STATISTICAL ANALYSIS PLAN

(Short) study title:	A Phase 2a Randomized Double-Blind Placebo-Controlled Trial To Evaluate The Efficacy And Safety Of Varoglutamstat (PQ912) In Patients With Early Alzheimer's Disease With A Stage Gate To Phase 2b (Viva-Mind)
Name of the sponsor:	VIVORYON THERAPEUTICS N.V.
Protocol identification:	V6.0 17MAY2023 NCT03919162
Version and date of SAP:	V2.0 (28OCT2024)

VERSION HISTORY

Version	Date	History list
1.0	06AUG2024	Final version
2.0	28OCT2024	Updated document incorporating additional SAP clarifications

APPROVAL PAGE

I hereby declare that I have read and reviewed this document. To the best of my knowledge, the content accurately states the intended analyses and output to be provided. This document is intended for an agreement on analysis and reporting details between the sponsor, ADCS and Certara Inc.

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LIST OF ABBREVIATIONS

Aβ	Amyloid Beta
AβO	Amyloid Beta Oligomers
ABC	ADNI Battery Composite
AchEI	Acetylcholinesterase Inhibitor
AD	Alzheimer's Disease
ADaM	Analysis Data Model
ADCOMS	AD Composite Score
ADAS-Cog-13	Alzheimer's Disease Assessment Scale-Cognitive Subscale -13
ADAS-Cog-Exec	Alzheimer's Disease Assessment Scale-Cognitive and Executive Function Composite Score
ADNI	Alzheimer's Disease Neuroimaging Initiative
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
APOE	Apolipoprotein E
ARIA-E	Amyloid-Related Imaging Abnormalities Related To Underlying Vasogenic Edema
ARIA-H	Amyloid-Related Imaging Abnormalities Related To Hemosiderin Deposits
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
C-SSRS	Columbia-Suicide Severity Rating Scale
CDISC	Clinical Data Interchange Standards Consortium
CDR-SB	Clinical Dementia Rating- Sum of Boxes
CFC2	Cognitive-Functional Component 2
CPK	Creatinine Phosphokinase
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety & Monitoring Board
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EEG	Electroencephalogram
eGFR	Estimated Glomerular Filtration Rate
FAQ	Functional Activities Questionnaire
GCP	Good Clinical Practice
HAV	Hepatitis A Virus
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA	Human leukocyte antigen

ICH	International Conference on Harmonisation
LAR	Legally Authorized Representative
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
MCI	Mild Cognitive Impairment
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-To-Treat
MMRM	Mixed-Effect Model Repeated Measure model
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NfL	Neurofilament Light (Protein)
NPI	Neuropsychiatric Inventory
P-tau	Phosphorylated tau
PD	Pharmacodynamic
pE-Aβ	Pyroglumated form of β-Amyloid
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per Protocol
PQ912	Varoglutamstat
QC	Glutaminyl Cyclase
qEEG	Quantitative Electroencephalogram
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAF	Safety population
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SSC	Study Steering Committee
sTREM2	Soluble Variant Triggering Receptor Expressed on Myeloid Cells
SUSAR	Serious Unexpected Suspected Adverse Reaction
SOC	MedDRA System Organ Class
T-tau	Total tau
T_3	Triiodothyronine
T_4	Thyroxine
TEAE	Treatment Emergent Adverse Events
TO	Target Occupancy
TSH	Thyroid-Stimulating Hormone
ULN	Upper Limit of Normal
VILIP	Visinin-Like Protein
vMRI	Volumetric Magnetic Resonance Imaging
VS	Vital Signs
WBC	White Blood Cell

1 GENERAL

This Statistical Analysis Plan (SAP) describes in detail the methods and presentation of the data analyses which will be conducted by Certara Inc. for study PBD 01187. This plan is written in agreement with protocol version V6.0 17MAY2023, and 28NOV2023 annotated case report form (CRF) version MSC 013.

The protocol and the (annotated) CRF are the primary source for this document, together with the relevant Good Clinical Practice (GCP) and International Council on Harmonization (ICH) guidelines. Furthermore, sponsor requirements for reporting will be considered.

The statistical analysis and summary tabulations described in this SAP will provide the basis of the results sections of the clinical study report (CSR) for this trial.

This plan is to be finalized prior to first subject entry in case of an open-label or single-blind study, or prior to an interim analysis or database lock in case of a double-blind study.

PK data and results are handled by a separate PK vendor. Any PK analysis will be described in a separate PK analysis plan, and the final PK results will be provided in a PK report to be added as appendix to the CSR.

Overview of Planned Analyses
This SAP focuses on the analysis planned to be conducted at the end of the Phase 2A and 2B. Any additional analyses or data reporting conducted for Data Safety & Monitoring Board (DSMB) activities will be detailed in a separate document.

2 STUDY INFORMATION

2.1 Study Objective(s)

2.1.1 Objectives – Phase 2A

2.1.1.1 Primary Objectives

- To determine the highest safe and well-tolerated dose of varoglutamstat over the safety reporting period (from first dose to completion of 8 weeks at the originally assigned full dose), which will include assessment of the proportion of participants who experience any Adverse Event of Special Interest (AESI).
- To evaluate early evidence for efficacy of varoglutamstat as measured by the Alzheimer's Disease Neuroimaging Initiative (ADNI) Battery Composite (ABC) and by pharmacodynamics changes on Electroencephalogram (EEG) spectral analysis

2.1.1.2 Secondary Objectives

The secondary objective concerns the PK objective in phase 2A. The objective is to measure varoglutamstat levels in plasma and to establish the sufficiency of target occupancy (TO) of Glutaminyl Cyclase (QC) in plasma following at least 8 weeks of treatment at the dose levels being tested.

2.1.2 Objectives – Phase 2B

2.1.2.1 Primary Objectives

The primary objective in phase 2B is to evaluate the efficacy of varoglutamstat as measured by the Clinical Dementia Rating-sum of boxes (CDR-SB) over a 72-week treatment period.

2.1.2.2 Secondary Objectives (Efficacy)

Key Efficacy Objective
The key secondary objective in phase 2B is to evaluate the efficacy of varoglutamstat as measured by CFC2, a cognitive-functional composite, over 72 weeks.

Other Secondary Efficacy Objectives

Other secondary efficacy objectives in phase 2B are to evaluate the efficacy of varoglutamstat as measured by the:

- Composite mean of standardized scores from the ADNI Battery Composite (ABC)
- Quantitative EEG (global relative theta wave power)
- Functional Activities Questionnaire (FAQ)
- Alzheimer's Disease Assessment Scale-Cognitive Subscale 13 (ADAS-Cog-13)
- Neuropsychiatric Inventory (NPI)

2.1.2.3 Secondary Objectives (Safety)

The safety and tolerability of varoglutamstat in phase 2B will be assessed by the following measures:

- Rates of all AEs (Serious AEs [SAEs], Treatment emergent AEs [TEAEs], AESIs)
- Drug discontinuation rates
- Mortality rates
- Suicidality on the Columbia-Suicide Severity Rating Scale (C-SSRS)
- Frequency and severity of abnormalities on
    - vital signs
    - ECG
    - safety labs

2.1.2.4 PK Objectives

The pharmacokinetics of varoglutamstat in phase 2B will be assessed by the measurement of:

- Varoglutamstat levels in plasma
- Varoglutamstat levels in Cerebrospinal Fluid (CSF) (optional)

2.1.2.5 Exploratory Objectives

The exploratory objectives in phase 2B are to investigate longitudinal treatment effects of varoglutamstat as assessed by the changes in:

- Brain volume measured by cranial MRI
- Mini-Mental Status Examination (MMSE)
- Montreal Cognitive Assessment (MoCA)
- CSF disease-relevant biomarkers including: Aβ1-42, t-tau, p-tau-181, YKL40,

neurogranin, and NfL.
- Quantitative EEG (qEEG) network connectivity measures
- Alzheimer's Disease Composite Score (ADCOMS)
- Alzheimer's Disease Assessment Scale-Cognitive and Executive Function Composite Score (ADAS-Cog-Exec)
- Relative QC activity in CSF

Exploratory objectives also include comparing treatment to placebo on changes in the primary outcomes measure (CDR-SB), key secondary outcome measure (CFC2), within subgroups defined separately by: (i) APOE genotype (E4 carrier vs non E4 carrier), and (ii) Mild Cognitive Impairment (MCI) vs. Mild probable Alzheimer's Disease (AD), as well as comparing plasma-based amyloid biomarker and CSF amyloid, p-tau, and total tau test results.

