Statistical Analysis Plan NewAmsterdam Pharma

Protocol title:	A Phase 2a, Proof-of-Concept, Open-Label Study to Evaluate the Pharmacodynamics, Pharmacokinetics, and Safety of Obicetrapib in Patients with Early Alzheimer's Disease (Hetero/Homozygote APOE4 Carriers)
Protocol number:	TA-8995 AD-1
Protocol version/date:	V4.0/ 30 November 2021
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Signature page

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DocuSigned by:

[redacted]

Version history

Version	Version date	Description
1.0	24 APRIL 2023	Original document
2.0	5 JUNE 2023	Added campesterol, sitosterol to analysis
3.0	22 AUGUST 2023	Changed analysis based on available data points, meaning CSF analysis all Wilcoxon and post hoc plasma analysis will be performed on 12 patients.
4.0	28 NOVEMBER 2023	Addition of analysis plan on new outcomes. Removed sentence from V3 description because it was left in error.

List of abbreviations

Abbreviation	Definition
AD	Alzheimer's Disease
AE	Adverse event
ApoA1	Apolipoprotein A1
ApoA2	Apolipoprotein A2
ApoB	Apolipoprotein B
ApoE	Apolipoprotein E
APOE E4	Apolipoprotein E – E4 genotype
Aβ	Amyloid β
CDR-SB	Clinical Dementia Rating scale – Sum of Boxes
CFC	Cognitive functional composite
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
ECG	Electrocardiogram
EOT	End of treatment
ET	Early termination
GFAP	Glias fibrillary acidic protein
HbA1c	Hemoglobin A1c
HDL-ApoE	High-density lipoprotein with apolipoprotein E
HDL-C	High-density lipoprotein cholesterol
ICF	Informed consent form
LDL-C	Low-density lipoprotein cholesterol
MMSE	Mini-mental state exam
MRI	Magnetic resonance imaging
NIA-AA	National Institute on Aging and Alzheimer's Association
Non-HDL-c	Non-high-density lipoprotein cholesterol
PD	Pharmacodynamic
PK	Pkarmacokinetic
pTau	Phosphorylated Tau
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sTREM2	Soluble triggering receptor expressed on myeloid cells 2
TC	Total cholesterol
TG	Triglycerides
tTau	Total Tau

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1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from NewAmsterdam Pharma BV Protocol TA-8995 AD-1. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2. Study overview

2.1 Study objectives

2.1.1 Primary objective

The primary objective of this study is to evaluate the pharmacodynamics (PD) (apolipoproteins/lipid particles and cholesterol efflux) of obicetrapib in cerebrospinal fluid (CSF) and plasma (apolipoproteins/lipid particles) in patients with early Alzheimer's Disease (AD) (hetero/homozygote APOE4 carriers).

2.1.2 Exploratory objectives

The exploratory objectives of this study are to evaluate:

- other PD markers of obicetrapib (additional lipoproteins, neurodegeneration, and inflammation) in patients with early AD.
- the cognitive effects of obicetrapib in patients with early AD.
- the pharmacokinetics (PK) of obicetrapib in patients with early AD.

The safety objective of this study is to evaluate the safety and tolerability of obicetrapib in patients with early AD.

2.2 Study design

2.2.1 Overview

POPULATION: The population for this study includes men and women, 50 to 75 years of age at Screening, with a clinical diagnosis of AD Stage 3 or 4 based on the National Institute on Aging-Alzheimer's Association (NIA-AA) Research Framework criteria. Patients must have an APOE genotype of E4/E4 or E3/E4.

STUDY DESIGN AND DURATION: This study will be a proof of concept, Phase 2a study in patients with early AD to evaluate the PD, cognitive effects, PK, and safety and tolerability of obicetrapib therapy. Study duration for individual patients will approximately be 36 weeks (Screening: 1 to 8 weeks, Treatment: 24 weeks, and Follow-up: 4 weeks).

Screening Period

At the Screening Visit, patients and their study partners will be required to sign an informed consent form (ICF) before any study-related procedures are performed. After signing the ICF, patients will be assessed for study eligibility.

Treatment Period

Patients will come to the site on Day 1 (Visit 2) to begin treatment. Approximately 10 to 15 eligible patients will receive obicetrapib 10 mg once a day.

During the 24-week Treatment Period, the study drug will be administered by the patient orally and once daily on Days 1 through 168. Patients will return to the site every 6 weeks (+/- 6 days) for study assessments.

