the actual intervention considered. For the primary analysis, we may need to consider an appropriate estimand.

The interim analysis calculations are based on the Missing At Random assumption, corresponding to a hypothetical estimand.

No calculations will involve unblinded data from active treatments from several ISTs unless agreed by all owners of compounds involved in the calculation.

The patients and data will be classified into the analysis set(s) during a classification meeting according to the definitions above after the study database has been released, but before the blind has been broken.

The primary endpoint includes data transferred from the LCS study, covering the full period from enrolment in the LCS until enrolment in the POC.

9. Descriptive statistics

9.1. Final report

Unless otherwise specified, summary statistics (n, arithmetic mean, standard deviation [SD], median, lower and upper quartiles, minimum and maximum values) will be presented for continuous variables, and counts and, if relevant, percentages will be presented for categorical variables.

Unless otherwise specified, descriptive statistics will be given for the subpopulations corresponding to preclinical versus prodromal patients, positive versus negative Apolipoprotein E (ApoE4) genetic status and the four combinations thereof.

Unless otherwise specified, data listings will include site, treatment group, patient screening number, sex, age, race (when collected), and baseline weight. Listings will not include research participants from other IST's if their treatment status is still blinded in the relevant IST.

9.2. Interim report for DSMB

This section is not finalized.

10. Patient disposition

10.1. Final report

Patient disposition will be summarised by treatment group and include the number of patients who completed and the number of patients who withdrew from treatment, as well as the number of patients in each analysis set.

The number of patients who withdrew from treatment will be summarised by treatment group and primary reason for withdrawal (withdrawal of consent, concomitant medication, adverse event, loss to follow-up, IST stopped) as well as by treatment group and all reasons for withdrawal.

10.2. Interim report for IDMC

10.3. This section is not finalized Interim report for DSMB

This section is not finalized.

We will also need to include ongoing patients.

11. Demographics and baseline characteristics

Demographics (including sex, age, country, race(when collected)), other baseline characteristics (including height, weight, BMI, subgroup classification), and baseline efficacy variables (including RBANS, CDR status, CSF biomarker status) will be summarised by treatment group and per combination of subpopulation and treatment group (preclinical versus prodromal patients, positive versus negative Apolipoprotein E (ApoE4) genetic status and the four combinations thereof), as well as per combination of treatment group and analysis set.

12. Recent and concomitant medication

Recent and concomitant medication will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary

Medications will be classified according to the start and stop time and summarized by anatomical therapeutic chemical (ATC) code, generic drug name, treatment group, and period (if different (treatment) periods are included in the study, specify by period):

- medication discontinued prior to first dose of IMP
- concomitant medication continued after first dose of IMP
- concomitant medication started at or after first dose of IMP

If concomitant medications are collected after withdrawal from treatment in studies with follow-up of withdrawn patients, present concomitant medication started after withdrawal from treatment separately:

- concomitant medication started after last dose of IMP

13. Exposure and compliance

Research participants are requested to bring back all remaining trial medication including empty package material with them when attending visits (might not be possible for injectable product). Treatment compliance will be calculated for each intervention cohort (details will be found in the ISA). Compliance will be verified by the on-site monitor authorized by the Sponsor.

Exposure will be calculated based on total daily dose over treatment duration in months/years. Details of any exposure assessments required for the trial drug will be reported in the ISA.

14. Efficacy

This section covers only the final analysis. The interim analyses are similar with additional description in Section 18.1. This section is not completely final. More work is needed regarding the details of the approach. Besides, the assumptions need justification.

The primary efficacy analyses are based on a Bayesian cognitive progression model (BCPM). This cognitive progression model incorporates the following aspects:

- Repeated measures for the cognitive endpoint over the recurring 6-month visit schedule, including pre- and post-intervention
- Patient-level random effect
- Proportional treatment effect for slowing of disease progression rate. If there are several active treatment arms, the ISA will describe how this will be modelled.