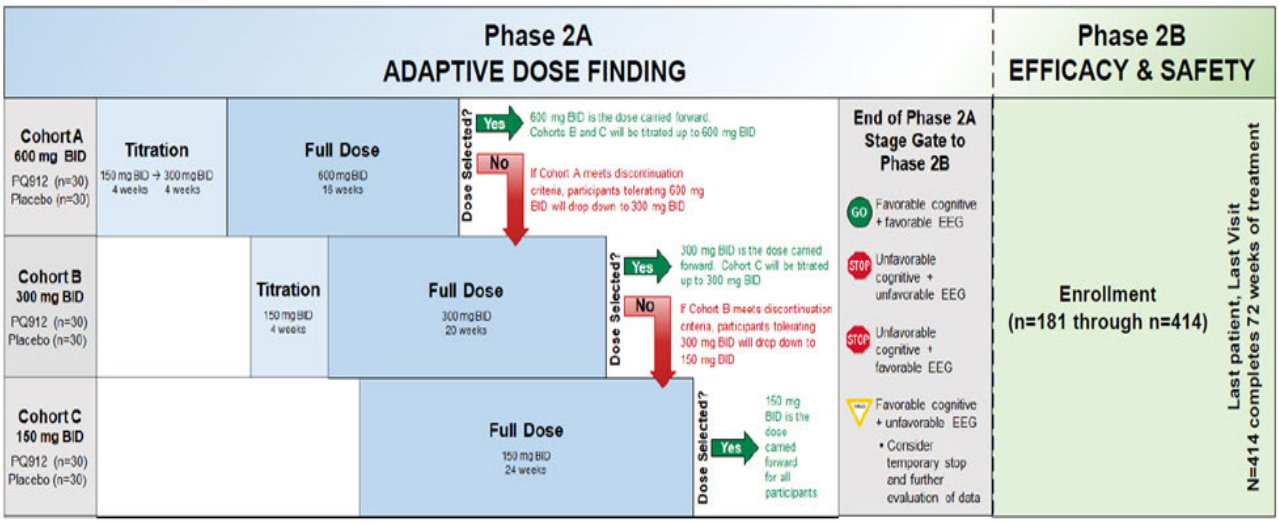
2.2 Design of the Study

Phase 2A is a multi-center, randomized, double-blind, placebo-controlled, parallel group clinical trial in participants with early AD, with a stage gate to phase 2B, used to determine the highest dose of varoglutamstat that is safe and well tolerated with sufficient plasma exposure and a calculated TO in CSF.

At the end of phase 2A, an interim analysis will be conducted to inform a stage gate decision on whether to proceed with phase 2B.

Phase 2B is a multi-center double-blind placebo-controlled trial of varoglutamstat vs placebo in early AD over a treatment period of 72 weeks (18 months).

2.3 Study medication



2.4 Sample size

This is a multi-center double-blind placebo-controlled trial of varoglutamstat treatment for approximately 72 weeks.

2.4.1 Phase 2A

The sample size justification for phase 2A is based on the co-primary endpoint for EEG Theta power and the ABC score. Both sample size justifications are based on using a one-sided two sample t-test for the 24-week endpoint under the assumption of equal variances. A sample size of

90 participants is assumed for each of the treatment arms, and a dropout of 5% in the placebo arm and 10% in the active arm by 24 weeks is anticipated, for a final 24-week sample size of 86 and 81 respectively.

EEG
A doubling of the mean placebo within-participant change at 12 weeks is assumed, to 0.032 units, with a standard deviation of 0.032 units. Then, under the given sample size a one-sided two sample t-test at 5% significance level using equal variances has 90% power to reject the null hypothesis of no difference in favor of a benefit to the drug, if the active arm change is 0.018 units, which is about 45% less than the hypothesized placebo arm change.

ADNI
The null hypothesis of no difference against the one-sided alternative that active arm is doing worse than placebo, is tested at a 40% significance level. For this test, there is a 70% power to reject the null hypothesis and declare evidence of harm, and thus stop the trial, if the true change in treatment group is -1.31 points and a difference between placebo arm and active arm is -0.29, which is 29% worse than placebo. There is a 60% probability to stop if the change is -1.20 points, which is 19% worse than placebo, at 24 weeks.

2.4.2 Phase 2B

The primary endpoint is the within-participant change in CDR-SB from baseline to week 72, compared between the varoglutamstat treatment group and the placebo group. The accrued sample size is 414 participants (n 207 active, n 207 placebo). No more than 25% drop out is anticipated.

The study has 80% power to detect an effect size of 0.7 points in CDR-SB. This is about 37% of the expected ~1.9-point mean change in CDR-SB in the placebo arm, assuming 40% of the enrolled study sample has MCI (expected mean change of 1.2 points) and 60% has mild AD dementia (expected 2.3-point change).

For additional perspective, if the observed effect of varoglutamstat on CDR-SB at the final analysis is 0.5 points, and if variances are similar to published data, the final p-value would be about p 0.04.

2.5 Study Flow-Chart

Visit Number	1	2	3	4	5	6	7	8	9	10	11 EOT/Early Term	12 Post Tx Safety Follow Up[17]
Study Visit Time Point	Screening (-90 d)	Baseline (Week 0)	Wk 4 (±7 d)	Wk 8 (±7 d)	Wk 12 (±7 d)	Wk 16 (±7 d)	Wk 24 (±7 d)	Wk 36 (±7 d)	Wk 48 (±7 d)	Wk 60 (±7 d)	Wk 72 (±7 d)	Wk 76 (±7 d)
Informed Consent	X											
Eligibility Review	X	X										
Randomization[1]		X										
Med History/Demographics	X											
Modified Hachinski Ischemic Scale	X											
Weight & Height[2]	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X
Neurological Examination	X											
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[4]	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (resting)	X						X				X	
B12 and folate (blood tests)	X											
Clinical Safety Blood Tests[5]	X	X	X	X	X	X	X	X	X	X	X	X
Hemoglobin A1c (HbA1c)	X					X	X		X		X	X
Testosterone (blood test)	X					X	X		X		X	X
Thyroid Function (TSH, T4, T3)	X					X	X		X		X	X
Urinalysis[6]	X	X		X		X	X	X	X		X	X
Infectious Disease Serology[7]	X											
APOE (blood test)		X										
HLA (blood test)		X										
CYP2C19 (blood test)		X										
PrecivityAD® biomarker assays	X											
Blood Collection for Biobanking	X	X	X	X		X[8]	X		X		X	
Blood Collection for PQ912 levels[8]			X	X		X	X		X		X	
Blood Collection for QC in Serum[8]	X		X	X		X	X		X		X	

Visit Number	1	2	3	4	5	6	7	8	9	10	11 EOT/Early Term	12 Post Tx Safety Follow Up[17]
Study Visit Time Point	Screening (-90 d)	Baseline (Week 0)	Wk 4 (±7 d)	Wk 8 (±7 d)	Wk 12 (±7 d)	Wk 16 (±7 d)	Wk 24 (±7 d)	Wk 36 (±7 d)	Wk 48 (±7 d)	Wk 60 (±7 d)	Wk 72 (±7 d)	Wk 76 (±7 d)
Cranial MRI[9]	X						X				X	
Lumbar Puncture (LP) for CSF biomarkers[10]	X						X				X	
Post-LP Safety Telephone[11]	X						X				X	
Columbia-Suicidality Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X	X	X	X	X	
MoCA	X						X		X		X	
MMSE	X						X		X		X	
CDR	X				X		X		X		X	
ADAS-Cog-13		X			X[14]		X	X	X	X	X	
FAQ		X					X		X		X	
ABC - Category Fluency		X					X		X		X	
ABC - Trail Making Test A & B		X					X		X		X	
ABC - Digit Symbol Substitution		X					X		X		X	
ABC - Boston Naming Test		X					X		X		X	
ABC – RAVLT (Immediate & Delayed)		X					X		X		X	
ABC – Number Span Forward & Backward		X					X		X		X	
NPI		X					X		X		X	
Quantitative EEG[12]		X					X				X	
Research Satisfaction Survey		X					X		X		X	
Dispense Study Drug[13]		X	X	X	X	X	X	X	X	X		
Study Drug Instruction Phone Call[15]			X									
Study Drug Accountability			X	X	X	X	X	X	X	X	X	
Treatment Blinding Questionnaire[16]											X	

1 Randomization must occur at the baseline visit after eligibility is confirmed.

2 Height is done at screening only.

3 Vital signs include sitting blood pressure, pulse, temperature, and respiration rate.

4 The reporting period for all AEs and SAEs starts at the screening visit (i.e. when the patient or LAR signs consent). The end of the reporting period for both SAEs and AEs is 30 days after the study drug has been discontinued.

5 Clinical Safety Laboratory Tests will be performed by a Central Laboratory. Assessment includes the following: Hematology (hemoglobin, hematocrit, platelets, RBC, WBC, differential count, and absolute neutrophil count), Chemistry (sodium, potassium, chloride, calcium, ALT, AST, LDH, alkaline phosphatase, GGT, phosphorus, bicarbonate, CPK, total protein, albumin, indirect bilirubin, direct bilirubin, total bilirubin, glucose, creatinine, BUN, uric acid , total cholesterol, LDL, HDL, triglycerides).

6 Urinalysis to include: pH, specific gravity, protein, glucose, ketones, urobilinogen, bilirubin, blood, leucocytes and nitrite

7 Infectious disease serology includes the following: Human Immunodeficiency Virus (HIV), Hepatitis A Virus (HAV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) and syphilis.

8 A blood sample to measure varoglutamstat (PQ912) level in plasma (PK) should be collected at week 4, week 8, week 24, week 48, and week 72 for all participants. A blood sample to measure glutaminyl cyclase (QC) in serum should also be collected at screening, week 4, week 8, week 24, week 48, and week 72 for all participants. During phase 2A, Cohorts A and B will also have a blood sample drawn at week 16 (at least 8 weeks at the originally assigned full dose).

Participants will have blood drawn just prior to their morning dose at each of these PK timepoints, and again between 2 and 6 hours after this routine morning dose. Date and time of study drug intake on the day of visits and day prior should be collected on source document worksheets, along with time of last meal, for entry into the EDC system. PK (plasma) samples to measure varoglutamstat level should be drawn at the time of lumbar puncture at week 24 and week 72. Date and time of study drug intake on the day of lumbar puncture should be collected on source document worksheets, for entry into the EDC system.

