Official Title: A Multi-center, Randomized, Double-blind, Placebo-controlled, 24 months Study in Patients with amnestic Mild Cognitive Impairment or Very Mild Alzheimer's Disease to Investigate the Safety, Tolerability and Immune Response of Repeated Subcutaneous Injections of ABvac40.

NCT Number: NCT03461276

Document Date: Statistical Analysis Plan;
Version Addendum 02 to SAP Version 1.0;
17 August 2023

STATISTICAL ANALYSIS PLAN

Compound:	ABvac40
Study Title:	A Multi-center, Randomized, Double-blind, Placebo-controlled, 24 months Study in Patients with Amnestic Mild Cognitive Impairment or Very Mild Alzheimer's Disease to Investigate the Safety, Tolerability and Immune Response of Repeated Subcutaneous Injections of ABvac40
Study Number:	AB1601
Development Phase:	II
Protocol Version:	Version 5.0: 22May2020, including Amendment 3
Sponsor:	ARACLON BIOTECH, S.L. a GRIFOLS company, Via de la Hispanidad, 21, 50009 Zaragoza, SPAIN
Plan Version/Date:	Addendum 02 to SAP Version 1.0
Plan History:	SAP Version 1.0, 25Nov2021 Addendum 01, 10Dec2021
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CONFIDENTIAL

Approvals

Upon review of this document, including table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing, and figure production can begin.

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Table 1-1: List of Abbreviations

Abbreviation	Description
AD	Alzheimer's Disease
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living
AE	Adverse Event
a-MCI	Amnestic Mild Cognitive Impairment
ANCOVA	Analysis of Covariance
a-PET	Amyloid Positron Emission Tomography
ARIA	Amyloid Imaging Related Abnormalities
ARIA-E	ARIA-vasogenic edema and/or sulcal effusion
ARIA-H	ARIA-micro-hemorrhage
ATC	Anatomical Therapeutic Chemical
BADL	Basic Activities of Daily Living
BMI	Body Mass Index
CDR	Clinical Dementia Rating scale
CI	Confidence Interval
CS	Clinically Significant
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
DBL	Database Lock
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ELISA	Enzyme-linked Immunosorbent Assay
EQ-5D-5L	EuroQol 5 dimensions
IADL	Instrumental Activities of Daily Living
ICH	International Conference on Harmonisation
IGE	Investigator Global Evaluation
ITT	Intent-to-Treat
KLH	Keyhole limpet hemocyanin
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
MCI	Mild Cognitive Impairment
mITT	Modified Intent-to-Treat
MMSE	Mini Mental State Examination
MMRM	Mixed-Model Repeated Measures
MRI	Magnetic Resonance Imaging

Abbreviation	Description
NCS	Not Clinically Significant
OD	Optical Density
PP	Per Protocol
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
RBANS	Repeatable Battery of the Assessment of Neuropsychological Status
SAESI	Serious Adverse Event of Special Interest
SAP	Statistical Analysis Plan
SB	Sum of Boxes
SD	Standard Deviation
SI	Severity Index
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TMT	Trail Making Test
VAS	Visual Analogue Scale
VM-AD	Very Mild Alzheimer's Disease
WHO-DD	World Health Organization Drug classification Dictionary

1 INTRODUCTION

This SAP is addendum 02 to SAP version 1.0, 25Nov2021. Due to the extent of changes required to SAP version 1.0 and addendum 01 to SAP version 1.0, it was decided that the details of the planned statistical analyses for the study would be clearer if the SAP was rewritten and presented as a stand-alone document addendum 02 to SAP Version 1.0.

1.1 Purpose and Scope of Analysis Plan

The purpose of this statistical analysis plan (SAP) is to provide detailed information to aid in the implementation of the statistical analysis of the study data. It briefly summarizes the protocol, describes the analysis sets that will be analyzed, and describes the analyses to be performed. The details of the specific statistical methods that will be used are provided. Post database lock (DBL), it may become apparent that the planned analyses should be modified, e.g., modeling assumptions are untenable. Any modification to the original analysis plan will be identified and described in the clinical study report (CSR).

Table, figure, and listing specifications are in separate documents. This analysis plan is meant to supplement the study protocol. If differences occur between analyses described in the SAP and the current protocol, those found in this SAP will assume primacy.

This SAP is written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports and will be finalized prior to DBL.

1.2 Study Rationale

The purpose of this Phase II study is to confirm in patients with amnestic mild cognitive impairment (a-MCI) or very mild Alzheimer's Disease (vm-AD) the level of safety and tolerability obtained in the ABvac40 Phase I clinical trial (a randomized, placebo-controlled, parallel group, double-blinded, single-center, phase I pilot study to assess tolerability and safety of repeated subcutaneous administration of two single-doses of ABvac40 applied to patients with mild to moderate Alzheimer's disease – AB1203 Study). In addition, the study is aimed to better characterize the immune response elicited by ABvac40 and to explore its effects on Alzheimer's Disease (AD) biomarkers.

2 PROTOCOL SUMMARY

2.1 Study Design

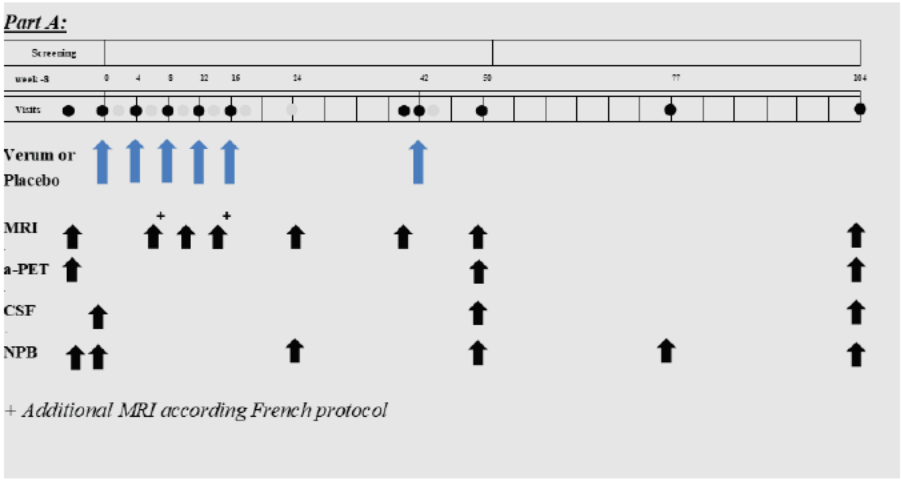
This is a multi-center, prospective, longitudinal, randomized, double-blind, placebo-controlled, two parallel treatment groups (ABvac40 and placebo), confirmatory phase 2 clinical trial, designed in two parts: Part A, to evaluate repeated subcutaneous injections of ABvac40 to determine the safety, tolerability, and immune response in patients with amnestic mild cognitive impairment (a-MCI) or very mild Alzheimer's disease (vm-AD). Part B, to assess the safety, tolerability and efficacy of a delayed-start vaccination, and the long-term safety and tolerability of ABvac40 in patients receiving a booster after their Part A vaccination scheme.