Safety Follow-up Period

Patients will be contacted by phone for a Safety Follow-up Visit (Visit 7) approximately 4 weeks (+/- 6 days) after the end of the Treatment Period for collection of AEs.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION: The study drug will consist of 5 mg obicetrapib tablets.

Two tablets of study drug (10 mg in total) will be administered by the patient orally and once daily on Day 1 to Day 168 at approximately the same time each morning.

Table 1. Study procedures

Study period	**Screening**	**Treatment Period**					**Follow-Up ☎ (V7)**
		Baseline (V2)	**V3**	**V4**	**V5**	**EOT/ET[9] (V6)**	
Day (±Visit Window)	**1-8 weeks**	**D1**	**D42 ±6d**	**D84 ±6d**	**D126 ±6d**	**D168 ±6d**	**D198 ±6d**
Informed consent[1]	X						
Inclusion/exclusion criteria	X	X					
Demographic data	X						
Medical history and baseline conditions	X						
C-SSRS		X	X	X	X	X	
Height and weight[2]	X					X	
Vital signs[3]	X	X	X	X	X	X	
ECG[4]	X					X	
FSH test[5]	X						
Urine pregnancy test[5]	X					X	
Hematology, chemistry and urinalysis	X	X[6]	X[7]	X[6]	X[7]	X	
HbA1c	X						
Thyroid function	X						
Folic acid and vitamin B12 levels	X						
APOE E4 testing	X						
MRI-cerebrum[11]	X						
Physical examination	X	X		X		X	
Neurological examination	X	X		X		X	
Prior and concomitant medications	X	X	X	X	X	X	
Dispense study drug		X	X	X	X		
Study drug administration[8]		X	X	X	X	X	
Study drug compliance check			X	X	X	X	
Adverse events	X	X	X	X	X	X	X
CDR	X						
MMSE	X	X		X		X	
CFC		X				X	
Plasma sample for PD and PK		X		X[12]		X[12]	
CSF sample for PD and PK	X			X[10]		X	

APOE E4 = apolipoprotein E-E4; CFC = Cognitive-Functional Composite; CDR = Clinical Dementia Rating; ECG = electrocardiogram; EOT = End of Treatment; ET = Early Termination; HbA1c = hemoglobin A1c; MMSE = mini-mental state examination; MRI = magnetic resonance imaging.

Note: In cases of COVID-19 limitations, it is the Investigator's responsibility to assure the safety of patients, including phone or video contact to assess the patient's well-being including any adverse event, collection of study samples and clinical data as best as possible, and direct shipment of study drug to the patient, if necessary. Where available and appropriate, home health care may be considered to facilitate monitoring of safety and study continuity. Documentation of these cases and the study site's management of patients should be recorded in the Investigator study files. In the absence of a COVID-19 impact, it is expected that Investigators and patients follow the protocol requirements as set forth.

1. Signed informed consent must be obtained before any study-related procedures are performed.
2. Height and weight will be measured at the Screening Visit and will be used to calculate body mass index. Weight only will be measured at the EOT visit. Measurement of weight should be performed with the patient dressed in indoor clothing, with shoes removed, and bladder empty.
3. Vital signs will include body temperature, heart rate, and triplicate blood pressure (systolic and diastolic) measurements.
4. A single, standard 12-lead ECG will be performed by the Investigator or trained site personnel at the Screening Visit and at the EOT visit.
5. FSH test and urine pregnancy test will be performed in women <55 years of age
6. Only clinical chemistry panel to be performed (Appendix B)
7. Clinical chemistry and part of hematology (PT, PTT, INR and platelets) only (Appendix B)
8. Study drug will be administered by the patient orally and once daily on Days 1 through 168. Study drug should be administered at approximately the same time each morning.
9. Early Termination Visit only for patients who withdraw prematurely from the study.
10. Optional lumbar punction.
11. MRI is to be performed only in patients without historical MRI available within 6 months of the Screening Visit.
12. A single trough PK sample will be drawn on Day 84 and 168 prior to dose to measure trough levels of obicetrapib

2.2.2 Randomization and blinding

Patients who meet all eligibility criteria will be enrolled into the study. All patients will be treated with obicetrapib 10 mg. No blinding or randomization is required.

2.2.3 Study drug

Patients will be treated with 10 mg obicetrapib once a day.