9 All MRIs must be performed per imaging protocol and must use the same scanner throughout study.
- **Screening MRI:** if a patient has **not** had an MRI performed within 6 months of screening (i.e. within 6 months from the date of informed consent), then an MRI must be performed as part of the screening requirements for this study, per the imaging protocol, and should be one of the last screening procedures performed to determine final eligibility in order to prevent patients from undergoing unnecessary MRIs. If a patient **has** had an MRI within 6 months of screening (i.e. within 6 months from the date of informed consent) **but** the MRI does not follow the study-specific imaging protocol, that MRI can be used to help determine eligibility; however, another MRI must be performed per the imaging protocol, and must occur as close to, and prior to, the baseline visit, after all other eligibility criteria have been confirmed.
- **Week 24 MRI:** the protocol window for MRI at week 24 is 7 days before and up to 7 days after the week 24 visit time point. If a participant is terminating early at 36 weeks or after, obtain MRI. If MRI is performed on the same day as a lumbar puncture at week 24, the MRI must be conducted before the lumbar puncture. Otherwise, at least a 3-day window between MRI and the lumbar puncture is required.
- **Week 72 MRI:** the protocol window for MRI at week 72 is 14 days before and up to14 days after the week 72 visit time point. If a participant is terminating early at 36 weeks or after, obtain MRI. If MRI is performed on the same day as a lumbar puncture at week 72, the MRI must be conducted before the lumbar puncture. Otherwise, at least a 3-day window between MRI and the lumbar puncture is required.

10 Visit windows for CSF are: up to 90 days prior to first dose of study drug and within 7 days of the week 24 and 72 study visit. If a patient is terminating early, they do not need to undergo lumbar puncture. Sites should make every attempt to complete screening procedures within a period of 60 days from the time of informed consent. However, sites will be allowed a period of up to 90 days from informed consent if additional time is needed to complete the lumbar puncture and receive CSF AD biomarker results.

11 Post lumbar puncture safety follow up telephone call must occur 1 to 3 days after the lumbar puncture is performed.

12 Quantitative EEG is required for all participants in phase 2A, and substudy participants only in phase 2B. This procedure should be performed by qualified study personnel. The qEEG data will be de-identified and sent to a blinded, third party vendor for central review and analysis. If the quality of the baseline qEEG is deemed unacceptable by the third-party vendor, then the participant will be withdrawn from the substudy and the data will be excluded from the substudy analysis.

13 Participant will be instructed to take the first dose in the morning of the following calendar day.

14 The ADAS-Cog-13 conducted at week 12 will be used as part of the quarterly DSMB review of cognitive safety.

15 Participants will receive a phone call during from site study personnel in order to assess study drug tolerability. If tolerable, then the participant will be instructed to proceed with dose escalation at the cohort's respective time point.

16 Treatment blinding questionnaire to be administered to site PI and Raters.

17 Participants who terminate the study early will undergo a Post-Treatment Safety Follow-Up visit 4 weeks (± 7 days) following their Early Termination visit.

Please note: Unscheduled visits should generally follow the same schedule of events as the Week 4 safety visit. Please consult with ADCS Clinical Operations for further guidance as needed.

3 STUDY PARTICIPANTS FOR ANALYSIS

3.1 Analysis populations

The following populations will be evaluated and used for presentation and analysis of the data.

3.1.1 Modified Intent-to-Treat (mITT) population

The modified Intent-to-Treat (mITT) population will include all randomized participants who took at least one dose of study medication and who have a baseline assessment of the primary

endpoint(s) . This will be the primary analysis population used for the efficacy analyses, and statistical analysis will be done “as randomized”.

3.1.2 Pharmacokinetic (PK) population

The Pharmacokinetic (PK) population will include all randomized participants who have received at least one dose of the study treatment and who provided sufficient PK samples to reliably estimate one plasma PK concentration post-baseline.

3.1.3 Safety (SAF) population

The safety population includes all participants who have received at least one dose of the investigational drug, irrespective of satisfying other criteria. This population will be used for the analysis of safety and tolerability, and statistical analysis will be done “as dosed”.

3.1.4 eGRF population

The eGFR analysis set will include all randomized participants who took at least one dose of study medication and who have a baseline assessment of the eGFR data derived with CKD-EPI formula (see Section 8.1.12). This will be the primary analysis population used for the efficacy analyses, and statistical analysis will be done “as randomized”.

3.2 Protocol deviations

Any significant event that does not comply with the inclusion/exclusion criteria, study conduct (e.g., inadequate informed consent, unreported SAEs), or study procedures (e.g., use of prohibited medications as defined by the protocol; improper breaking of the blind) will be documented as a protocol deviation.

- ADCS DM will be responsible for producing the final protocol deviation file (formatted as a Microsoft Excel file), which will be finalized prior to database lock and shared with statistician for final analysis.
- Protocol deviation information received by the ADCS, via email and the Protocol Deviation eCRF, will be reviewed by the ADCS study team to verify that the eCRF information documents a protocol deviation. When required, the ADCS will procure additional information to verify that the reported information pertains to a protocol deviation. The ADCS Clinical Operations team will ensure pertinent information regarding protocol deviations is documented and communicated appropriately.
- Classification of deviations from the protocol as minor or major will be decided.
- Minor protocol deviations are occurrences of noncompliance with IRB-approved CT protocol requirements that do not impact subject safety, rights or welfare, and do not affect study data quality or scientific integrity. Minor protocol deviations typically involve administrative non-conformities. Major protocol deviations are occurrences of noncompliance with IRB-approved clinical trial (CT) protocol requirements that impact subject safety, rights or welfare, or study data quality or scientific integrity (outcome measures). Instances of serious or continuing noncompliance may also be classified as major protocol deviations. Major protocol deviations include those related to concomitant medications, inclusion and exclusion criteria, informed consent, study treatment (Investigational Product), randomization, and procedural conduct.

[1] EEG Theta power and ABC score for phase 2A, or CDR-SB for phase 2B.

- Once deviations are classified as major or minor, the ADCS and Vivoryon teams review these classifications independently before having a quarterly meeting in which both groups review and come to a consensus as to whether a deviation should be classified as major or minor.

All protocol deviations will be presented in a tabulation and data listing.

3.3 Blind Data Review Meeting

There will be a Clean File Meeting scheduled prior to Database lock for both phase 2A and phase 2B, and this will be described in the Data Management documentation. During these meetings, any (outlier) data that are a result of unambiguous measurement errors will also be discussed and documented, and it may be decided to exclude these from the analyses. Team decisions will be documented in meeting minutes or NTF and shared with statistician for implementation. As there is no per-protocol analysis set, there is no need for a Blind Data Review Meeting (BDRM) to classify participants.

4 STUDY ENDPOINTS

4.1 Phase 2A

4.1.1 Primary endpoint(s)

The primary endpoints in phase 2A are:

- The proportion of participants, for each dose, who experience any AESI during the safety evaluation period, which is from first dose to completion of 8 weeks at the full originally assigned dose.

- The within-participant change from baseline to week 24 in the composite mean of standardized scores from the ABC (9-item), compared between active arm and placebo.

- The within-participant change from baseline to week 24 in qEEG global relative theta wave power (4-8 Hz), compared between active and placebo arms.

4.1.2 Safety & Tolerability endpoints

Safety and tolerability endpoints are:

- Rates of all AEs, SAEs, TEAEs
- AESI
- Drug discontinuation rates
- Mortality rates
- Suicidality on the C-SSRS
- Vital signs
- ECG
- Clinical safety labs

4.1.3 PK endpoint(s)

The PK endpoints in phase 2A are:

- PK plasma concentration of PQ912 ($[PQ912]_{p\ asma}$), and of its metabolites PQ1345, PQ1529.
- Estimated PK CSF concentration of PQ912 [redacted]
- PQ912 $TO_{est\ mated}$ (%) [redacted]. This endpoint will be derived only for patients exposed to varoglutamstat.

In the event that actual CSF PK sampling data are available, the same TO formula will be used for the derivation of the TO_{actua} (%) endpoint.

4.2 Phase 2B

4.2.1 Primary endpoint

The primary endpoint in phase 2B is the within-participant change from baseline to week 72 in CDR-SB, compared between active arm and placebo.

4.2.2 Secondary endpoint(s)

Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint in phase 2B is the within-participant change from baseline to week 72 in the efficacy of varoglutamstat assessed by CFC2, compared between active and placebo.

Other Secondary Efficacy Endpoints

- The within-participant change from baseline to week 72 in the composite mean of standardized scores from the ABC (9-item) compared between active arm and placebo.
- The within-participant change from baseline to week 72 in qEEG (global relative theta wave power), compared between active and placebo.
- The within-participant change from baseline to week 72 in FAQ, compared between active and placebo.
- The within-participant change from baseline to week 72 in ADAS-Cog-13, compared between active and placebo.
- The within-participant change from baseline to week 72 in NPI, compared between active and placebo.

4.2.3 Exploratory endpoints

Exploratory endpoints include the within-participant change between active and placebo in:

- Brain volume measured by cranial MRI including change in hippocampal volume, ventricular volume, whole brain volume and cortical thickness.
- Mini-Mental State Examination (MMSE)
- Montreal Cognitive Assessment (MoCA)
- CSF biomarkers (Aβ1-42, t-tau, p-tau-181, YKL-40, neurogranin, NfL)
- qEEG connectivity network
- AD Composite Score (ADCOMS)
- ADAS-Cog-Exec

[2] Lues I, Weber F, Meyer A, Bühring U, Hoffmann T, Kühn-Wache K, Manhart S, Heiser U, Pokorny R, Chiesa J, Glund K. A phase 1 study to evaluate the safety and pharmacokinetics of PQ912, a glutaminyl cyclase inhibitor, in healthy subjects. Alzheimer's Dement (N Y). 2015 Oct 3;1(3):182-195.

The following endpoints are not addressed in the current SAP and will be considered for potential post-hoc analyses:

- Relative change from screening (100%) to week 72 in QC activity in CSF
- Changes in the primary outcome measure (CDR-SB), key secondary outcome measure (CFC2), and in the TO measure, within subgroups defined separately by: (i) APOE genotype (E4 carrier vs non E4 carrier), and (ii) MCI vs Mild probable AD.