2.1.1 Part A

Part A of the study will last for up to 24 months (from V0 to V25) and at least 18 months (up to V23) during which randomized study participants will receive five monthly (every four weeks) immunizations plus a booster shot at month 10 (V18). During the study, two interim analyses will be performed to assess safety, tolerability and biological activity of the treatment (including data from the collected disease biomarkers). These analyses will be reviewed by an independent Data Safety Monitoring Board (DSMB).

Additionally, after all patients complete their 18-month visit (V23) of Part A, a statistical analysis will be performed to determine whether Part B of the study should be discontinued. The study scheme for Part A is shown in Figure 1.

Figure 1: AB1601 Study Schematic – Part A

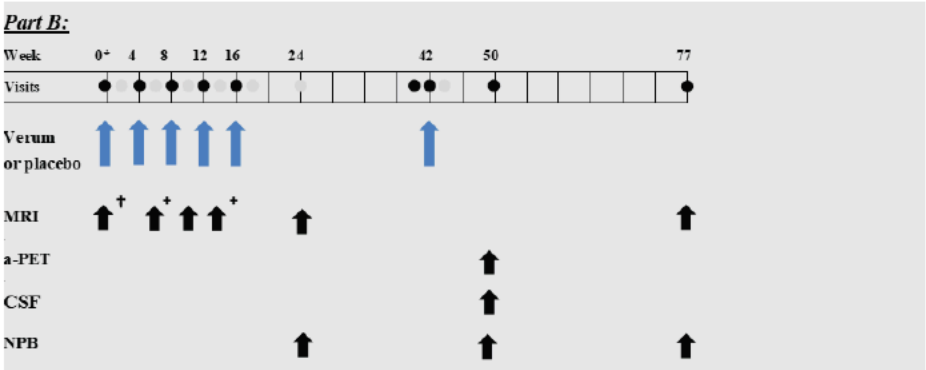


2.1.2 Part B

Part B of the study will last for 18 months (from V1B to V22B). The scheme of visits will mirror the Part A scheme. The first visit of Part B (V1B) will take place at least 18 months after the patient started Part A (i.e., patient should have completed V23 which is month 18 of Part A to enter Part B). The study scheme for Part B is shown in also included in Figure 2.

The patients randomized to the placebo group during Part A will receive five monthly (every four weeks) immunizations with ABvac40 plus a booster shot after 6 months (Placebo arm Part A / ABvac40 arm Part B), whereas the patients randomized to the ABvac40 group during Part A will receive placebo following this schedule, except in V13B (Week 16), where they will receive an ABvac40 booster shot (ABvac40 arm Part A / Placebo+Booster arm Part B). Given the extended inclusion period of Part A, the V13B booster will take place at different timepoints relative to the patients' last immunization.

Figure 2: AB1601 Study Schematic – Part B



2.2 Study Objectives

2.2.1 Part A (Randomized, Double-blind, Placebo-controlled – 18 to 24 months follow-up)

2.2.1.1 Primary Safety Objective

The primary safety objective of the study is to evaluate the safety and tolerability of repeated doses of ABvac40 in a population of patients with a-MCI or vm-AD.

2.2.1.2 Primary Efficacy Objective (Immunogenicity)

The primary efficacy objective (immunogenicity) of the study is to assess the immune response produced during the study by repeated doses of ABvac40 in a population of a-MCI or vm-AD.

2.2.1.3 Secondary (Exploratory) Efficacy Objectives

The secondary (exploratory) efficacy objectives of the study are:

- Characterizing the immune response elicited by repeated doses of ABvac40 in a population of a-MCI or vm-AD.
- Assessment of the changes in the disease biomarkers elicited by ABvac40 in the overall study population.
- Assessment of the changes in cognition and quality of life elicited by ABvac40 in the overall study population.

2.2.2 Part B (ABvac40 Delayed Start, Open Label [Part A assignment will remain blinded for investigators and patients] – 18 months follow-up)

2.2.2.1 Exploratory Safety Objective

- To evaluate the safety and tolerability of repeated doses of ABvac40 after delayed start in patients receiving placebo during Part A, and the long-term safety and tolerability of ABvac40 in patients receiving a booster after their Part A vaccination scheme.

2.2.2.2 Exploratory Efficacy Objective (Immunogenicity)

- To assess the immune response produced by repeated doses of ABvac40 after delayed start in patients receiving placebo during Part A.
- To assess the immune response triggered by a second ABvac40 booster in patients receiving ABvac40 during Part A.

2.2.2.3 Exploratory Efficacy Objective (Other)

- To assess the changes in the disease biomarkers elicited by ABvac40 in the overall study population.
- To assess the changes in cognition and quality of life elicited by ABvac40 in the overall study population and according to the treatment scheme during Part A and B.
- To assess the immunological memory, characterizing the immune response ex vivo elicited by the booster in patients who have received ABvac40 during Part A
- To assess the potential relationship between antibody titration, biomarkers and cognitive state.
- To define the optimal ABvac40 treatment scheme.

2.3 Study Population

Patients (between 55-80 years of age) diagnosed either with a-MCI or vm-AD will be included in the trial. To ensure sufficient precision for the primary safety and efficacy endpoints of the study a minimum of 60 patients with a-MCI or vm-AD per treatment group (ABvac40 and placebo) are required. The amyloid Positron Emission Tomography (a-PET) positive and a-PET negative patients will be independently randomized following a 1:1 ratio between ABvac40 and placebo (Part A).

Participants in Part A will have to complete at least their 18-month visit (V23) to be eligible for Part B of the study.

All patients who have participated in Part A who have not experienced any drug reaction and have no Magnetic Resonance Imaging (MRI) safety findings before the first immunization in Part B, may participate in Part B. On completion of Part A of the study, the database containing Part A data will undergo DBL prior to reporting of Part A results. Additionally, Part A and B data will undergo DBL prior to reporting of Part B results.

3 GENERAL STATISTICAL CONSIDERATIONS AND REPORTING CONVENTIONS

The following general analysis and reporting conventions will be used:

- The following treatment labels will be used for presentation of results in the statistical tables:
  - Statistical testing of primary and secondary efficacy outcomes in Part A of the study and summaries of Adverse Events (AE)s across parts A and B of the study will be presented by the following treatment groups:
    - ABvac40
    - Placebo
  - Summary statistics for all other parameters (Part A and Part B, combined) will be presented by the following treatment sequences:
    - ABvac40 arm Part A / Placebo+Booster arm Part B
    - Placebo arm Part A / ABvac40 arm Part B
- Visits will be presented in outputs in terms of weeks, with a suffix of “A” or “B” to indicate the study part (e.g. Week 0A, Week 2A…… Week 0B, Week 2B, etc…).
- Only available data will be included in summary statistics and no substitutions or imputations of missing values will be performed.
- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form n (%). Percentages will not be presented for counts of 0, while percentages of 100 will be reported as a whole number (i.e. “100%”). All other percentages will be presented to 1 decimal place. To ensure completeness, summaries for categorical variables will include all categories, even if no patients had a response in a particular category. Denominators will include patients with non-missing data, unless otherwise specified. The number of patients with missing data for categorical variables will be summarized without a percentage.
- Continuous variables will be summarized using mean, 95% confidence interval (CI) for mean, standard deviation (SD), first quartile (Q1), third quartile (Q3), minimum, maximum, median, and number of patients. The mean, median, Q1, Q3 and CI will be rounded and reported to 1 more level of precision than the original observations, and the SD will be rounded and reported to 2 more levels of precision than the original observations. The minimum and maximum will be reported to the same precision as the original data.
- Following SAS default rules, the median will be reported as the rounded average of the two middle sorted values if the dataset contains even numbers of non-missing data.