Let a cognitive endpoint at visit j for research participant i be labelled Y_{ij}, for j= …,–1, 0, 1, 2, …. The reference to negative visits corresponds to cognitive endpoint values from the LCS study, pre-intervention. The Y_{i0} observation corresponds to the baseline visit at the time of the start of intervention. Visits j=1,2,3, refer to the post baseline, on treatment visits (each 6-months separated). Within a specific subgroup, the cognitive progression model is

$$Y_{ij} = \begin{cases} \gamma_i + \sum_{v=j}^{-1} \alpha_v + \epsilon_{ij} & j = \cdots, -2, -1 \\ \gamma_i + \epsilon_{ij} & j = 0 \\ \gamma_i + \exp(\theta_{t_i}) \sum_{v=1}^{j} \alpha_v + \epsilon_{ij} & j = 1,2,3 \ldots \end{cases}$$

The γ_i , *i=1,…,k*, parameters are the random effects specific to a research participant. These random effects represent the mean cognitive total score at the time of treatment (randomization). The α_j parameters represent the change in the mean cognitive score from one visit to the next. The α_j, for j=0,1,2,3, are restricted to be negative (decline), representing the mean change from visit *j*–1 to *j*, restricted to be, on average, negative. For research participant *i*, the treatment arm is labelled t_i. The cognitive progression rate ratio (CPRR) for treatment T is the parameter $\exp(\theta_T)$. For a control, or placebo treatment, the CPRR is assumed to be 1 ($\theta_T = 0$). Thus, the CPRR parameter for a generic intervention *T* represents the multiplicative change to the mean decline of a research participant on a control or placebo treatment. If the CPRR is less than 1 then the rate of decline for an intervention *T* is slower than for a control treatment. The value of the CPRR represents the proportional slowing of the disease. A value of CPRR = 0.75 corresponds to a 25% slowing in the rate of decline and a value of 0.25 represents a 75% slowing in the rate of decline. The errors for the individual observations are modelled as independent normal distributions with a standard deviation of σ. Within each defined subgroup (strata), *g*=1,2,3,4, corresponding to the cognitive status and ApoE4 status (g=1 is (+,+), g=2 is (+,–), g=3 is (–,+), and g=4 is (–,+)), a separate set of α's and σ are modelled (α_g and σ_g). In the primary analysis, the same CPRR is assumed across these subgroups.

The prior distributions for the RBANS total score variable, within each subgroup are presented in this section. Alternative endpoints analysed using this BCPM will have these prior parameters specified separately. The research participant level random effects are modelled as

$\gamma_i \sim N(\mu, 12^2)$, *i=1,..,k*

with hyper-priors by sub-group:

$$\mu \sim N(\mu_{sg}, \tau_{sg}^2)$$

where for clinically negative: μ_{sg} =100, τ_{sg} =2.25 and for clinically positive: μ_{sg}=88.75, τ_{sg}=3.75 (the parameters don't change for ApoE4 status)

The prior for the individual visit effects are modelled as:

$$-\alpha_v \sim IG(0.01, 1).$$

The prior for the variance component for the error term is

$$\sigma^2 \sim IG(81, 9).$$

The prior distribution for the log-CPRR is

$$\theta \sim N(0, 0.25^2)$$

The prior distribution of the treatment effect is centered on no treatment effect (0). A one-SD change in the prior effect is, exp(–0.25) = 0.78, and a two-SD decline in the rate is exp(-0.5)=0.61. This prior was selected to allow the PoC data to shape the posterior distribution for the treatment effect, yet to provide a small amount of pessimism on the treatment effect.

For each intervention a separate instance of the model is run. The exact same model specification is used for each, but the model is run separately with each intervention and collection of placebos.

The primary analysis considers only observed observations and does not impute missing data.

For each run of this primary analysis model, the following model summaries will be presented

1. For the CPRR: the posterior mean, standard deviation, and the following percentiles: 2.5%, 10%, 25%, 50%, 75%, 90%, 97.5%. In addition, the posterior probability that the CPRR is less than 1 and less that 0.90 will be presented.
2. For the log-CPRR: the posterior mean, standard deviation, and the following percentiles: 2.5%, 10%, 25%, 50%, 75%, 90%, 97.5%.
3. For each of the mean rates of decline on the control, in each strata (the α_g), the posterior mean, median, standard deviation, and 95% credible interval will be presented (2.5th to 97.5th percentiles).