Compliance to the study drug regimen will be evaluated by counting unused tablets and capsules. During the Treatment Period, if compliance is not between 80% and 120%, inclusive, the patient will be counselled about the importance of compliance to the regimen. If the limits are exceeded at 2 consecutive visits, a decision will be made by the Investigator and Sponsor as to whether the patient should be withdrawn from the study.

2.2.4 Sample size determination

No formal sample size determination was performed. A total number of 10 to 15 patients is considered sufficient for this proof-of-concept study.

2.3 Study endpoints

2.3.1 Primary pharmacodynamic endpoints

The primary PD endpoint is the change from baseline in levels of apolipoprotein A-I (ApoA-I), apolipoprotein E (ApoE), small high-density lipoprotein (HDL) particles, in both CSF as well as plasma and ABCA1-driven cholesterol efflux in CSF measured at Day 168.

2.3.2 Exploratory pharmacodynamic endpoints

Exploratory analyses may be performed to further investigate the PD of obicetrapib. These may include, but might not be limited to, the following assays at selected time points:

<u>Changes From Baseline Levels in Lipoproteins and Apolipoproteins in Plasma</u>

At Baseline (Visit 2), at Day 84 (Visit 4), and the End of Treatment (Day 168, Visit 6), the following parameters will be measured:

- LDL-C
- Total cholesterol (TC)
- Non-HDL-C
- TG
- ApoB

<u>Changes From Baseline Levels in Lipoproteins and Apolipoproteins in CSF and Plasma</u>

At Screening (Visit 1) or Baseline (Visit 2), at Day 84 (Visit 4), and at the End of Treatment (Day 168, Visit 6), the following parameters will be measured:

- HDL-C
- HDL-ApoE
- Apolipoprotein A-II (ApoA-II)

Note, baseline levels of CSF lipoproteins and apolipoproteins will be determined at Screening (Visit 1) since CSF sampling is required for inclusion. Baseline levels of plasma lipoproteins and apolipoproteins will be determined at Baseline (Visit 2). CSF sampling for CSF lipoproteins and apolipoproteins at Day 84 (Visit 4) is optional.

Change From Baseline Levels in AD Biomarkers in CSF

At Screening (Visit 1), at Day 84 (Visit 4), and at the End of Treatment (Day 168, Visit 6), the following parameters will be measured in the CSF:

- Tau and phosphorylated tau at Thr181 (p-Tau 181)
- Aβ1-42, Aβ1-40, Aβ1-42/Aβ1-40 ratio
- Neurogranin
- Neurofilament light
- Glial fibrillary acidic protein (GFAP)
- sTREM2
- YKL40
- Inflammatory markers (eg, interferon [IFN]-γ, IL-10, IL-12p70, IL-17A, IL-6, TNF-α)

Note, CSF sampling for AD biomarkers in CSF at Day 84 (Visit 4) is optional.

Change From Baseline Levels in AD Biomarkers in Plasma

At Baseline (Visit 2), at Day 84 (Visit 4), and the End of Treatment (Day 168, Visit 6), the following parameters will be measured in the plasma:

- Tau and p-Tau epitopes
- Aβ1-42, Aβ1-40, Aβ1-42/Aβ1-40 ratio
- Neurofilament light

Correlation Between the Change From Baseline Levels in CSF p-Tau 181 and CSF ApoA-I, ApoE, and Cholesterol Efflux Capacity

At Screening (Visit 1) and at the End of Treatment (Day 168, Visit 6), p-Tau 181, ApoA-I, ApoE, and cholesterol efflux capacity will be measured in the CSF.

Change From Baseline Levels in 24-Hydroxycholesterol and 27-Hydroxycholesterol in CSF and Plasma

At Baseline (Visit 2), Day 84 (Visit 4), and the End of Treatment (Day 168, Visit 6), 24 hydroxycholesterol and 27 hydroxycholesterol will be measured in the CSF and plasma samples.

Note, CSF sampling for 24-hydroxycholesterol, 27-hydroxycholesterol, desmosterol, and lathosterol in CSF at Day 84 (Visit 4) is optional.

2.3.3 Exploratory cognition endpoints

Disease Progression Measured With the Cognitive-Functional Composite

At Baseline (Visit 2) and the End of Treatment (Day 168, Visit 6), the CFC test will be administered to allow tracking of disease progression.