- P-values will be rounded and reported to 4 decimal places if greater than or equal to 0.0001. If the rounded p-value is less than 0.0001, '<0.0001' will be reported. If the rounded p-value is greater than 0.9999, '>0.9999' will be reported.
- Unless otherwise specified, the baseline value for all measures will be the last non-missing value recorded prior to the first dose of study treatment. For measurements that occur on the date of the first dose of study treatment with time collected, the measurement will be considered the baseline value if the measurement time is prior to the time of the first dose.
- No preliminary rounding will be performed; rounding will only occur after analysis. To round, consider digit to right of last significant digit: if < 5 then round down, if ≥ 5 then round up.
- All listings will be sorted in order of patient, parameter (when applicable), and time of assessment (e.g., visit, time, and/or event).
- Dates in listings will be displayed as YYYY-MM-DD (e.g., 2022-12-01).
- Where relevant, each listing will present Study Days which will be numbered relative to the initiation of study treatment administration.
    - The start of treatment (Day 1) for Part A is defined as the date in which a patient receives the first study treatment in Part A. The start of treatment (Day 1) for Part B is defined as the date in which a patient receives the first study treatment in Part B.
    - Day -1 is defined as the day before the first administration of study treatment within study Part (A or B). There is no Study Day 0.
    - Negative Study Days occur prior to initial administration of study treatment. Positive Study Days occur the day of initiating study treatment and thereafter.

  All dates presented in listing will be accompanied by study day.
- The following details will be footnoted in each table, listing and figure output: program name, programmer name, date of creation of output. Each table and figure will include a footnote referencing the corresponding listing and table number, respectively.
- All analyses will be performed using SAS System version 9.4.

3.1 Analysis Sets

3.1.1 Intent-to-Treat (ITT) Analysis Set

The ITT Analysis Set will include all randomized patients who received any study treatment.

Analysis of all secondary efficacy endpoints will be carried out using the ITT Analysis Set. Patients will be analyzed according to their randomized treatment assignment, regardless of the treatment received.

3.1.2 Modified Intent-to-Treat (mITT) Analysis Set

The mITT Analysis Set will comprise of all patients in the ITT Analysis Set who have a baseline and at least one post-baseline anti-Aβ40 antibody assessment (Optical Density (OD) in enzyme-linked immunosorbent assay (ELISA) without pre-adsorption).

Analysis of the primary efficacy endpoint will be carried out using the mITT Analysis Set. Patients will be analyzed according to their randomized treatment assignment, regardless of the treatment received.

3.1.3 Per Protocol (PP) Analysis Set

The Part A PP Analysis Set will comprise of all patients in the ITT Analysis Set who received all doses of study medication (on V1, V4, V7, V10, V13 and V18 in Part A), have attended the safety visit after booster (V20 in Part A), and have no major protocol deviations that could affect the efficacy analyses.

Analysis of the primary efficacy endpoint and secondary efficacy endpoints relating to the characterization of immune response and the assessment of disease biomarkers in Part A will be repeated using the Part A PP Analysis Set.

The Part B PP Analysis Set will comprise of all patients in the ITT Analysis Set who received all doses of study medication (on V1B, V4B, V7B, V10B, V13B and V18B in Part B), have attended the safety visit after booster (V20B in Part B), and have no major protocol deviations that could affect the summary of efficacy.

During the blind review meeting, decisions will be made regarding the PP Analysis Set in terms of whether deviations in Part A affect Part B for inclusion in analysis set.

Summaries of the primary efficacy endpoint and secondary efficacy endpoints relating to the characterization of immune response and the assessment of disease biomarkers over the entire duration of the study (Parts A and B combined), will be repeated using patients who are in Part A PP Analysis Set and the Part B PP Analysis Set.

Patients will be analyzed according to their randomized treatment assignment, regardless of the treatment received.

3.1.4 Per Protocol Cognition (PPc) Analysis Set

The Part A PPc Analysis Set will comprise of all patients in the ITT Analysis Set who received all doses of study medication (on V1, V4, V7, V10, V13 and V18 in Part A), have attended the safety visit after booster (V20 in Part A), have no major protocol deviations that could affect the efficacy analyses or major protocol deviations that have been classified as “Use of disallowed concomitant medication”, relating to use of Anti-Alzheimer Disease medication.

Analysis of secondary efficacy endpoints relating to the assessment of cognition and quality of life in Part A will be repeated using the Part A PPc Analysis Set.

The Part B PPc Analysis Set will comprise of all patients in the ITT Analysis Set who received all doses of study medication (on V1B, V4B, V7B, V10B, V13B and V18B in Part B), have attended the safety visit after booster (V20B in Part B), have no major protocol deviations that could affect the efficacy analyses or major protocol deviations that have been classified as “Use of disallowed concomitant medication”, relating to use of Anti-Alzheimer Disease medication.

During the blind review meeting, decisions will be made regarding the PPc Analysis Set in terms of whether deviations in Part A affect Part B for inclusion in analysis set.

Analysis of secondary efficacy endpoints relating to the assessment of cognition and quality of life over the entire duration of the study (Parts A and B combined), will be repeated using patients who are in Part A PP/PPc Analysis Set and the Part B PP/PPc Analysis Set. (See Section 3.1.3)

Patients will be analyzed according to their randomized treatment assignment, regardless of the treatment received.

3.1.5 Safety Analysis Set

The Safety Analysis Set will include all randomized patients who received any study treatment. All safety analyses will use the Safety Analysis Set. Patients will be analyzed according to the treatment received, regardless of the treatment assigned.

3.2 Determination of Sample Size

For the primary safety endpoint, the sample size was determined to ensure the probability of detecting an AE that occurs with a minimum rate of 5% within the ABvac40 treated dose cohort is greater than 95%. Using Hanley's [1] simple approximation, a minimum of 60 patients per treatment group is required, i.e., total study sample size of 120 patients.

The total sample size of 120 patients, when considering a dropout rate of 40% during the clinical trial, should result in approximately 70 patients completing the study. In assessing the primary efficacy endpoint of no difference in the mean maximum change from baseline in anti-Aβ40 antibody signal (OD), a one-sided t-test with a significance level of 0.025 will be employed. Assuming a difference of 1.778 O.D. between the active group and placebo group means with associated standard deviations of 2.0 and 1.0, respectively, there is greater than 85% power to reject the null hypothesis of no difference in the mean maximum change from baseline in anti-Aβ40 antibody signal between the treatment groups. It should be further noted that the study may be insufficiently powered to demonstrate efficacy in clinical or other biomarker outcomes.

3.3 Treatment Misallocations

For patients with errors in treatment allocation, they will be reported for efficacy and safety analyses as follows:

If a patient is:

• Randomized and not treated (treatment is defined as exposure to study treatment) then by definition they will be excluded from the efficacy and safety analyses as actual treatment is missing.

• Treated but not randomized, then by definition they will be excluded from the efficacy analyses since randomized treatment is missing, but they will be reported under the treatment actually received for all safety analyses.