4.2.4 PK endpoint(s)

The PK endpoints in phase 2B are same as for phase 2A for the additional assessments after week 24.

4.2.5 Safety & Tolerability endpoints

The safety and tolerability endpoints are described in Section 4.1.2.

5 STATISTICAL ANALYSIS

5.1 General considerations

All evaluations will be exploratory in nature, unless stated otherwise in the statistical analysis plan.

Appropriate rounding will be performed for the summary statistics: arithmetic mean, median, standard deviation (SD) and confidence limits will be presented with one more decimal than the original data; first and third quartiles, minimum and maximum values will be presented with the same precision as the original data. In frequency tables, percentages will be presented with 1 decimal. P-values will be presented with 3 decimals, and those smaller than 0.001 will be replaced by <0.001.

Unless otherwise specified, all significance testing will be 2-tailed using α 0.05. Tests will be declared statistically significant if the calculated p-value is ≤ 0.05.

Descriptive statistics presented in general summary tables will be the number of non-missing observations (n), mean, SD, minimum, median, first and third quartiles, and maximum for quantitative data. For categorical data, frequency counts and percentages will be determined.

Change from baseline is calculated by subtracting the baseline value from the observed post-baseline value at any subsequent visit.

Baseline is defined as the last value measured prior to first study treatment administration (Week 0/Visit 2), unless otherwise specified. See detail in Section 5.3.

If available in the database, data for screening failures will not be presented in summary tables, except for disposition and end-of-study displays. Data for screening failures will be listed as available.

5.1.1 Study Treatment Group

Study treatment group labels for analysis and results presentation are PQ912 and Placebo.

For the as treated presentations, patients with at least one exposure to Varoglutamstat (i.e. at least one kit of PQ912 administered) will be presented as PQ912, unless otherwise decided.

5.2 Missing or Excluded data

Imputation will be done for sensitivity analyses on the primary and key secondary endpoint of Phase 2B, as specified. Details of the sensitivity analyses are presented in Section 5.7.1.1.

For efficacy analyses, partial or missing dates will not be imputed. The relative study days, where determined, will be calculated for full dates only.

For safety endpoints being presented with descriptive statistics only, no imputation will be performed. All these analyses will be performed on data available at the visit considered. In summary tables, the number of patients without missing data will be presented (per visit, if applicable) unless otherwise specified. In calculations of percentages, participants with missing data will not be considered in numerator or denominator unless otherwise specified.

- In case of (partially) missing onset dates, the AE will be handled as follows:
    - If full start date is available, and on or after first dosing date, the AE is considered treatment emergent.
    - In case full stop date is available and prior to first dosing date, the AE is considered prior.
    - If the day part of the start date is missing:
        - The AE is considered treatment emergent if the month and year of the start date are the same or after the month and the year of the first dosing date.
    - If the day and month part of the start date are missing:
        - The AE is considered treatment emergent if the year of the start date is the same or after the year of the first dosing date.
    - In case the start date is completely missing:
        - If stop date is fully available and on or after the first dosing date, the AE is considered treatment emergent.
        - If the stop date is partially missing, but the month and year (or year alone in case of missing month) are after the month and year (or year alone) of the first dosing date, the AE is considered treatment emergent.
    - In case full start date and full stop date are missing, the AE is considered treatment emergent.
    - In all the cases where full date is not available for the start date, if also stop date is only partially available and the partial stop date indicates that certainly the AE stopped before first dosing (using the algorithm above), then the AE will not be considered as treatment emergent.

  In case of partial dates, the study days will also be imputed according to the algorithm above. More specifically:

Date imputation for AEs	Start date	Stop date
Only the day is missing	If (month and year are same as of first dosing date) and (stop date indicates AE did not stop before first dosing[1]) then impute first dosing date. Otherwise impute first day of the month	Impute the end of the month[2].
Both the day and month of the date are missing	If (year is same as of first dosing date) and (stop date indicates AE did not stop before first dosing[1]), then impute first dosing date; otherwise impute 01-Jan	Impute 31-Dec[2].
Completely missing date	If (stop date indicates AE did not stop before first dosing[1]) then impute first dosing date	No imputation

[1] if none of the following applies: (non missing AE stop date < start dosing date) and (partial AE stop date with year < year of start dosing date) and (partial AE stop date with same year of start dosing date and AE month < month of start dosing date)
[2] Set to last date of treatment if the analysis end date imputed is after that date.

- In case intensity is missing for a certain TEAE, this will be regarded as severe.
- In case causality is missing for a certain TEAE, this will be regarded as related.
- In case seriousness is missing for a certain AE, this is discussed and addressed prior to database lock and unblinding.

Regarding prior/concomitant medication, a similar approach will be followed for partially missing dates, as done for AEs as described above, considering that a comedication with a stop date prior to start of study treatment is prior, and all other medications are considered concomitant.

No other participants will be replaced. Data from patients who withdraw will be included in the analysis up to and including their last assessment.

Based on the Clean File Meeting (see Section 3.3), certain values can be decided to be excluded from analyses. These values will be listed, but not included in descriptive statistics, plots or statistical analyses. This may be (outlier) data that are a result of unambiguous measurement errors.

5.3 Mapping of analysis visits

Assessments performed at all visits, including unscheduled and early termination visits will be remapped according with the table below. The assessments performed at the time point closer to the nominal timepoint, with no missing value, will be considered for analysis. In case of two equidistant assessment, the one taken before the nominal timepoint will be used for analysis. In case of multiple assessments on the same day, the one associated with the nominal visit will be used for analysis (instead of the unscheduled or early termination one).

The date of first exposure to study medication will be considered as Day 1, study day will be derived as difference between the date and the first study medication day plus 1, all prior days will have negative values.

For CDR-SB (see Section 5.7.1):

Analysis visit	Nominal Timepoint	Specified Interval
Baseline (Visit 2)	-1	Prior to Day 2
Week 12 (Visit 5)	Day 84	Day 2 - 126
Week 24 (Visit 7)	Day 168	Day 127 - 252
Week 48 (Visit 9)	Day 336	Day 253 - 420
Week 72 (Visit 11)	Day 504	Day ≥ 421

For ADAS-Cog-13 (Section 5.7.2.5):

Analysis visit	Nominal Timepoint	Specified Interval
Baseline (Visit 2)	-1	Prior to Day 2
Week 12 (Visit 5)	Day 84	Day 2 - 126
Week 24 (Visit 7)	Day 168	Day 127 - 210
Week 36 (Visit 8)	Day 252	Day 211 - 294
Week 48 (Visit 9)	Day 336	Day 295 - 378
Week 60 (Visit 10)	Day 420	Day 379 - 462
Week 72 (Visit 11)	Day 504	Day ≥ 463

For NPI (Section 5.7.2.6), ADNI ABC (Section 5.7.2.2), FAQ (Section 5.7.2.4), MMSE (Section 5.8.2), ADCOMS (Section 5.8.6), ADAS-Cog-Exec (Section 5.8.7), CFC2 (Section 5.7.2.1), MoCA (Section 5.8.3):

Analysis visit	Nominal Timepoint	Specified Interval
Baseline (Visit 2)	-1	Prior to Day 2
Week 24 (Visit 7)	Day 168	Day 2 - 252
Week 48 (Visit 9)	Day 336	Day 253 - 420
Week 72 (Visit 11)	Day 504	Day ≥ 421

For qEEG (Sections 5.7.2.3, 5.8.5), MRI (Section 5.8.1), ECG (Section 5.10.4), CSF biomarkers (Section 5.8.4):

Analysis visit	Nominal Timepoint	Specified Interval
Baseline (Visit 2)	-1	Prior to Day 2
Week 24 (Visit 7)	Day 168	Day 2 - 336
Week 72 (Visit 11)	Day 504	Day ≥ 337

For PK and QC (Section 5.9):

Analysis visit	Nominal Timepoint	Specified Interval
Baseline (Visit 2)	-1	Prior to Day 2

Week 4 (Visit 3)	Day 28	Day 2 - 42
Week 8 (Visit 4)	Day 56	Day 43 - 84
Week 16 (Visit 6)	Day 112	Day 85 - 140
Week 24 (Visit 7)	Day 168	Day 141 - 252
Week 48 (Visit 9)	Day 336	Day 253 - 420
Week 72 (Visit 11)	Day 504	Day ≥ 421

For physical examination (Section 5.10.8), vital signs (Section 5.10.3), safety laboratory (Section 5.10.2), C-SSRS (Section 5.10.6):

Analysis visit	**Nominal Timepoint**	**Specified Interval**
Baseline (Visit 2)	-1	Prior to Day 2
Week 4 (Visit 3)	Day 28	Day 2 - 42
Week 8 (Visit 4)	Day 56	Day 43 - 70
Week 12 (Visit 5)	Day 84	Day 71 - 98
Week 16 (Visit 6)	Day 112	Day 99 - 140
Week 24 (Visit 7)	Day 168	Day 141 - 210
Week 36 (Visit 8)	Day 252	Day 211 294
Week 48 (Visit 9)	Day 336	Day 295 - 378
Week 60 (Visit 10)	Day 420	Day 379 - 462
Week 72 (Visit 11)	Day 504	Day 463 - 518
Week 76 (Visit 12)	Day 532	Day ≥ 519

Questionnaire scores for ABC, ADCOM, ADAS-Cog-13, ADAS-Cog-Exec, CFC2 will be produced based on re-mapped questionnaire subscore components that are flagged for analysis according with the rules described above. In these cases, the remapping procedure above won't be applicable for scores generated at the pertaining analysis visits.