The primary analysis for an intervention will be considered successful if the posterior probability that the CPRR is less than 0.90 is greater than 0.85. The following analyses will be done on specific subsets of participants:

1. The primary analysis for an intervention will be done on the FAS all controls be based on comparing all randomized participants to the intervention to all participants in the same strata as the specific intervention randomized to a control. This is the dataset called FAS-All controls. We refer to the strata for an intervention as the "signature."
2. An analysis based on the dataset FAS-Concurrent controls. An analysis based on the dataset FAS-IST controls.
3. An analysis based on the dataset FAS-All controls but only including measurements for j=0,1,2,…
4. An analysis of different control arms will be conducted in order to check for poolability. This is based on the dataset FAS-Concurrent controls-controls only. All intervention specific controls will be analyzed in a single common run of the BCPM and compared to the control group in the IST: A "treatment effect" CPRR will be fit for each control group (with one intervention chosen to have CPRR=1) for the blinded placebo. The posterior mean and 95% credible interval of the ratio of the CPRR between control arms will be presented. If the 95% credible interval for an intervention's control group does not include 1, this group will be considered to have a different cognitive progression rate.
5. A single instance of the model will be run on the dataset FAS-All controls (each treatment with its own θ_t) with an adjustment for the calendar time of enrolment of the participant in the trial, specific to the strata will be included. The model for the outcome is

$$Y_{ij} = \begin{cases} \gamma_i + \sum_{v=j}^{-1} \alpha_v + \delta_B + \epsilon_{ij} & j = \cdots, -2, -1 \\ \gamma_i + \delta_B + \epsilon_{ij} & j = 0 \\ \gamma_i + \exp(\theta_{t_i}) \sum_{v=1}^{j} \alpha_v + \delta_B + \epsilon_{ij} & j = 1,2,3 \ldots \end{cases}$$

Where *B* is an indicator for the "bucket" of time in which a participant was enrolled (specifically the timing of the baseline observation). The indicator *B* will be based on semi-annual buckets starting and working backwards from the last participant enrolled. The following modelling of the time effects will be used.

$\delta_B \sim N(\delta_{B-1}, \tau^2)$, *B=S*, …, N_B*

Where S* is defined as the first 6-month period prior to an intervention starting enrolment in the trial, with the number of 6-month buckets, N_B, a function of the calendar time enrolling the participant. The parameter is modelled as

$\tau^2 \sim IG(0.01, 0.01)$.

An additional analysis will be conducted where there is a different vector of the δ, where the δ are separate for the clinically +ve and clinically –ve strata.

6. An analysis of the model will be conducted where the CPRR will be separate by each individual strata.
7. The effect of covariates will be examined. As the RBANS values are normalized, the focus will on models, where the covariates influence the change over time. As the actual covariate will typically be assessed at baseline, this will only use data at and after baseline. Analyses of the BCPM with standardized covariates $Z_1, \ldots, Z_c$, will be conducted by the following model

$$Y_{ij} = \begin{cases} \gamma_i + \epsilon_{ij} & j = 0 \\ \gamma_i + \exp\left(\theta_{t_i} + \sum_{c=1}^{C} \beta_c Z_{ic}\right) \sum_{v=1}^{j} \alpha_v + \epsilon_{ij} & j = 1,2,3 \ldots \end{cases}$$

Where the prior distribution of the coefficients for each covariate will be

$$\beta_c \sim N(0, 10^2), c = 1, \ldots, C$$

Each continuous covariate will be standardized by the patient-weighted mean and standard deviation for each covariate. Indicator variables will be left as 0/1 variables.

Exploratory analyses will be conducted on an array of covariates.

Subset analyses and additional analyses for each intervention will be specified in the intervention specific SAP.