• Randomized but received incorrect treatment at any time during the study, then they will be reported under their randomized treatment group for all efficacy analyses. For all safety analyses, they will be reported under the actual treatment received. If a patient received both ABvac40 and placebo throughout the trial, they will be reported under the ABvac40 treatment group for all safety analyses other than summaries of AEs. Details of how AEs will be reported in such circumstances are provided in section 7.2.1 below.

3.4 Protocol Deviations

All protocol deviations relating to parts A and B of the study will be categorized as major or minor and assessed at a data review meetings prior to DBL for parts A and B respectively, to determine the impact of each on the PP and PPc Analysis Sets.

4 STUDY VARIABLES

4.1 Safety Variables (Part A and Part B)

4.1.1 Primary Safety Variable – Adverse Events

AEs experienced by the patients will be collected throughout the entire study and will be coded using version 20.0 of the Medical Dictionary for Regulatory Activities (MedDRA). Serious AEs of special interest (SAESI)s will be defined as:

- Amyloid Related Imaging Abnormalities (ARIA), either
  - ARIA-micro-hemorrhage (ARIA-H), or
  - ARIA-vasogenic edema and/or sulcal effusion (ARIA-E)

- Aseptic Meningo-Encephalo-Myelitis

4.1.2 Secondary Safety Variables

- Withdrawal criteria (study continuation decision)
- Physical examination:
  Complete physical examinations will be performed at all face-to-face visits. These assessments include examination of the neck (including thyroid), eyes, ears, throat, abdomen, skin/mucous membranes, and cardiovascular, respiratory, genito-urinary, and musculoskeletal systems.
- Neurological examination:
  Neurological examinations are performed at all face-to-face visits. These assessments include cortical function, cranial nerves, motor function, reflexes, sensory function, gait, and posture.
- Concomitant medication
  Each medication will be coded to Anatomical Therapeutic Chemical (ATC) classification codes using the World Health Organization Drug classification Dictionary (WHO-DD), version WhoDrug B2 2017Q3 and defined as either a prior or concomitant medication, depending on the start and end dates of the medication, relative to the date of first dose of study treatment.

  Prior medications will be defined as any medication ended prior to the first dose of study treatment.
  Concomitant medications will be defined as any medication started on or after the start of study treatment or any medication taken prior to the start of study treatment and continued after the start of study treatment.
- Vital signs:
  The following vital signs parameters will be monitored: blood pressure, heart rate, respiratory rate, body temperature).
- Electrocardiogram (ECG):
  The following ECG parameters will be recorded: HR, PR interval, QRS and QT.
- Laboratory Assessments:
  Laboratory assessments will be performed for the following: Hematology, Toxicology (reactive protein), Biochemistry, Coagulation, Serology and Urine sampling. Appendix 9.3 provides a list of that laboratory test parameters that will be recorded.

4.2 Efficacy Variables (Part A and Part B)

4.2.1 Primary Outcome Variable

Maximal increment (MΔ) of anti-Aβ40 antibody signal (estimated by ELISA (signal OD values) in each patient, from baseline.

4.2.2 Secondary Outcome Variables

4.2.2.1 Characterization of Immune Response

- Levels of anti-keyhole limpet hemocyanin (KLH) (Part A and Part B) and anti-Aβ42 antibodies in plasma (Part A only - anti-Aβ42 antibodies in plasma are not analysed by Araclon)
- Level of anti-Aβ40 antibodies in Cerebrospinal Fluid (CSF)
- Level of anti-Aβ40 antibodies in plasma

- Analysis of the peripheral blood cell subsets by immunophenotyping – Part A only (not analysed by Araclon)
- Levels of antibody secreting cells (only analysed in Part A and not analysed in Part B)
- Levels of cytokine-secreting cells (IFN-γ and IL-4) – Part A only (samples from only a small number of patients were analyzed. Hence, data for this analysis will not be reported)

4.2.2.2 Assessment of disease biomarkers:

- Levels of Aβ40 and Aβ42 peptides in plasma
- Cortical fibrillary amyloid deposition assessed by a-PET scans.
- Levels of CSF biomarkers [Aβ42, Aβ40 (Part A and B) and Tau, P-tau, neurofilament light and neurogranin (Tau, P-tau, neurofilament light and neurogranin were only analysed in Part A and were not analysed in Part B)] and other Aβ peptide species (other Aβ peptide species were not analysed by Araclon) (Part A and Part B)
- Brain volumetric changes (including hippocampal and ventricle changes) and atrophy of the hippocampus using MRI.

4.2.2.3 Assessment of cognition and quality of life:

- Mini Mental State Examination (MMSE):
  - an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30. A score of 23 or lower is indicative of cognitive impairment
  - the following parameters will be summarized/analyzed as outlined in section 6.3:
    - total MMSE score
- Clinical Dementia Rating (CDR) scale:
  - a 5-point scale used to characterize six domains of cognitive and functional performance applicable to Alzheimer disease and related dementias: Memory, Orientation, Judgment & Problem Solving, Community Affairs, Home & Hobbies, and Personal Care.
  - the following parameters will be summarized/analyzed as outlined in section 6.3:
    - CDR-Sum of Boxes (CDR-SB), derived as the sum of the six individual domain scores and can range from 0 to 18.
    - Global CDR, as recorded on a scale of 0–3: no dementia (CDR = 0), questionable dementia (CDR = 0.5), MCI (CDR = 1), moderate cognitive impairment (CDR = 2), and severe cognitive impairment (CDR = 3).
- Repeatable Battery for the Assessment of Neuropsychological Status (RBANS):
  - assesses five cognitive domains, i.e., Immediate Memory, Visuospatial/constructional, Language, Attention, and Delayed Memory. The test consists of 12 subtests and the score on each subtest contributes to one of the five domains.
  - the following parameters will be summarized/analyzed as outlined in section 6.3:
    - Scores derived for each of the five domains
    - Total score, which can range from 40 to 160, derived as the sum of the five domain scores.
- Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL), MCI:
  - a 24-item scale that includes 6 basic activities of daily living (BADL) items and 16 instrumental activities of daily living (IADL) items that provide a total score from 0-78, with a lower score indicating greater severity
  - the following parameters will be summarized/analyzed as outlined in section 6.3:
    - ADCS-ADL-MCI (item 1-24) total score
- Columbia Suicide Severity Rating Scale (C-SSRS)
  - The following parameters will be summarized as outlined in section 6.3:

        - Most severe ideation (on a scale of 0 to 5)
        - Suicidal behaviour (yes/no)
- Trail Making Test (TMT)
    - consists of two parts in which the patient is instructed to connect a set of 25 dots as quickly as possible while still maintaining accuracy. There are two parts to the test: in the first, the targets are all numbers from 1 to 25 and the test taker needs to connect them in sequential order; in the second part, the dots go from 1 to 13 and include letters from A to L.
    - the following parameters will be summarized/analyzed as outlined in section 6.3:
        - Time required to complete trail A.
        - Time required to complete trail B.
- Investigator Global Evaluation (IGE)
- EuroQol 5 Dimensions (EQ-5D-5L)
    - comprises of 2 sections: a descriptive system questionnaire and a Visual Analogue Scale (VAS).
    - the EQ-5D-5L descriptive system comprises of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), with each dimension measured on the following increasing scale of severity: 1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, and 5=extreme problems.