For C-SSRS data, all remapped assessments will be flagged for analysis and data will be combined so to present the number of distinct study participants who have at least one event recorded within analysis visit window interval.

Other endpoints will not be remapped and will be presented as per visit data collected in CRF.

5.4 Multiple Comparisons/Multiplicity

No multiplicity correction will be used for the Phase 2A analyses, as there are two co-primary endpoints.

For phase 2B, type-I errors will be controlled for the primary and key secondary efficacy endpoint by using a hierarchical approach. The primary objective of the trial is met when primary endpoint analysis for CDR-SB is statistically significant. If the primary hypothesis is met, then a test for a statistically significant difference will be conducted for the cognitive-functional composite CFC2, however at 4% significance level, using the same analysis as above. 1% significance will be retained for the remining secondary endpoints. If the result of the CFC2 hypothesis test is statistically significant, then 5% alpha will be retained for the subsequent secondary endpoints. This gatekeeper strategy will control the joint type I error for all outcomes

at the 5% level. The secondary endpoints will be evaluated according with the following hierarchical order:

- Composite mean of standardized scores from the ADNI Battery Composite (ABC)
- Quantitative EEG (global relative theta wave power)
- Functional Activities Questionnaire (FAQ)
- Alzheimer's Disease Assessment Scale-Cognitive Subscale 13 (ADAS-Cog-13)
- Neuropsychiatric Inventory (NPI)

In case one endpoint is decided not to be evaluated (prior to unblinding), such endpoint will be considered as removed from the hierarchy.
For all other exploratory efficacy endpoints, any statistically significant p-values will be viewed as exploratory only (i.e. with p-value added for descriptive purposes).

5.5 Analysis of Phase 2A

Based on Phase 2A data, the following interim analyses will be performed.

- Dose selection is based on the rate of AESIs in phase 2A, and the optimal dose of varoglutamstat will be carried forward to efficacy studies in phase 2B, if the interim analysis is passed. See Section 5.5.1 for further details on the dose selection process.

- A full interim futility analysis will also be conducted, by analyzing the ABC score and the EEG theta power, and presenting safety, tolerability. See Section 8.1.1 for details of ABC score derivation and Section 5.5.2 for further details on this analysis.

The unblinded statistician will share the results with the DSMB, who will provide findings to the SSC for a decision on study continuation, study stop or study pause to allow more analyses for further necessary information, as indicated in Figure 1.

5.5.1 Dose selection/Safety stopping rule

During Phase 2A, continuous safety evaluation using a pre-defined safety stopping boundary will help determine which dose will be carried forward to phase 2B. If the first 30 participants assigned to a given dose in the active arm complete 8 weeks at full dose without hitting the stopping boundary, that dose will be selected as safe. The highest dose selected as safe will be the dose selected by the phase 2A portion of the trial. The Pocock boundary is only valid until the first dose selection criterion is met (i.e., the highest safe dose is selected).

This stopping boundary focuses on AESIs as follows.

Assignment to a given dose will be halted and the dose discontinued if an excessive number of participants in the active arm of the cohort experience an AESI within the dose selection safety reporting period. A Pocock sequential boundary, computed using the exact binomial distribution, will be used to monitor the AESI rate for each dose: if the number of participants assigned to that dose who have experienced a AESI within the safety evaluation period is greater than or equal to b_k, then the stopping rule will have been met (see **Table 1**). In this case the dose will be discontinued.

Table 1: Accrual will be halted to a dose cohort if the number of participants with a AESI is equal to or exceeds b_k out of k participants.

Number of Participants, k	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Boundary, b_k	-	2	2	2	2	3	3	3	3	3	3	3	3	3	3
Number of Participants, k	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Boundary, b_k	3	4	4	4	4	4	4	4	4	4	4	4	4	4	4

This sequential boundary is equivalent to testing the null hypothesis, after each participant, that the event rate in the active arm of that dose cohort is less than or equal to 2.5%, using an exact one-sided level 0.0054 test. If the null hypothesis is rejected in favor of the alternative hypothesis that the event rate > 2.5%, then the stopping rule will have been met accrual to that dose will be halted at that point, and the dose will be discontinued.

If the first 30 participants assigned to a given dose in the active arm complete 8 weeks at full dose without hitting the stopping boundary, that dose will be selected as safe. If all cohorts have acceptable AESI rates, then all cohorts will continue to the end. If a higher dose is selected as safe, assignment to lower doses will stop, and all current participants on a lower dose will be titrated up to the selected dose. Future accrued participants will be assigned to the selected dose. If more than one dose cohort is active and if a lower dose hits its stopping boundary, then all participants on a higher dose will be titrated down to the lowest dose which has not yet been stopped. The highest dose selected as safe will be considered the optimal dose and selected for phase 2B.

Tolerability and safety data will also be summarized, again using all data available at the time of the interim data freeze; the tolerability and safety analysis will use the safety population as determined by the available data. For AESI rates, an exact lower one-sided 95% confidence interval will be computed in each arm of each dose cohort.

5.5.2 Interim futility analysis description

There will be an interim analysis for futility at the end of phase 2A, and this analysis will be conducted when the last participant enrolled in phase 2A (participant # PPD) has had the opportunity to be on the assigned dose for 24 weeks and has passed the visit window for the Week 24 assessment (the interim data freeze). The data will be used ‘as is’ at the time of the interim data freeze, and analysis may be based on raw or (partially) CDISC data.

The efficacy outcome measures for the futility analysis are:

- The within-participant change in the composite mean of standardized scores from the ABC, compared between active arm and placebo.
- The within-participant change in qEEG (global relative theta wave power), compared between active and placebo. Additional endpoint details are provided in Section 5.7.2.3.

There is a test of hypothesis for each measure, and a stopping rule which depends on the outcomes of these statistical tests. The interim futility analysis will use all available data on the ABC score and the EEG theta power endpoints at the time of the interim data freeze, using the mITT population as determined by the available data.

5.5.2.1 Hypothesis tests for the futility stopping rule

The ABC Score hypothesis test The null hypothesis is that within participant rate of change of ABC Score is equal between arms, against the alternative that the rate of decrease is greater for active arm than for the placebo arm. Higher ABC Score is better; hence the alternative indicates harm from the drug. See derivation details in Section 8.1.1.

The test will be carried out at a one-sided 40% significance level, using the mixed effects model specified in Section 5.5.2.3. Rejection of the null hypothesis will indicate a statistically significant harm from treatment, and a value NO will be recorded for the continuation of the study from this hypothesis test. Otherwise, a value of YES (no statistically significant evidence of cognitive harm) will be recorded from this hypothesis test.

The EEG theta power hypothesis test. The null hypothesis is that within participant change of theta power is equal between arms from baseline to post-baseline (measured at week 24 and at the final or termination visit), against the alternative that increase is greater for placebo than for the active arm. Higher theta power is worse; hence the alternative indicates benefit of the drug.

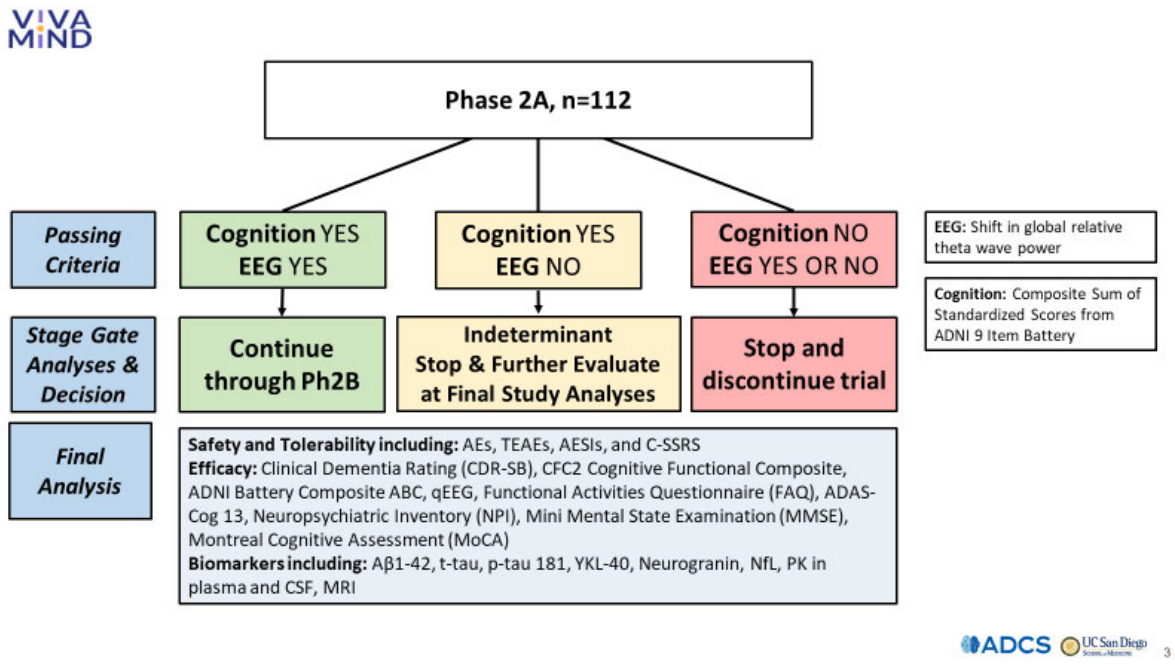
The test will be carried out at a one-sided 5% significance level, using the mixed effects model specified in Section 5.5.2.3. Rejection of the null hypothesis will indicate a statistically significant benefit of treatment, and a value of YES will be recorded for the continuation of the study from this hypothesis test. Otherwise, a value of NO (no statistically significant evidence of benefit) will be recorded from this hypothesis test.