14.1. Secondary endpoints

Each secondary cognitive endpoint will be analysed using the same primary endpoint progression model and a traditional mixed model for repeated measures (MMRM) analysis. Modifications are needed as these are not normalised by sex and age. Thus, assumptions on μ and τ should be re-considered.

Subset analyses and additional analyses for each intervention will be specified in the intervention specific SAP.

15. Safety

This section describes only the final analysis. For the interim analyses, only key safety analyses will be performed. If there is a major safety signal, the DSMB will recommend stopping the IST. The interim analyses are covered by the DSMB charter.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard summary tables and listings will be produced. All AEs with an onset between start of treatment and end of the residual effect period (REP). The REP will be defined in the ISA.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on Sponsor standards. No hypothesis testing is planned.

Statistical analysis and reporting of AEs will concentrate on treatment-emergent AEs. To this end, all AEs occurring between start of treatment and end of the REP will be considered 'treatment-emergent'. The REP is defined in the ISA. AEs that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of AEs will be tabulated by system organ class and preferred term after coding according to the current version of the MedDRA.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

Shift analyses from baseline to post-baseline visits.

Details of any specific safety assessments required for the trial drug will be reported in the ISA.

15.1. Definitions of adverse events

Adverse event (AE)

An adverse event is defined as any untoward medical occurrence in a clinical investigation research participant administered an intervention and which does not necessarily have a causal relationship with this intervention.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an intervention, whether or not considered related to the intervention.

Adverse Reaction (AR)

An AR is defined as a response to an intervention which is untoward and unintended. Response in this context means that a causal relationship between an intervention and an adverse event is at least a reasonable possibility.

Adverse Events of Special Interest (AESI)

Intervention Specific Appendices may define their AESI, if any, for the intervention and appropriate assessments and monitoring. AESI need to be reported within the same timeframe that applies to SAE.

Serious adverse event (SAE)

A SAE is defined as any AE which:

- results in death of the clinical investigation research participant,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect,
- any other significant medical event, deemed serious for any other reason when based upon appropriate medical judgment, which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Intensity (Severity) of AEs and SAEs

The intensity (severity) of the AE/SAE will be assessed by the PI and should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated, causing minimal discomfort and not interfering with usual activities

Moderate: Enough discomfort to cause interference with usual activity

Severe: Incapacitating or causing inability to work or to perform usual activities

Causal relationship of AEs and SAEs

Medical judgment by the PI should be used to determine any causal relationship to the AE/SAE, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Possibly related: There is a reasonable possibility of a causal relationship between the investigational intervention and the AE/SAE. The assessment of causality will be made against the reference safety information (e.g. as found within the Investigator's Brochure or SPC).

Unrelated: There is no reasonable possibility of a causal relationship between the investigational intervention and the AE/SAE.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of an intervention.
- The event is known to be caused by or attributed to the intervention class.
- A plausible time to onset of the event relative to the timing of the intervention.
- Evidence that the event is reproducible when the intervention is re-introduced.
- No medically sound alternative aetiologies that could explain the event (eg, pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (eg, Stevens-Johnson syndrome).
- An indication of dose-response (ie, greater effect size if the dose or intensity of the intervention is increased, smaller effect size if dose or intensity is diminished).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the timing of the intervention is evident (eg, pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the intervention concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (eg, after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g., situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the intervention continues or remains unchanged.

16. Pharmacokinetic/Pharmacodynamic analyses

No PK assessments are required in the Master Protocol. If any specific assessments are required for an intervention, they will be articulated in the Intervention Specific Appendix of the Master Protocol and relevant statistical analyses will be described in the ISA of the master SAP.

17. Data monitoring committees

An IDMC, and a separate Data Safety Monitoring Board (DSMB), both independent of the Sponsor and the Intervention Owners, will be established to assess the progress of the clinical trial, including unblinded safety (DSMB) and efficacy (IDMC) assessment at specified intervals, and to recommend to the PSC and ASC whether to continue, modify, or stop interventions within the trial. Measures are in

place to ensure confidentiality and blinding of the Sponsor and all other trial participants. The tasks and responsibilities of the IDMC and DSMB will be specified in IDMC and DSMB Charters, respectively. The IDMC and DSMB will maintain written records of all their meetings.