    - the following parameters will be summarized/analyzed as outlined in section 6.3:

        - Overall severity index (SI), calculated for each patient, at each visit as: $SI = [100-(\Sigma s_i-5) \times 5]$, where s is the severity recorded for dimension i.

          The SI for a patient can take values from 100='Best imaginable health state' down to 0='Worst imaginable health state', at each visit.

        - Visual Analogue Scale (VAS), recording the patient's self-rated health on a vertical scale, ranging from 100 = 'Best imaginable health state' down to 0 = 'Worst imaginable health state'.

5 SUMMARY OF STUDY POPULATION

5.1 Patient Disposition

The following disposition information will be summarized for all patients screened:

- The number of patients screened
- The number of patients who screen failed (patients who fail screening once, are re-screened, and are treated in the study are counted as screen failures and as enrolled patients. Patients who fail screening twice are counted only once as screen failures.)
- The number of patients who received any study treatment in each of Part A and Part B.
- The number of patients who received all immunizations in each of Part A and Part B
- The number of patients in the Safety, ITT, mITT, PP and PPc Analysis Sets
- The number and percentage of patients who completed each of Part A and Part B of the study
- The number and percentage of patients who discontinued from each of Part A and Part B of the study and the reason for premature study discontinuation
- The distribution of the number of days relative to first dose of study treatment (i.e., date of discontinuation – date of first dose + 1) for patients who prematurely discontinue from each of Part A and Part B of the study

- The number and percentage of patients who continued into Part B of the study

A listing of patient disposition for all patients randomized will also be presented.

5.2 Protocol Deviations

Protocol deviations will be identified during the study and evaluated before the database lock. The type/category of protocol deviations and severity (i.e., minor and major) will be summarized and listed.

5.3 Demographics

Demographic characteristics including age, sex, race, tobacco usage (never, former current), alcohol usage (never, former, current), drug habit (never, former, current), highest level of education (some school, high school graduate, college graduate, university degree), baseline height, baseline weight and calculated baseline body mass index (BMI = baseline weight (kg)/baseline height $(m)^2$) will be summarized by study treatment group for the ITT analysis set. Missing categories will be presented where necessary.

A listing of demographic characteristics will also be presented.

5.4 Baseline Disease Characteristics

Baseline disease characteristics (recorded during Part A): study disease (a-MCI or vm-AD), a-PET status, ApoE genotype and time from disease diagnosis (days from diagnosis to signing of study informed consent) will be summarized by study treatment group for the ITT analysis set.

A listing of baseline disease characteristics will also be presented.

5.5 Medical History

Medical history will be coded using MedDRA version 20.0 and summarized by study treatment group, system organ class (SOC) and preferred term (PT) for the ITT analysis set.
A listing of patient medical history will also be presented.

6 EFFICACY ANALYSIS METHODS

6.1 Part A

6.1.1 Analysis of Primary Outcome Variable

Change in anti-Aβ40 antibody signal from baseline to each post-baseline efficacy assessment visit will be a calculated as: post-baseline OD – baseline OD.

The maximal increment (MΔ) in anti-Aβ40 antibody signal for a patient will be defined as the maximum change from baseline in anti-Aβ40 antibody signal across all post-baseline visits. A comparison of the average MΔ in anti-Aβ40 antibody signal between the ABvac40 and placebo groups will be performed using a one-sided t-test.

The trial will be considered successfully confirmatory regarding efficacy (immunogenicity) of ABvac40 if the average MΔ of anti-Aβ40 antibody signal (OD in ELISA) in the ABvac40 group is significantly greater than the average MΔ of anti-Aβ40 antibody signal in the placebo group. i.e.

- Null hypothesis: average MΔ anti-Aβ40 (ABvac40) ≤ average MΔ anti-Aβ40 (placebo)
- Alternative hypothesis: average MΔ anti-Aβ40 (ABvac40) > average MΔ anti-Aβ40 (placebo)

If the assumption of normality of the distribution of MΔ in anti-Aβ40 antibody signal is violated, a Mann–Whitney U test will be used to compare the treatment groups.

In addition, the average MΔ of anti-Aβ40 antibody signal between the two treatment groups will be compared using an Analysis of Covariance (ANCOVA) model, using the MΔ anti-Aβ40 antibody signal as the dependent variable, baseline anti-Aβ40 antibody signal (OD in ELISA) as covariate and treatment group and amyloid positivity as fixed effects.

The number and percentage of patients reaching a value greater than or equal to the treatment MΔ will be tabulated by treatment group for each visit.

MΔ negative values will not be imputed to zero.

The number and percent of Positive Responders/Non-Responders will be presented for the ABvac40 treatment group, by visit.

Each analysis will be performed using the mITT Analysis Set. In addition, a listing of anti-Aβ40 antibody signal will be presented, along with the calculated change from baseline and a flag/flags indicating the maximal increment(s) for each patient.

6.1.2 Sensitivity Analyses for Primary Outcome

No adjustments will be made for multiple testing of study parameters. Therefore, interpretation of p-values for these sensitivity analyses should be considered descriptive in nature.

The following analyses will be performed for the primary outcome:

1. The primary analyses will be repeated for the PP Analysis Set.
2. The primary analysis (t-test) will be repeated, using the mITT Analysis Set to test the hypothesis:
    - Null hypothesis: average MΔ anti-Aβ40 (ABvac40) - average MΔ anti-Aβ40 (placebo) ≤ 1.778
    - Alternative hypothesis: average MΔ anti-Aβ40 (ABvac40) - average MΔ anti-Aβ40 (placebo) > 1.778
3. The change in anti-Aβ40 antibody signal from baseline to each post-baseline efficacy visit will be analyzed using a Mixed-Model Repeated Measures (MMRM), using the mITT Analysis Set.

    The MMRM will include change from baseline in anti-Aβ40 antibody signal as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline anti-Aβ40 antibody signal and baseline age as covariates; and measures within-patient at each visit as a repeated measure. The variance-covariance matrix will be assumed to be unstructured. If the procedure does not converge then a compound symmetric variance-covariance matrix will be used instead.

    The least squares (LS) mean change from baseline will be presented for each treatment group (ABvac40 and placebo) for each post-baseline scheduled visit, along with the LS mean treatment difference (ABvac40 – placebo), 95% CI for mean treatment difference and p-value for comparison of treatment groups.

    The following is sample SAS® code for the MMRM:

```
proc mixed data=pp method=ml;
   class Patient Treatment Visit a_PET;
   model change = Baseline a_PET Treatment Visit age
                  Treatment*Visit / s;
   repeated Visit / type=un subject=Patient r;
   lsmeans Treatment*Visit / pdiff cl;
run;
```

A plot of LS means over time will be presented by treatment group.

6.1.3 Analysis of Secondary Outcome Variables

No adjustments will be made for multiple testing of study parameters. Therefore, interpretation of p-values for the analyses of secondary outcomes should be considered descriptive in nature.

The following analyses will be performed for all secondary outcomes specified in section 4.2.2 of this SAP (above), using the ITT Analysis Set:

1. The MMRM analysis described in section 6.2 will be repeated for all continuous parameters.

   With the exception of levels of anti-Aβ40 antibodies in CSF and plasma, the dependent variable will be the change from baseline in secondary outcome as the dependent variable; treatment, protocol-specified visits, treatment-by-visit interaction, and amyloid positivity as the fixed effects; baseline secondary outcome and baseline age as covariates; and measures within-patient at each visit as a repeated measure.