5.5.2.2 The Futility Stopping Rule

If the ABC Score statistical test records NO, the trial will stop. If both the ABC Score and the EEG theta power statistical tests record YES, the trial will continue. Otherwise, the stopping rule will be undetermined, the trial will pause, and the decision whether to continue the trial will be undertaken jointly by the SSC and the sponsor.

The characteristics stated here are justified below (Figure 1), where details of the implementation of the stopping rule are presented.

Figure 1 Framework of Phase 2A stopping rule



5.5.2.3 Interim – Statistical analysis

For both the ABC cognitive futility outcome measure and the qEEG futility outcome measure the interim analysis will use the within-participant change from baseline as the dependent variable in a mixed effects model, using SAS PROC MIXED with a Maximum Likelihood (ML) approach. All available outcomes in the mITT set will be included, without imputation for missing data.

Fixed effect covariates in the model will be *APOE* status (e4 carrier vs. non-carrier), initial diagnosis (MCI or mild AD dementia), site, baseline measure of the outcome, time, treatment group (active or placebo), and time by treatment group interaction. Sites with 5 or fewer participants included in the mITT will be pooled. The model will include random effects for intercept and time (i.e., random slopes).

A one-sided Wald test of hypothesis will be conducted on the contrast statement testing differences in slope in active versus placebo treatment at the stated significance level. The specific hypothesis tests are indicated above.

Time from baseline visit will be treated as a continuous variable, and the SAS code will be similar to the following:

```
proc mixed method=ml;
  class subjid visit apoe diagn site treatment;
  model <var_cfb>=baseline time*baseline time*apoe time*diagn site time
treatment time*treatment /
       solution cl ddfm=kenwardroger tech=nmsimp;
  random intercept time /sub=subjid ;
run;
```

The code will be appropriately adapted if the analysis is conducted using R Software.

If the model fails to converge at the specified settings, then the
mixed effects model like above will be used, dropping the time by baseline term. In case the model fails to converge after modification, model diagnostics will be used to investigate and take corrective action. The process used to arrive at the final model will be fully documented.
As a sensitivity analysis, a one-sided two sample t-test at 24 weeks will also be conducted for each measure.

In both the ABC and qEEG analyses, if the data shows marked non-normality, appropriate data transformation will be considered.

5.5.3 Interim analysis reports to the DSMB

The following reports will be provided to the DSMB by an unblinded statistician:

- The interim futility analysis.
- A safety report, in the form of an updated quarterly DSMB report, which contains all data as of the date of data freeze.

5.6 Analysis of Phase 2B – Baseline presentations

This section provides the description of baseline outputs to be created for Phase 2B.

5.6.1 Inclusion/exclusion criteria

An individual patient listing of deviations from the inclusion and exclusion criteria will be presented.

5.6.2 Demographics

Descriptive tabulations of the screening data for demographics will be made. Demographic data (including weight and height measurements) per treatment group and overall will be presented. Appropriate descriptive statistics for age, height, weight, BMI, ethnicity, race, sex and education will be given. The summary will be created for each analysis population (mITT, SAF, PK) separately. Additionally, demographic data will be listed.

5.6.3 Baseline characteristics

The following relevant baseline characteristics will be listed and summarized per treatment group and overall (frequency and percentage).

- Initial diagnosis (MCI / Mild probable AD)
- APOE status
- Site

5.6.4 Participant disposition

A summary of participant disposition will be tabulated for all participants by treatment group and overall. Furthermore, a listing displaying the disposition information on a per participant level will be created.

The summary will include:
- Number of screened participants
- Number of participants randomized
- Number of participants treated

- Number of mITT, SAF and PK participants
- Number of participants who completed the study
- Number of participants who prematurely withdrew the study and reasons for withdrawal

The Medical Writer will create a flow diagram for inclusion in the CSR based on this information.

5.6.5 Medical history

Medical history from CRF will be tabulated for SAF per System Organ Class (SOC) and Preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology list and presented as number/percentage of patients in each SOC and PT for the SAF. SOC and PT will be presented in descending order of frequency of occurrence based on SOC and PT. These data will also be listed on a per participant level.

5.6.6 Other Screening data

Other data collected at screening or baseline only will be listed.

5.7 Analysis of Phase 2B – Statistical analysis of primary and secondary efficacy endpoints

This section provides the description of the statistical analyses for phase 2B. The analyses to be performed for Phase 2A are described in Section 5.5.

5.7.1 Analysis of Primary efficacy Endpoint

The primary study hypothesis in phase 2B is that treatment with varoglutamstat will result in a reduction in within-participant change on total CDR-SB score relative to the placebo group at week 72 in the mITT population. Only patients with at least a valid baseline and postbaseline assessment will contribute to the analysis model. See CDR-SB derivation details in Section 8.1.2.

The primary analysis will use the within-participant change in CDR-SB as the outcome in an MRMM, using SAS PROC MIXED with a Maximum Likelihood (ML) approach. All available outcomes in the mITT population will be used, with no additional imputation for missing data.

Fixed effects in the model will be APOE status (e4 carrier vs. non-carrier, see Section 8.1.13), initial diagnosis (MCI or mild AD dementia), site, baseline CDR-SB, treatment group (active or placebo), visit, and visit x treatment group interaction. Visit is treated as a class variable. All sites with 5 or fewer participants will be pooled. In case of missing APOE status genotype, the most frequent APOE genotype will be imputed for analysis. A similar approach will be used in case of missing initial diagnosis. Randomization strata will be used for analysis, in case they differ from data collected in EDC. The SAS code will be similar to the following.

```
proc   xed  e hod=  ;
  c ass subj d v s   apoe d agn s  e  rea  en ;
   ode  <var_cfb>=base  ne apoe d agn s  e v s    rea  en  v s  *  rea  en  /
     so u  on c  ddf =kr;
  repea ed v s  /sub=subj d  ype=un;
   s eans v s  * rea  en  / d ff c ;
run;
```

The covariance structure will be specified as follows. An unstructured covariance matrix will be used in the model (type un). If the model fails to converge, diagnosis (MCI or mild AD) will be removed from the model. If the model still does not converge, the following structures for the within-subject covariance will be applied, sequentially, until the structure is found that results in convergence of the model: Huynh-Feldt, Toeplitz, Autoregressive (AR(1)), and Compound Symmetry.

Error degrees of freedom will be calculated using the Kenward-Roger approximation (ddfm KR) if an UN structure is used; otherwise, a sandwich estimator will be utilized (via PROC MIXED option EMPIRICAL combined with computation of the denominator degrees of freedom using the between-within method (ddfm BW)) to estimate the variance-covariance matrix and degrees of freedom will be calculated using the between-within method.

In case the model fails to converge after all these modifications, model diagnostics will be used to investigate and take corrective action. The process used to arrive at the final model will be fully documented, if deviating from the above. The primary endpoint will be tested using model-adjusted least squares means at the week 72 visit. Point estimates, standard errors, two-sided 95% confidence intervals, and p-values will be presented. LS mean differences in change from baseline will be tabulated and graphed.

In case the data shows marked non-normality, appropriate data transformation will be considered.

In addition, descriptive statistics will be provided per treatment and visit for both the observed values as well as the change from baseline, and all data will be listed.

5.7.1.1 Sensitivity analysis

The following sensitivity analysis will be conducted to support the principal analysis.

For the primary analysis, a placebo (reference) multiple imputation (PMI) will be applied using PROC MI with the MONOTONE option using predictive mean matching (option REGPMM) to impute missing data for any participants (i.e. from both treatment arms) who discontinue treatment early, irrespective the reason for drop-out, and for which no data was collected after treatment discontinuation. The pMI method assumes the statistical behavior of placebo- and drug-treated participants after dropout is the statistical behavior of placebo-treated participants. A total of 20 imputed data sets will be created. A first step will be implemented to perform a partial imputation and get monotone missing pattern (mcmc chain multiple impute monotone). The seed 202407 will be used for the analysis. The same model as presented in Section 5.7.1 will be used, but with inclusion of additional baseline covariates age, ADAS-COG-13, FAQ. In case of failure of the model imputation approach, the following covariates will be excluded in the following order: site, and initial diagnosis. The model will be used to each of the imputed datasets separately after applying the imputation techniques. The results of the 20 imputed datasets will be combined via pooling of the estimated parameters using Rubin's combining rules to obtain a final estimate of the treatment difference with a 95% confidence interval and p-value.

5.7.2 Analysis of Secondary Efficacy Endpoints

All secondary efficacy endpoints will use the mITT set for analysis, with statistical significance handled as described in Section 5.4.

5.7.2.1 Cognitive Functional Composite-2 (CFC2)

The key secondary endpoint in phase 2B is the within-participant change in CFC2 from baseline to week 72, compared between the varoglutamstat treatment group and the placebo group. Endpoint derivation details are provided in Section 8.1.10.

The change from baseline CFC2 composite will be analyzed via a MMRM analysis model using the same approach as specified for the primary analysis (see Section 5.7.1), including the adjustment for baseline CFC2 data instead of the CDR-SB score. There will be no imputation for missing data.

In addition, descriptive statistics will be provided per treatment and visit for both the observed values as well as the change from baseline, and all data will be listed.

5.7.2.2 ADNI Battery Composite (ABC) Score

For derivations to obtain the ABC score, see Section 8.1.1.

As for the primary endpoint, the change from baseline in ABC score will also be analyzed using the MMRM analysis model (see Section 5.7.1), including the adjustment for baseline ABC score data instead of the CDR-SB score.

In addition, descriptive statistics will be provided per treatment and visit for both the observed values as well as the change from baseline, and all data will be listed.

5.7.2.3 Quantitative EEG (global relative theta wave power)

Analyzing electroencephalogram (EEG) is done by using quantitative EEG (qEEG), collecting the global relative theta power (4-8 Hz) as a numerical analysis of the EEG data.