18. Interim analyses

18.1. Interim analyses for the IDMC

The POC Trial as such will not control for the Type I error. For each IST, the sample size and the stopping criteria are set in consideration of the Type I error, which is evaluated by simulation.

The interim analyses will be conducted every three months. It will be the same time for all ISTs, but the analyses will be made separately. The actual analysis will follow the principles for the primary efficacy analysis described in Section 14.

For each evolution analysis conducted in which an intervention has reached a minimum exposure to research participants, an analysis of graduation (success) will be conducted. With the same constraints, an analysis of futility will be conducted. The default criterion is at least 50 research participants with 12 months of follow up in an intervention cohort, but this can be specified within an ISA. The details of these analyses are:

1. If the posterior probability of a CPRR<0.90 is greater than 0.85 then the intervention meets graduation criteria and will be labelled a success. This analysis concludes a super superiority, meaning there is high probability of at least a 10% slowing in the rate of decline is met for the intervention

2. If the posterior probability of a CPRR<0.90 is less than 0.05 then the futility criteria is met for that intervention. Thus, if there is high probability of less than a 10% slowing in the rate of decline, the intervention will be declared futile.

The sponsor will only be informed of the decision to continue or stop the trial and will not be unblinded to the results until the study has ended.

18.2. Interim analyses for the DSMB

This section is not finalized.

19. Sample size considerations

The maximum exposure for a research participant to an intervention is 4 years. The time of follow-up (a maximum of 4 years) and maximum number of research participants enrolled to an intervention cohort is defined in the ISA. Complete power calculations and operating characteristics for each intervention will be detailed in the ISA.

A suggestion for a general strategy for power calculations for some generic possible choices of number of subjects, subgroups, and length of follow-up is given in the master protocol.

20. Statistical software

Final study reports will be generated using SAS version 9.4 or later. The efficacy models described in this master SAP will be coded in C++ version XXX or later. The ISA will specify further software used for a specific sub trial.

Appendix I gives example SAS code to fit a simplified version of the primary analysis.

21. Changes to analyses specified in the protocol

There are no changes to analyses specified in the protocol.

22. Details on data handling

Details on data handling will be specified in the ISA.

23. Transfer of data from LCS

Transfer of data from LCS has two purposes. One is avoiding screening assessments, when a similar assessment has been done shortly before. The other point is that the primary endpoint analysis includes data from the LCS as reflection of the status and development of the research participant during their time in the LCS.

At the screening visit (V1), some assessments performed in the LCS within the past 3 to 12 months prior to the screening visit of the PoC trial will be considered acceptable and will not be necessarily re-assessed:

• If the PoC screening visit is performed the same day or within (≤) 3 months of a LCS visit, then the clinical outcome assessments that are the same in both studies will be performed only once

• If the PoC screening visit is performed more than (>) 3 months after a LCS visit, then the clinical outcome assessments will need to be re-performed.

At screening Visit 2, in order to reduce invasive assessments, repetition of examinations and subject burden, the following existing data performed in the LCS within pre-defined time intervals may be eligible:

- Secondary and exploratory clinical outcome assessments within the past 3 months prior to V1
- Lumbar puncture for CSF sampling done in the LCS within past 12 months prior to V1
- MRI performed in the LCS within past 6 months prior to V1.

24. Communication of results

Sharing of placebo data will be conducted between each study cohort. Research participants, Investigators and everyone involved in the conduct or analysis or with any other interest in this trial conduct will not be blinded across different intervention cohorts but will remain blinded with regard

to the randomized treatment arm assignments within their intervention cohort until after database lock.

The randomization code will be kept secret and only accessed by the External Statistical Clinical Research Organisation (CRO) and the Independent Data Monitoring Committee (IDMC), until an intervention completes its exposure in the trial.