   For the analysis of levels of anti-Aβ40 antibodies in CSF and plasma, the dependent variable with the be recorded outcome value (i.e. not the change from baseline) and the baseline outcome covariate will be removed from the model.

   The following factors may also be included in the model: ApoE carrier status, baseline use of AD symptomatic medication and clinical subgroup – MCI or vmAD, if found to be significantly associated with the response measure ($p < 0.15$).

2. A plot of LS mean change over time will be presented by treatment group.

All analysis will be repeated for baseline a-PET positive and baseline a-PET negative patients separately for the following parameters:

1. Disease biomarkers – all parameters listed in section 4.2.2.2 above.
2. Cognition assessment – MMSE, CDR-SB, RBANS, ADCS-ADL MCI, C-SSRS, IGE, EQ-5D-5L and TMT.

6.2 Parts A and B Combined

The primary endpoint will be summarized by treatment sequence and visit, using the mITT analysis set. All secondary endpoints will be summarized by treatment sequence and visit, using the ITT analysis set. In addition to all summary statistics listed in section 3 above, the 95% confidence intervals for the mean response will be provided.

A plot of the mean concentration of each endpoint over time, along with 95% CI for mean, will be presented by treatment sequence.

7 SUMMARY OF SAFETY ASSESSMENTS

All summaries will be presented using the Safety Analysis Set.

7.1 Study Treatment Compliance

Percentage compliance to study drug administration will be calculated as:

% Compliance = (Number of doses of study drug taken in Part A*100)/6, rounded to 1 decimal place, where 6 = number of planned doses for Part A

% Compliance = (Number of doses of study drug taken in Part B*100)/6, rounded to 1 decimal place,

where 6 = number of planned doses for Part B

Compliance will further be categorized into the following groups: (<80%, ≥80% to 100%).

Summaries of the calculated compliance and the categorized compliance will be presented by treatment sequence and study part. The denominator for the percent of patients within each compliance category will be the number of patients in the safety analysis set who entered the specific study part. A listing of study treatment compliance will also be presented.

7.2 Summary of Primary Safety Outcome

7.2.1 Adverse Events

Adverse events will be classified as Treatment-Emergent AEs (TEAEs) or non-Treatment-Emergent AEs (non-TEAEs), based on the comparison of the AE onset date/time with the start date/time of study treatment.

- A TEAE will be defined as an AE which starts or worsens in severity during or after the first administration of study treatment.
- A non-TEAE will be defined as an AE which starts or worsens in severity prior to the start of the first administration of study treatment.

The following algorithm will be used to identify the treatment group under which each AE will be summarized:

For SAESIs:

- AEs that start or worsen in severity at any time after a patient's first dose of ABvac40 will be associated with the ABvac40 treatment group.
- AEs that start or worsen in severity after first dose of Placebo, but before first dose of ABvac40, will be associated with the Placebo treatment group

For non-SAESIs:

- For patients randomised to the ABvac40 arm Part A / Placebo+Booster arm Part B treatment sequence:
    - AEs that start or worsen in severity at any time during or after a patient's first dose of study drug in part A and prior to their booster ABvac40 vaccination will be associated with the treatment received at their last injection prior to the AE.
    - AEs that start or worsen in severity during or after a patient's booster ABvac40 vaccination will be associated with the ABvac40 treatment group.

- For patients randomised to the Placebo arm Part A / ABvac40 arm Part B treatment sequence:
    - AEs will be associated with the treatment received at their last injection prior to the AE.

For the purposes of classifying AEs as treatment emergent and to assign treatment groups, partial AE start and end dates will be imputed to allow comparison with the study treatment date start and end dates. Section 9.1.1 below presents the imputation rules. Note, the imputed dates will be used for classification purposes and treatment group assignment purposes only and the original partial AE dates will be presented in data listings.

An overall summary of AEs will be presented by treatment group, by providing counts and percentages of patients with any: TEAE, non-TEAE, Treatment related TEAEs, TEAE leading to treatment discontinuation, TEAEs leading to death, Treatment-Emergent Serious AE (TESAE), Treatment-

Emergent SAESIs, Treatment related TESAEs, TESAEs leading to treatment discontinuation and TESAEs leading to death.

Counts and percentages of patients will be presented by treatment group, SOC and PT for the following: TEAEs, non-TEAEs, TEAEs leading to study withdrawal, Treatment-Emergent SAESIs and TESAEs.

Counts and percentages of patients with TEAEs will be presented by treatment group, SOC, PT and maximum causality.

Counts and percentages of patients with TEAEs will be presented by treatment group, SOC, PT and maximum severity.

For summaries by maximum causality/severity, if a patient reported more than one AE with the same PT, the AE with the maximum causality/severity will be presented. If the causality/severity of an AE is missing, the causality/severity will be treated as missing in summaries. If a patient reported more than one AE within the same SOC, the patient will be counted only once under the maximum causality/severity within the SOC.

The denominator for the percentages for the ABvac40 group will be all patients in both the ABvac40 arm Part A / Placebo+Booster arm Part B and Placebo arm Part A / ABvac40 arm Part B treatment sequences who took at least one dose of ABvac40 throughout the study.

The denominator for the percentages for the Placebo group will be all patients in both the ABvac40 group Part A / Booster group Part B and the Placebo arm Part A / ABvac40 arm Part B treatment sequence who took at least one dose of Placebo.

In Part B, the safety population will be those subjects who received at least one dose.

AEs will be listed by treatment group and patient identifier. In addition, patients with SAEs and AEs leading to premature discontinuation of treatment period from the study will be individually listed.

7.3 Summary of Secondary Safety Outcomes

7.3.1 Withdrawal Criteria (Study Continuation Decision)

Summary of withdrawal criteria and study continuation decision will be presented as part of the summary of disposition, see section 5.1 above.

7.3.2 Physical Examination

Physical examination results will summarized in the form of a shift table, presenting the shift in results (Normal, Abnormal non-clinically significant, Abnormal clinically significant, Not done) from baseline to each post-baseline visit, by treatment sequence group for Part A and Part B.

A listing of physical abnormalities will also be presented.

7.3.3 Neurological Examination

Neurological examination results will summarized in the form of a shift table, presenting the shift in results (Normal, Abnormal non-clinically significant, Abnormal clinically significant, Not done) from baseline to each post-baseline visit, by treatment sequence group for Part A and Part B.

A listing of neurological abnormalities will also be presented.

7.3.4 Prior and Concomitant Medications

Prior and concomitant medications will be summarized separately, by treatment sequence, medication class (ATC level 2) and medication sub-class (ATC level 4). Summaries of concomitant medications will be presented for Part A only, Part B only and separately for parts A and B combined.

Medications will be sorted alphabetically by ATC level 2 and ATC level 4. If the ATC level 4 term is missing, the ATC level 3 term will be used in the medication summary table and data listing.

Appendix 9.1.2 outlines the conventions that will be used to impute missing or partial medication start/end date information in order to determine whether a medication is prior or concomitant.

A listing of prior and concomitant medications will also be presented. Medication start/end dates will be presented as recorded in the electronic Case Report Form.