As for the primary endpoint, the change from baseline in qEEG will also be analyzed using the MMRM analysis model (see Section 5.7.1), including the adjustment for baseline qEEG data instead of the CDR-SB score. There will be no imputation for missing data. In addition, descriptive statistics will be provided per treatment and visit for both the observed values as well as the change from baseline, and all data will be listed.

5.7.2.4 Functional Activities Questionnaire (FAQ)

The FAQ is a 10-item questionnaire which rates the patient on their ability to carry out 10 complex activities of daily living. Each item is rated on a scale from 0 to 3, with higher scores meaning a greater impairment, and the total summed FAQ disability score ranges from 0 to 30 (see Section 8.1.6).

The change from baseline FAQ total score will be analyzed via a MMRM analysis model using the same approach as specified for the primary analysis (see Section 5.7.1), including the adjustment for baseline FAQ total score data instead of the CDR-SB score. There will be no imputation for missing data.

In addition, descriptive statistics will be provided per treatment and visit for both the observed values as well as the change from baseline (only for the total score), and all data (including details on item-level) will be listed.

5.7.2.5 Alzheimer's Disease Assessment Scale-Cognitive Subscale 13 (ADAS-Cog-13)

The ADAS-Cog-13 is a rater-administered scale with thirteen performance subtests. Higher scores reflect poorer performance and greater impairment. Total scores range from 0 (best) to 85 (worst). See derivation details in Section 8.1.4.

The change from baseline ADAS-Cog-13 total score will be analyzed via a MMRM analysis model using the same approach as specified for the primary analysis (see Section 5.7.1), including the adjustment for baseline ADAS-Cog-13 total score data instead of the CDR-SB score. There will be no imputation for missing visits; when applicable, missing data will be prorated as described in Section 8.1.4.

In addition, descriptive statistics will be provided per treatment and visit for both the observed values as well as the change from baseline (only for the total score), and all data (including details on subtest-level) will be listed.

5.7.2.6 Neuropsychiatric Inventory (NPI)

The NPI is an instrument to assess psychopathology in AD. The NPI evaluates both the frequency and severity of 12 items: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant motor behavior, sleep and appetite/eating disorders. Result on each frequency assessment range from 1 (occasionally, less than once per week) to 4 (very frequently, once or more per day or continuously), results on severity assessments are scored 1 to 3 (1 mild, 2 moderate, 3 severe). The overall score ranges from 0 to 144. See derivation details in Section 8.1.7.

The change from baseline NPI total score will be analyzed via a MMRM analysis model using the same approach as specified for the primary analysis (see Section 5.7.1), including the adjustment for baseline NPI total score data instead of the CDR-SB score. There will be no imputation for missing data. In addition, descriptive statistics will be provided per treatment and visit for both the observed values as well as the change from baseline (only for the total score), and all data (including details on subtest-level) will be listed.

5.8 Analysis of Exploratory Endpoints

5.8.1 Brain volume and cortical thickness measured by cranial MRI

Imaging analysis is done using volumetric magnetic resonance imaging (vMRI). Variables measured are the whole brain volume, bilateral ventricular volume and bilateral hippocampal volume. There will also be 6 cortical thickness areas measured: hippocampus, entorhinal, precuneus, isthmus of cingulate gyrus, mid temporal gyrus, and supramarginal gyrus. For vMRI, post-baseline change in brain volume is collected as an atrophy variable (QUARC), and this variable is already presenting a change value. Baseline values are collected as volume measures.

The change from baseline for each of the three vMRI measures will be analyzed via a MMRM analysis model using the same approach as specified for the primary analysis (see Section 5.7.1), including the adjustment for baseline vMRI data instead of the CDR-SB score. There will be no imputation for missing data. In addition, descriptive statistics will be provided per treatment and visit for the atrophy and the volume variables, and all data (including potential other collected vMRI measures) will be listed.

5.8.2 Mini-Mental Status Examination (MMSE)

The Mini-Mental State Examination (MMSE) is widely used brief mental status screening assessment. The MMSE measures orientation to time and place, immediate recall, short-term verbal memory, calculation, language, and construct ability. The MMSE total score ranges from 0-30, where a lower score indicates more cognitive impairment. See derivation details in Section 8.1.8.

The change from baseline for the total MMSE score will be analyzed via a MMRM analysis model using the same approach as specified for the primary analysis (see Section 5.7.1), including the adjustment for baseline total MMSE score data instead of the CDR-SB score. There will be no imputation for missing visits. In addition, descriptive statistics will be provided per treatment and visit for both the observed values as well as the change from baseline (only for the total score), and all data (including details on question-level) will be listed.

5.8.3 Montreal Cognitive Assessment (MoCA)

The MoCA is a brief screening instrument designed to detect cognitive dysfunction. It assesses a range of different cognitive domains, including attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The maximum total score is 30 points, with lower scores meaning more cognitive impairment. See derivation details in Section 8.1.9.

The change from baseline for the total MoCA score will be analyzed via a MMRM analysis model using the same approach as specified for the primary analysis (see Section 5.7.1), including the adjustment for baseline total MoCA score data instead of the CDR-SB score. There will be no imputation for missing visits.
In addition, descriptive statistics will be provided per treatment and visit for both the observed values as well as the change from baseline (only for the total score), and all data (including details on item-level) will be listed.

5.8.4 CSF disease-relevant biomarkers

The change from baseline for each of the CSF biomarkers (Aβ1-42, t-tau, p-tau-181, YKL40, neurogranin, NfL) will be analyzed via a MMRM analysis model using the same approach as specified for the primary analysis (see Section 5.7.1), including the adjustment for baseline biomarker data instead of the CDR-SB score. There will be no imputation for missing data.
In addition, descriptive statistics will be provided per treatment and visit for both the observed values as well as the change from baseline, and all data will be listed.

5.8.5 qEEG network connectivity measures

The change from baseline for qEEG connectivity measures (alpha AECC Global, lower alpha AECC Global, upper alpha AECC Global) will be analyzed via a MMRM analysis model using the same approach as specified for the primary analysis (see Section 5.7.1), including the adjustment for baseline endpoint data instead of the CDR-SB score. There will be no imputation for missing data.
In addition, descriptive statistics will be provided per treatment and visit for both the observed values as well as the change from baseline, and all data will be listed.

5.8.6 AD Composite Score (ADCOMS)

ADCOMS [3]is a weighted cognitive-functional composite outcome comprised of the 6 box scores from the CDR; four subtests from the ADAS-Cog (*Delayed Word Recall*, Orientation, *Word Finding Difficulty* & *Word Recognition*); and two subtests from the MMSE (*Copying Intersecting Pentagons* and *Orientation to Time*). The derivation of ADCOMS is provided in Section 8.1.3.

The change from baseline for the ADCOMS score will be analyzed via a MMRM analysis model using the same approach as specified for the primary analysis. There will be no imputation for missing data.

In addition, descriptive statistics will be provided per treatment and visit for both the observed values as well as the change from baseline for ADCOMS, and its individual data will be listed. Since the ADCOMS is a composite of other measures listed elsewhere, these will not be listed in the ADCOMS listing.

5.8.7 ADAS-Cog-Exec

The ADAS-Cog-Exec[4] is a cognitive composite outcome constructed as an optimally weighted composite of scores on ADAS-Cog-13 (*Word Recall, Delayed Word Recall, Orientation, and Number Cancellation subtests; Trail-Making A & B, Digit Symbol Substitution and Category Fluency*) and cognitive components of the CDR (*Memory, Orientation, Judgement & Problem Solving*). The derivation of ADAS-Cog-Exec is provided in Section 8.1.5.

The change from baseline for the ADAS-Cog-Exec total score will be analyzed via a MMRM analysis model using the same approach as specified for the primary analysis (see Section 5.7.1), including the adjustment for baseline ADAS-Cog-Exec total score data instead of the CDR-SB score. There will be no imputation for missing data. In addition, descriptive statistics will be provided per treatment and visit for both the observed values as well as the change from baseline for the ADAS-Cog-Exec total score, and its individual data will be listed. Since the ADAS-Cog-Exec total score is a composite of other measures listed elsewhere, these will not be listed in the ADAS-Cog-Exec listing.

5.8.8 Relative QC activity

QC activity is collected as absolute values. For each participant, the QC activity at week 24 should be normalized to his/her activity at screening as follows:

Relative QC activity (%) 100 * (QC activity at week 24 / QC activity at screening).

A lower relative QC activity means a positive result.

Absolute value and relative QC activity evaluated on serum will be summarized by visit for the PK set by means of descriptive statistics per treatment and visit.

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[3] Wang J, Logovinsky V, Hendrix SB, Stanworth SH, Perdomo C, Xu L, Dhadda S, Do I, Rabe M, Luthman J, Cummings J. ADCOMS: a composite clinical outcome for prodromal Alzheimer's disease trials. Journal of Neurology, Neurosurgery & Psychiatry. 2016 Sep 1;87(9):993-9.

[4] Jacobs DM, Thomas RG, Salmon DP, Jin S, Feldman HH, Cotman CW, Baker LD, Alzheimer's Disease Cooperative Study EXERT Study Group, Alzheimer's Disease Neuroimaging Initiative. Development of a novel cognitive composite outcome to assess therapeutic effects of exercise in the EXERT trial for adults with MCI: The ADAS-Cog-Exec. Alzheimer's & Dementia: Translational Research & Clinical Interventions. 2020;6(1):e12059.

Summaries will also be produced for the QC activity in CSF if data are available as post-hoc.