Mini-Mental State Examination

At Screening (Visit 1), Baseline (Visit 2), Day 84 (Visit 4), and the End of Treatment (Day 168, Visit 6), the MMSE will be administered.

2.3.4 Exploratory pharmacokinetic endpoints

Mean Plasma Levels of Obicetrapib at Steady State in CSF and Plasma

At Screening obicetrapib concentrations will be measured in the CSF. At Day 1 (Visit 2) obicetrapib concentrations will be measured in plasma. At Day 84 (Visit 4) and the End of Treatment (Day 168, Visit 6), obicetrapib concentrations will be measured in the CSF and plasma samples.

3. Statistical methodology

3.1 General considerations

3.1.1 Analysis day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. Day 0 will be seen as Baseline.

3.1.2 Definition baseline

Unless otherwise stated, Baseline will be defined as the last measurement prior to the first dose of study drug.

3.1.3 Summary statistics

Categorical data will generally be summarized with counts and percentages of participants. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum.

3.1.4 Handling of dropouts and missing data

Date Values

In cases of incomplete dates (e.g. AE, concomitant medication, and medical history start and/or stop dates), the missing component(s) will be assumed as the most conservative value possible. For example, if the start date is incomplete, the first day of the month will be imputed for the missing day and January will be imputed for the missing month. If a stop date is incomplete, the last day of the month will be imputed for the missing day and December will be imputed for the missing month. Incomplete start and stop dates will be listed as collected without imputation.

Date imputation will only be used for computational purposes such as treatment-emergent status. Actual data values, as they appear in the original CRFs, will be presented within the data listings.

Non-Date Values

For the analyses of primary, secondary and cognitive efficacy endpoints, no imputation will be made for missing values. Safety data will be used according to availability, with no imputation for missing data.

3.2 Analysis populations

3.2.1 Intent-To-Treat (ITT) population

The Intent-to-Treat (ITT) Population will include all patients who receive at least 1 dose of study drug.

3.2.2 Per-Protocol (PP) population

The Per-Protocol (PP) Population will include all patients who have a study drug compliance percentage of at least 80% over the entire study duration. The PP Population will be the primary population used for the PD and PK analyses, and for the analyses of the effects of obicetrapib on cognition.

3.2.3 Safety population

The Safety Population will include all patients who receive at least 1 dose of study drug, same as the ITT population. The Safety Population will be the primary population used for the safety analyses.

3.3 Subject data and study conduct

3.3.1 Subject disposition

Subject disposition will be presented for all participants. Counts and percentages of participants who are included, complete the study, complete the treatment, prematurely discontinue from the study, reasons for study discontinuation, and primary reason for early termination was due to COVID-19 will be summarized by treatment and overall. For each scheduled visit, counts and percentages of participants who do not complete the visit, partially complete the visit in-person, or complete the visit virtually will be summarized. The denominator for calculating percentages will be based on the number of included participants.

Data listings for subject disposition and exclusion and inclusion criteria violations will be provided.

3.3.2 Protocol deviations

The Protocol Deviations will be identified as either CSR reportable or non-CSR reportable deviations. Counts and percentages of participants with CSR reportable protocol deviations by deviation category will be summarized for all participants. A listing of CSR-reportable protocol deviations will be generated.

CSR Reportable Deviations include:

1) Violations of Inclusion/Exclusion Criteria
2) Subject Met Withdraw Criteria and was Not Withdrawn
3) Subject Reviewed the Wrong Dose
4) Subject Took an Excluded Med or Had a Change to a Required Medication
5) Procedure Missed that Impacts Safety and/or Data Integrity
6) Violation of SAE/Safety Reporting Requirements

3.3.3 Analysis populations

Counts and percentages of participants in each analysis population will be summarized by treatment and in total based on all randomized participants. Reasons for exclusion from PP population will also be summarized.

3.3.4 Demographic and baseline characteristics

Demographic and Baseline characteristics including age, sex, education in years, APOE genotype, and cognition/function level (CDR global at baseline, MMSE at baseline, CFC at baseline) will be summarized for the ITT Population. If the variable is categorical, frequency and proportions will be mentioned. If normal distributed and numerical mean and SD will be shown. If non-normal numerical, median and IQR 25-75 will be shown. If they differ from the ITT Population, summaries will also be provided for the PP Population and the Safety Population.

3.3.5 Medical history

Counts and percentages of participants with medical history will be summarized based on ITT population.