7.3.5 Vital Signs

Vital signs parameters will be summarized by timepoint within each scheduled visit and treatment sequence group for Part A and Part B. The summaries will include change from baseline to each timepoint within each scheduled post-baseline visit. A listing of vital signs results will also be presented.

7.3.6 Electrocardiogram

ECG parameters HR, PR interval, QRS and QT will be summarized by study visit and treatment sequence group for Part A and Part B.

Each of the ECG parameters were classified as normal or abnormal at each visit. Using this information, the overall ECG finding at each visit will be categorized as:

- Abnormal – if any one of the individual ECG parameters are abnormal at that visit
- Normal – if all the individual ECG parameters are normal at that visit
- Missing – if at least one of the individual ECG parameters is missing and none of the non-missing ECG parameters are abnormal.

These categorizations of ECG findings will be summarized using a shift table, presenting the count and percentage of patients whose categorizations change or remain the same from baseline to each post-baseline scheduled visit. The shift table will be presented by treatment sequence and will include "Missing" as a result category

A listing of ECG findings and results will also be presented.

7.3.7 Laboratory Assessments

Appendix 9.3 provides a list of laboratory assessments that will be summarized.
Continuous parameters will be summarized by scheduled visit and treatment sequence group for Part A and Part B. The summaries will include change from baseline to each scheduled post-baseline visit.

In addition, the laboratory results will be categorized as

- Normal
- Abnormal Low – Clinically Significant (CS)
- Abnormal Low – Not Clinically Significant (NCS)
- Abnormal High – CS
- Abnormal High – NCS

based on laboratory normal ranges and the categorization of clinical significance of out of range results. These categorizations will be summarized using shift tables, presenting the count and percentage of patients whose categorizations change or remain the same from baseline to each post-baseline scheduled visit for each parameter. Shift tables will be presented by treatment sequence and will include "Missing" as a result category.

Laboratory results with discrete or categorical results will be summarized using frequency tables presenting the count and percentage of patients with results within each category of result, by scheduled visit and treatment sequence for Part A and Part B.

A listing of laboratory results will also be presented.

8 REFERENCES

[1] Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. JAMA 1983;249(13):1743-5.

9 APPENDICES

9.1 Imputation rules

9.1.1 AE date imputation

The following rules will be applied to impute AE start/end dates when partial AE start/end dates have been recorded. The imputed dates will be used for the determination of TEAEs only. The original partial AE dates will be presented in data listings.

AE start date imputation:

AE start date imputation will be based on a comparison of the partial AE start date and the treatment start date. Table 2-1 presents the notation that will be used to describe the rules for imputation of partial AE start dates.

Table 2-1 Notation for imputation of partial AE start dates

	Year	Month	Day
Partial AE start date	YYYY	MON	Not used
Study treatment start date	TRTY	TRTM	Not used

Table 2-2 presents a matrix of rules for the imputation of AE start dates.

Table 2-2 AE start date imputation

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	NULL Uncertain	NULL Uncertain	NULL Uncertain	NULL Uncertain
YYYY < TRTY	(D) = 01JULYYYY Before Treatment Start	(C)= 15MONYYYY Before Treatment Start	(C)= 15MONYYYY Before Treatment Start	(C)= 15MONYYYY Before Treatment Start
YYYY = TRTY	(B)= TRTSTD+1 Uncertain	(C)= 15MONYYYY Before Treatment Start	(A)= TRTSTD+1 Uncertain	(A)= 01MONYYYY After Treatment Start
YYYY > TRTY	E= 01JANYYYY After Treatment Start	(A)= 01MONYYYY After Treatment Start	(A)= 01MONYYYY After Treatment Start	(A)= 01MONYYYY After Treatment Start
Before Treatment Start		Partial indicates date prior to Treatment Start Date		
After Treatment Start		Partial indicates date after Treatment Start Date		
Uncertain		Partial insufficient to determine relationship to Treatment Start Date		
LEGEND:				

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
NULL		No imputation		
(A)		Max(01MONYYYY,TRTSTD+1)		
(B)		TRTSTD+1		
(C)		15MONYYYY		
(D)		01JULYYYY		
(E)		01JANYYYY		

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL (i.e. no imputation).
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:

    a. if the AE year is less than the treatment year and the AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).

    b. else, if the AE year is less than the treatment year and the AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:

    a. if the AE year is greater than the treatment year and the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).

    b. else, if the AE year is greater than the treatment year and the AE month is not missing, the imputed AE start date is set to the month start point (01MONYYYY).
4. If the AE start date year value is equal to the treatment start date year value:

    a. and the AE month is missing or the AE month is equal to the treatment start month, the imputed AE start date is set to one day after treatment start.

    b. else, if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).

    c. else, if the AE month is greater than the treatment start month, the imputed AE start date is set to the start month point (01MONYYYY).

Imputed AE date flag

If the year of the imputed date is not equal to YYYY then imputed date flag = Y, else if month of the imputed date is not equal to MON then imputed date flag = M, else if day of the imputed date is not equal to day of original date then imputed date flag = D, else imputed date flag = null.

9.1.2 Prior and concomitant medication date imputation

The following rules will be applied to impute medication start/end dates when partial medication start/end dates have been recorded. The imputed dates will be used to distinguish between prior and concomitant medications only. The original partial medication dates will be presented in data listings.

- The missing day of start date of a medication will be set to the first day of the month that the medication was taken.
- The missing day of end date of a medication will be set to the last day of the month of the occurrence.
- If the start date of a medication is missing both the day and month, the medication start date will be set to January 1 of the year of medication start.
- If the end date of a medication is missing both the day and month, the date will be set to December 31 of the year of occurrence.
- If the start date of a medication is null and the end date is not a complete date, then the start date will be set to the date of the first study visit.
- If the start date of a medication is null and the end date is a complete date
    - and the end date is after the date of the first study visit then the start date will be set to the date of the first study visit.
    - otherwise the start date will be set to the end date of the medication.
- If the end date of a medication is null and the start date is not a complete date, then the end date will be set to the date of the last study visit.
- If the end date of a medication is null and the start date is a complete date
    - and the start date is prior to the date of the last study visit then the end date will be set to the date of the last study visit.
    - otherwise, the end date will be set to the start date of the medication

Imputed medication date flag

If the year of the imputed date is not equal to the year of the original medication date then imputed date flag = Y, else if the month of the imputed date is not equal to the month of the original medication date then imputed date flag = M, else if the day of the imputed date is not equal to the day of the original medication date then imputed date flag = D, else imputed date flag = null. Imputed medication date flags will be created separately for both medication start and end dates.

9.2 Changes to protocol specified analyses

The definition of the ITT analysis set was changed from the protocol to the SAP and a mITT analysis set was introduced. In addition, the SAP specifies that the mITT analysis set will be used for the analysis of the primary endpoint and the ITT analysis set will be used for the analysis of all secondary efficacy endpoints.

The definition of the mITT analysis set is identical to the definition of the ITT analysis set in the protocol, ensuring that the population of patients entering the analysis of the primary endpoint remains as planned in the protocol.

The ITT analysis set was redefined in the SAP to remove the restriction of patients requiring a baseline and at least one post-baseline anti-Ab40 antibody assessment. This is to ensure that valid data from secondary endpoints are not excluded from the analysis, based on the availability of primary endpoint assessments.