The Sponsor and the External Statistical CRO will have access to unblinded data as the trial evolves. The Sponsor, External Statistical CRO, and the IDMC will follow detailed procedures in order to avoid unnecessary unblinding of any individual research participants or unblinding of ongoing combined trial results

On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines. Publications will be generated from the intervention specific appendices and their management will be articulated in the intervention specific appendices.

When a report on one IST using controls from other ISTs, there is a risk of indirect unblinding of individual subjects in those other ISTs, for example, due to presence or absence of specific rare adverse events, which combined with blinded information from the other ISTs can lead to certain or probable treatment classification. Before release of a report, this problem will be considered, potentially leading to blinding of selected details in the report before release.

25. References

Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Preliminary Clinical Validity. Journal of Clinical and Experimental Neuropsychology. 1998b;20(3):310-319.

PUBLIC SUMMARY[1]

The purpose of the EPAD Proof-of-concept (PoC) Platform Trial Protocol is to study multiple interventions for the secondary prevention of Alzheimer's dementia in people with prodromal or preclinical Alzheimer's disease. This document is the corresponding Statistical Analysis Plan (SAP). As the PoC Platform Trial was not initiated, the SAP has not been finalized. The role of this document is to make the material available for future use. Consequently, it has not been a priority to make the document have a finished appearance. In other words, the document includes unfinished parts.

As a master SAP, a key point is to describe the data sharing between the Intervention-specific trials and the consequences of this sharing. A second point is to describe the common methods, in particular, the interim analyses used to decide on whether the trials stop or continue. Each Intervention Specific Trial will have a dedicated SAP.

Each intervention specific trial will have interim analyses for efficacy made every 3 months, after 50 research participants have reached 12 months of follow-up. The primary endpoint is RBANS total score. The dataset for the analysis consists of all available data for the research participants in the intervention specific trial supplemented with placebo data from the other intervention specific trials within the relevant strata. The model is a Bayesian disease progression model, where the placebo group has an arbitrary development over time, in each of the up to four strata recruiting to the trial. The active treatment group is assumed to show a change from baseline multiplied by a common factor (CPRR: Cognitive Progression Rate Ratio), so a value below 1 means that the disease progression is delayed. If an interim analysis shows that the posterior probability of CPRR<0.90 is greater than 0.85, the intervention meets the success criterion. If the posterior probability of CPRR<0.90 is less than 0.05, the intervention is declared futile.

[1] This summary will be published on the EPAD website in case the Executive Summary cannot be published. In case the Executive Summary can be made publically available, you can simply copy/paste for the Public Summary

ANNEXES

Annex I. SAS code for simplified frequentist version of primary analysis

The SAS code below covers a simplified frequentist version of the model.

It includes two strata, referenced as 1 and 2 as well as a and b. Time points included are baseline (0) and 6, 12, 18 and 24 months. The dataset should include one record for each visit for each participant. Research participants are identified by rpid.

Parameters α are denoted, for example, as meana6. Parameter μ is denoted mean0. The variance of γ is the parameter s2pt. The parameter σ (the variance of ε) is denoted s2e.

```
proc nlmixed  data=rbansdata;

parms mean0=100 meana6=-5 meanb6=-2 meana12=-8 meanb12=-3 meana18=-11 meanb18=-4 meana24=-14 meanb24=-5
cprr=1 s2e=25 s2pt=100;

if (stratum=1) then
change=((time=6)*meana6)+((time=12)*meana12)+((time=18)*meana18)+((time=24)*meana24);

if (stratum=2) then
change=((time=6)*meanb6)+((time=12)*meanb12)+((time=18)*meanb18)+((time=24)*meanb24);

mean=mean0+((treat=0)*change)+((treat=1)*cprr*change)+pt;

random pt ~ normal(0,s2pt) subject=rpid;

model rbans ~ normal(mean,s2e);

estimate 'logcprr ' log(cprr);

ods output fitstatistics=fit;

ods output parameterestimates=est;

ods output convergencestatus=status;

ods output additionalestimates=addest;
```