3.3.6 Concomitant medications

Medication start and stop dates that are recorded on the CRF will be used to determine whether the medications are prior or concomitant to the study treatment. Concomitant medications are defined as those used on or after the first dose of study treatment. Prior medications are defined as those used prior to and stopped before the first dose of study treatment. The numbers and percentages of participants taking prior and concomitant medications will be summarized for the ITT population.

3.3.7 Study drug exposure and compliance

During every visit it is noted in the eCRF if the participant is compliant, with a 1 denoting the participant was compliant and a 0 denoting compliance was lower than 80%.

3.4 Efficacy assessment

The PP Population will be the primary population used for the PD and PK analyses, and for the analyses of the effects of obicetrapib on cognition. The drug compliance is noted after each visit. Drug compliance for overall study will be calculated with the mean of compliance of the variables noted below.

V3_drug_return_compliance_rate
V4_drug_return_compliance_rate
V5_drug_return_compliance_rate
V6_drug_return_compliance_rate

If at least 80%, participant will be included in the analysis.

3.4.1 Primary pharmacodynamic endpoints

Goal analysis: analyze change from baseline (V2; day 1) in levels of ApoA1, ApoE, and small HDL particles, in both CSF and plasma and ABCA1-driven cholesterol efflux in CSF at EOT (V6; day 168)

Variables:

- CSF and plasma ApoA1
- CSF and plasma ApoE
- CSF and plasma small HDL particles
- CSF ABCA1-driven cholesterol efflux

Methods: A Wilcoxon signed rank test will be used. We will be testing the difference between V2 (day 1; baseline) for plasma or V1 (Screening) for CSF and V6 (EOT; 168 days). Significant if $p<0.05$. No multiple testing correction will be performed due to the highly correlative nature of the variables and explorative nature of the trial.

3.4.2 Exploratory pharmacodynamic endpoints

Goal: Analyze change from baseline (V2; day1) in levels of lipoproteins and apolipoproteins in CSF and plasma, AD biomarkers in CSF and plasma at day 84 (V4) and EOT (V6; day 168).

Variables:

- Lipoproteins and apolipoproteins in plasma: LDL-C, total cholesterol, non-HLD-C, triglycerides and ApoB
- Lipoproteins and apolipoproteins in CSF and plasma: HDL-C, HDL-ApoE, and ApoA2
- AD biomarkers in CSF: pTau181, Ab42, Ab40, Ab42/40, NRGN, GFAP, sTREM2, YKL-40, and inflammatory cytokines
- AD biomarkers in plasma: pTau epitopes, Ab42, Ab40, Ab42/40, and NFL
- Lipids in CSF and plasma: 24-OHC, 27-OHC, desmosterol, lathosterol, campesterol, and sitosterolInoviv proteins CSF: ApoB (1 peptide), Clusterin (3 peptides)

Methods:

In case of CSF measurements, the Wilcoxon signed rank test will be performed between baseline and EOT. The measurements of V4 are not taken into consideration for the analysis.

The Friedman test will be used on the plasma samples to determine if there is a significant difference in any of the variables at the three time-points. Post-hoc analysis will include Wilcoxon signed rank test between Baseline and Day 84 and Baseline and EOT. A Bonferroni multiple testing correction will be applied at alpha-level 0.05 for multiple testing within the same variable. Post hoc analysis will only be performed on the patients who have all 3 measurements available.

3.4.3 Correlation analysis

Goal: Perform correlation analysis between the change from baseline levels in CSF pTau181 and CSF ApoA1, ApoE, and cholesterol efflux capacity

Variables:

- CSF pTau181
- CSF ApoA1
- CSF ApoE
- CSF cholesterol efflux

Methods: Use rate of change between V1 (baseline) and V6 (day 168; EOT) for each of the variables mentioned above. Only participants who have both time points available will be included in the analysis.

A Spearman's rank correlation analysis will be performed. Correlation is significant if $p<0.05$. If the correlation coefficient is ≥0.7 there is a strong correlation, a correlation coefficient ≥0.5 <0.7 is moderate, and ≥0.3 <0.5 is low.

3.4.4 Exploratory cognition endpoints

Variables:

- CFC
- MMSE

Methods:

The Friedman test will be used to test if there is an overall difference. Significant if $p<0.05$. Post-hoc analysis will include Wilcoxon signed rank test between Baseline and Day 84 and Baseline and EOT. A Bonferroni multiple testing correction will be applied at alpha-level of 0.05 for multiple testing within the same variable.