Additional per-protocol analysis sets were introduced.

> The Part A PPc Analysis Set comprising of all patients in the ITT Analysis Set who received all doses of study medication (on V1, V4, V7, V10, V13 and V18), have attended the safety visit after booster (V20), have no major protocol deviations that could affect the efficacy analyses or major protocol deviations that have been classified as “Use of disallowed concomitant medication”, relating to use of Anti-Alzheimer Disease medication.
>
> The Part B PPc Analysis Set will comprise of all patients in the ITT Analysis Set who received all doses of study medication (on V1B, V4B, V7B, V10B, V13B and V18B in Part B), have attended the safety visit after booster (V20B in Part B), have no major protocol deviations that could affect the efficacy analyses or major protocol deviations that have been classified as “Use of disallowed concomitant medication”, relating to use of Anti-Alzheimer Disease medication.

The PPc Analysis Sets will be used for the sensitivity analysis of secondary efficacy endpoints relating to the assessment of cognition and quality of life, while the PP Analysis Sets will be used for the sensitivity analysis of the primary efficacy endpoint and secondary efficacy endpoints relating to the characterization of immune response and the assessment of disease biomarkers.

Level of anti-Aβ40 antibodies in plasma has been added as a secondary outcome, to further characterize immune response.

Table 2-3 presents variables those were not analyzed by the Araclon or vendor:

Table 2-3 Variables not analyzed

Variables	Analyzed	
	Part A	**Part B**
Anti-Aβ42 antibodies in plasma samples	No	No (not planned)
Antibody secreting cells	Yes	No
Peripheral blood cell subsets by immunophenotyping	No	No (not planned)
Cytokine-secreting cells	Samples from only a small number of patients were analyzed. Hence, data for this analysis will not be reported.	No (not planned)
CFS biomarkers (Tau, P-tau, neurofilament light and neurogranin)	Yes	No
Other Aβ peptide species in CSF	No	No

Both the quantification of the Levels of cytokines in plasma; IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-15, TNF-α and IFN-γ and the analysis of cytokine -secreting cells in plasma had the common objective of characterizing the immune response type. Therefore, it was decided to proceed only with the analysis of cytokine-secreting cells (Th1 and Th2 response) to minimize execution times and costs associated with the study. However, samples from only a small number of patients were analyzed. Hence, data for this analysis will not be reported.

9.3 Laboratory test parameters

Table 3-1 provides a listing of laboratory test parameters that will be recorded throughout the study and details of which parameters will be summarized descriptively.

Table 3-1 List of laboratory test parameters

Lab Category	Lab Sub-Category	Test Parameter	Summarize
Biochemistry	Electrolytes	CALCIUM / SERUM	Y
Biochemistry	Electrolytes	CHLORIDES / SERUM	Y
Biochemistry	Electrolytes	PHOSPHORUS / SERUM	Y
Biochemistry	Electrolytes	POTASSIUM / SERUM	Y
Biochemistry	Electrolytes	SODIUM / SERUM	Y
Biochemistry	Enzymes	ALKALINE PHOSPHATASE	Y
Biochemistry	Enzymes	ALT-SGPT	Y
Biochemistry	Enzymes	AST-SGOT	Y
Biochemistry	Enzymes	CREATINE KINASE	Y
Biochemistry	Enzymes	GAMMA-GT	Y
Biochemistry	Enzymes	LDH / SERUM	Y
Biochemistry	Substrates	ALBUMIN / SERUM	Y
Biochemistry	Substrates	APOLIPOPROTEIN E	Y
Biochemistry	Substrates	BLOOD UREA NITROGEN (BUN) / SERUM	Y
Biochemistry	Substrates	CHOLESTEROL	Y
Biochemistry	Substrates	C-REACTIVE PROTEIN / SERUM	Y
Biochemistry	Substrates	CREATININE / SERUM	Y
Biochemistry	Substrates	FERRITIN	Y
Biochemistry	Substrates	GLUCOSE / SERUM	Y
Biochemistry	Substrates	TOTAL BILIRUBIN / SERUM	Y
Biochemistry	Substrates	TOTAL PROTEIN / SERUM	Y
Biochemistry	Substrates	TRIGLYCERIDES	Y
Biochemistry	Substrates	UREA / SERUM	Y
Biochemistry	Substrates	URIC ACID / SERUM	Y
Coagulation		aPTT	Y
Coagulation		FIBRINOGEN	Y
Coagulation		HAEMOGLOBIN A1C	Y
Coagulation		INR	Y
Coagulation		PROTHROMBIN TIME	Y
Coagulation		RATIO	Y
Hematology		BASOPHILS	Y
Hematology		BASOPHILS %	Y
Hematology		EOSINOPHILS	Y
Hematology		EOSINOPHILS %	Y
Hematology		ERYTHROCYTES	Y
Hematology		HAEMOGLOBIN	Y
Hematology		HEMATOCRIT	Y
Hematology		LEUKOCYTES	Y
Hematology		LYMPHOCYTES	Y
Hematology		LYMPHOCYTES %	Y
Hematology		MCH	Y
Hematology		MCHC	Y
Hematology		MCV	Y
Hematology		MONOCYTES	Y
Hematology		MONOCYTES %	Y
Hematology		MPV	Y
Hematology		PDW	Y
Hematology		PLATELETS	Y
Hematology		RDW	Y
Hematology		TOTAL NEUTROPHILS	Y

Lab Category	Lab Sub-Category	Test Parameter	Summarize
Hematology		TOTAL NEUTROPHILS %	Y
Homocysteine		HOMOCYSTEINE	Y
Hormones		FREE T4 (FREE THYROXINE)	N
Hormones		TSH (THYROID-STIMULATING HORMONE)	N
Immunology		ANTI-NUCLEAR ANTIBODIES	N
Immunology		IMMUNOFLUORESCENT PATTERN	N
Immunology		NATIVE dsDNA ANTIBODIES	N
Immunology		Native dsDNA antibodies result	N
Immunology		THYROGLOBULIN ANTIBODIES	N
Immunology		TPO ANTIBODIES	N
Serology		HEPATITIS B SURFACE ANTIGEN (HBsAg)	N
Serology		HEPATITIS C ANTIBODIES	N
Serology		HUMAN IMMUNODEFICIENCY VIRUS, 4TH GENERATION TEST	N
Serology		RHEUMATOID FACTOR	N
Serology		RPR TEST	N
Serology		TREPONEMA PALLIDUM TOTAL ANTIBODIES	N
Urinalysis		Bacterial flora	N
Urinalysis		Calcium oxalate crystals	N
Urinalysis		Epithelial cells	N
Urinalysis		Erythrocytes	N
Urinalysis		Leukocytes	N
Urinalysis		Normal sediment	N
Urinalysis		Uric acid crystals	N
Urinalysis		BLOOD	N
Urinalysis		DENSITY	N
Urinalysis		GLUCOSE	N
Urinalysis		KETONE	N
Urinalysis		LEUCOCYTES	N
Urinalysis		NITRITES	N
Urinalysis		PH	N
Urinalysis		PROTEINS	N
Urinalysis		UROBILIN	N
Urinalysis		UROBILINOGEN	N
Vitamins		FOLIC ACID (FOLATE)	Y
Vitamins		VITAMIN B12	Y