3.5 Pharmacokinetic assessment

Pharmacokinetic (PK) assessments will be performed on the PP population. PK values will be summarized using descriptive statistics per visit per matrix (CSF and blood).

3.6 Safety assessment

The Safety Population will be the primary population for the safety analyses. All safety endpoints will be summarized descriptively. No statistical inference will be applied to the safety endpoints.

AEs will be categorized by primary system organ class and preferred term as coded using the Medical Dictionary for Regulatory Activities (MedDRA) category designations. Summaries of AEs, including the number and percentage of patients who experience an AE, will be provided.

Laboratory values will be summarized descriptively, including the change from baseline. In addition, shift tables will be presented to describe the change in laboratory parameter values at post-baseline visits using normal range categories (low, normal, and high).

Vital signs will be summarized descriptively, including the change from baseline.

ECG results, as well as physical and neurological examination findings will be listed. Clinically relevant abnormal findings at baseline or during the study will be reported as baseline condition or AE, respectively.

4. Analysis timing

4.1 Interim analysis

No interim analysis was planned for this study.

4.2 Final analysis

After the study database is declared final, the final analysis will be generated. Final TFLs will be provided approximately one week after receival of all endpoint assessments.

5. Changes from protocol-specified statistical analysis

This SAP deviates from the statistical analysis described in v2.0 of the protocol. In the protocol it is stated that only descriptive statistics will be included and no formal hypothesis will be tested in the study. However, here we show several statistical analysis which are based on hypothesis testing.

Any deviations from the SAP will be described in the CSR.

6. Programming specifications

Analyses will be performed using R version 4.2.1 All available data will be presented in participant data listings which will be sorted by participant and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

Appendix A: Clinical laboratory analytes

Chemistry Panel

Alanine aminotransferase (ALT)	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase (AST)	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase (CK)
Creatinine	Estimated glomerular filtration rate (eGFR) [1]
Folic acid [2]	Gamma-glutamyl transferase
Glucose (fasting)	High-sensitivity C-reactive protein
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium
Sodium	Thyroid stimulation hormone (TSH) [2]
Thyroxine (T4) [2]	Total bilirubin
Total protein	Triiodothyronine (T3) [2]
Uric acid	Vitamin B12 [2]

[1] Calculated using the Chronic Kidney Disease Epidemiology Collaboration equation: https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr.
[2] Screening Visit only.

Endocrinology

Follicle-stimulating hormone – At screening visit only for women <55 years of age

Hematology

Hemoglobin A1c (HbA1c) [1]	Hematocrit
Hemoglobin	International normalized ratio (INR)
Partial thromboplastin time (PTT)	Platelets
Prothrombin time (PT)	Red blood cell count
White blood cell count and differential [2]	APOE E4 genotyping [1]

[1] Screening Visit only.
[2] Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy [1]
Nitrite	pH
Protein	Specific gravity
Urobilinogen	

[1] Microscopy is performed only as needed based on positive dipstick test results

Pregnancy Test

Urine – At screening and V6 for women <55 years of age

Pharmacodynamic parameters

CSF:

- ApoA-I, ApoE, small HDL particles and ABCA1-driven cholesterol efflux, HDL-C, HDL-ApoE, ApoA-II
- YKL40
- sTREM2
- 24-hydroxycholesterol and 27-hydroxycholesterol
- Tau and p-Tau 181, $A\beta_{1-42}$, $A\beta_{1-40}$, $A\beta_{1-42}/A\beta_{1-40}$ ratio, neurogranin, neurofilament light, GFAP
- Inflammatory markers (eg, IFN-γ, IL-10, IL-12p70, IL-17A, IL-6, TNF-α)

Plasma:

- TC, ApoA-I, ApoE, ApoB, LDL-C [1], Non-HDL-C, TG, small HDL particles and HDL-C, HDL-ApoE, ApoA-II
- 24-hydroxycholesterol and 27-hydroxycholesterol
- Tau and p-Tau epitopes, $A\beta_{1-42}$, $A\beta_{1-40}$, $A\beta_{1-42}/A\beta_{1-40}$ ratio, neurofilament light

[1] Measured by preparative ultracentrifugation, also referred to as beta quantification.