5.8.9 eGFR, Bun, and Creatinine Analyses

Following results observed in VIVIAD study, the activity of varoglutamstat on the glomerular filtration rate will be explored in the eGRF population (see Section 3.1.4). The change from baseline in eGFR using the CKD-EPI formula (see Section 8.1.12) will be analyzed via a MMRM analysis model using the same approach as specified for the primary analysis (see Section 5.7.1), including the adjustment for baseline eGFR data instead of the CDR-SB score. There will be no imputation for missing data. In addition, descriptive statistics will be provided per treatment and visit for both the observed values as well as the change from baseline, and its individual data will be listed.

This analysis will also be repeated for the eGFR endpoint data derived using MDRD formula (see Section 8.1.12), as well as for BUN and Creatinine endpoints.

5.8.10 Other statistical analyses

Post-hoc exploratory analysis may be conducted for subgroup presentations using descriptive statistics will be created for CDR-SB and CFC2, presenting the results based on the subgroups as defined by:

- APOE genotype (E4 carrier vs non E4 carrier)
- MCI vs. Mild probable AD

Statistical analysis for the comparison of plasma-based amyloid biomarker results using the PrecivityAD® test with CSF-based amyloid and p-tau test results using the Elecys® test will be described in a separate SAP.

5.9 PK analysis

Descriptive statistics will be provided for the PK concentrations in blood of PQ912, PQ1345, PQ1529, and for the PQ912 $TO_{est\ mated}$ (%) (see Sections 4.1.3 and 4.2.4) at each visit prior to study medication intake and by the following post-treatment timepoint categories: “<2h”, “2 to <3 h”, “3 to < 4h”, “4 to < 5h”, “5 to < 6h”, “> 6h”. These post-treatment categories may be adapted depending on the distribution of actual sampling timepoints. Mean summary values will also be plotted.

Values below the limit of quantification are imputed as 0 for the summaries.

Estimated PK CSF concentration will not be summarized. The same approach will be used for CSF PK concentration and TO_{actua} (%) if data are available for analysis.

5.10 Safety and tolerability evaluation

Safety and other exploratory analyses will be conducted on the Safety analysis population (SAF)

Safety outcome measures include AEs, laboratory assessments, physical examinations, vital signs, ECGs, concomitant medications, mortality rates, and the C-SSRS questionnaire.

Continuous values will be summarized by descriptive statistics (n, mean, SD, median, minimum, maximum).

Categorical variables will be summarized using the number and percentage of participants in each category for each treatment group and overall. The denominators for calculating the percentages will be based on the number of participants with non-missing assessments at a particular visit for the safety population.

5.10.1 Adverse events

A treatment emergent adverse event (TEAE) is defined as an adverse event that appears during or after first dose of study treatment and was absent before, or an adverse event that was already present but worsens during or after study treatment relative to the pre-treatment state. It is assumed that worsened events are collected in the database as new events, and therefore no differentiation or comparison needs to be made by the programmer.

AESI will be flagged in the EDC according to the following definitions:

- As per protocol v5.0: occurrence of any of the following treatment-emergent adverse events within the organ systems of skin or subcutaneous tissues and liver:
  - Discontinuation of participant due to an AE (any severity, including SAEs)
  - Adverse event related to liver with severity 3 and above according to Common Terminology Criteria for Adverse Events (CTCAE v 5.0) regardless of discontinuation.
  - Discontinuation of participant due to an extreme lab parameter related to the liver or bile organ system:
    - ALT or AST >8xULN
    - ALT or AST >5xULN for more than 2 weeks
    - ALT or AST >3xULN and (TBL >2xULN or INR >1.5)
    - ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - Adverse event related to skin or subcutaneous tissue with severity grade 2 and above according to CTCAE v 5.0.

- As per protocol v6.0: occurrence (occurrence of an AESI means the date when the criteria of an AESI are fulfilled, not the overall onset of an AE without meeting the criteria of an AESI) of any of the following TEAEs within the primary SOCs of Skin or subcutaneous tissue disorders or hepatobiliary disorders:
  - Discontinuation of participant due to an AE (any severity, including SAEs)
  - Adverse event in the primary SOC of hepatobiliary disorders with severity 3 and above according to CTCAE v 5.0 regardless of discontinuation.
  - Discontinuation of participant due to an extreme lab parameter related to the liver or bile organ system:
    - ALT or AST >8xULN
    - ALT or AST >5xULN for more than 2 weeks
    - ALT or AST >3xULN and (TBL >2xULN or INR >1.5)
    - ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - Adverse event in the primary SOC of Skin or subcutaneous tissue disorders with severity grade 3 and above according to CTCAE v 5.0.

Given the minor changes in their definitions, AESI records will be analyzed together irrespective of the protocol version. Unless otherwise specified, TEAE summaries will include only AEs starting before the end of treatment at Week 72 or at earlier treatment discontinuation.

An AE overview table will be created displaying the number of participants (and percentage) experiencing a TEAE and the number of TEAEs for: Any TEAE, Any mild/moderate/severe TEAE, Any related/unrelated TEAE, Any treatment-emergent serious AE (SAE), Any AESI, Any Death, and Any TEAE leading to study medication modification or discontinuation. Summary of AESI by severity will be remapped to CTCAE grading with mild, moderate, severe, life-threatening and death categories will be presented as grade 1 to 5, respectively. However, in TEAE summaries by categories mild/moderate/severe, any TEAE categorized as life-threatening, or death will be presented as severe.

All TEAEs are tabulated by System Organ Class (SOC) and Preferred Terms (PTs) within each SOC according to the MedDRA terminology list. TEAEs will also be tabulated by severity (mild/moderate/severe) and by relationship to study medication (related/unrelated), using frequency counts (number of participants with at least one event, and number of events) and percentage of participants with the event. Similar tables will be created for TEAEs leading to premature study medication discontinuation, SAEs AESIs and deaths, if applicable. These summary tables will be presented by decreasing frequency of occurrence based on SOC and PT.

An additional overview table and summary by SOC and PT of all TEAEs occurring after Week 72 (or after earlier treatment termination) will be produced.

The summary tables will be accompanied by individual participant listings of *all* AEs including information on AE number, actual AE description, date/time of start and end of AE (or ongoing), PT (MedDRA), SOC (MedDRA), severity, relationship, seriousness, action taken and outcome. Pre-existing AEs are not considered to be treatment-emergent, except in case of worsening during/after study treatment (to be collected as separate AE in the database). AEs starting prior to administration of the study drug will only be listed.

Separate listings will be created for SAEs, deaths and AESIs, if applicable.

For summary tables, an AE is considered related if the causality to the study medication is classified as ‘Definitely Related’, ‘Probably Related’ or ‘Possibly Related’. Otherwise, it will be considered unrelated for summary tables. The original description will be used in listings and all observed data will be listed.

5.10.2 Clinical laboratory data

The following laboratory safety data are collected for this study:

Hematology:

Hemoglobin, hematocrit, platelet count, RBC, WBC, differential count and absolute neutrophil count

Chemistry:

Sodium, potassium, chloride, calcium, ALT, AST, LDH, alkaline phosphatase, GGT, phosphorous, bicarbonate, CPK, total protein, albumin, direct bilirubin, indirect bilirubin, total bilirubin, glucose, creatinine, BUN, estimated Glomerular Filtration Rate (eGFR), uric acid, total cholesterol, LDL, HDL, triglycerides, B12 (screening), folate (screening)

Other:

Testosterone, TSH, T3, T4, hemoglobin A1c (HbA1c)

Urinalysis:

pH, specific gravity, protein, glucose, ketones, urobilinogen, bilirubin, blood, leucocytes and nitrite

Serology (screening):

Human Immunodeficiency Virus (HIV), Hepatitis A Virus (HAV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) and syphilis

Laboratory safety data will be summarized (n, mean, SD, median, first and third quartiles, minimum and maximum for quantitative data, or frequency and percentage for qualitative data) and listed per visit and treatment group. Change from baseline will be calculated and presented as well for quantitative data, using the same summary statistics.

For the liver function tests (AST, ALT, Alkaline Phosphatase, GGT and Total Bilirubin) the shift from baseline will also be presented by visit and to the maximum observed abnormality.
The following categories will be used to summarize the shift from baseline based on the upper limit of normal (ULN) range for ALT and AST:

- ≤ ULN
- > ULN to ≤ 3x ULN
- > 3x ULN to ⩽ 5x ULN
- > 5x ULN

The following categories will be used to summarize the shift from baseline based on the ULN range for alkaline phosphatase:

- ≤ ULN
- > ULN to ≤ 1.5x ULN
- > 1.5x ULN to ⩽ 2.5x ULN
- > 2.5x ULN

For GGT, the following categories will be used to summarize the shift from baseline based on the ULN range for GGT:

- ≤ ULN
- >ULN to ≤ 2.5x ULN
- > 2.5x ULN

The following categories will be used to summarize the shift from baseline based on the ULN range for Total Bilirubin:

- ≤ ULN
- > ULN to ≤ 1.5x ULN
- > 1.5x ULN to ⩽ 2.0x ULN
- > 2.0x ULN

For laboratory safety data, all recorded and determined laboratory safety data will be listed. Safety laboratory parameters will be presented in the tables and listings in the same units as supplied from the laboratory.
A separate listing will be created for participants with a maximum value of ALT or AST >3x ULN or a maximum total bilirubin value >2x ULN observed at any point during the entire study.

5.10.3 Vital Signs

Vital sign data consist of measurements for pulse rate, systolic and diastolic blood pressure, temperature and respiration rate. Vital signs will be summarized and listed per visit and per treatment group, using protocol visits. Change from baseline will be calculated and presented as well, using the same summary statistics.

In addition, the number and percentage of participants with at least one post-treatment vital sign measurement for each of the following criteria will be summarized:

- Systolic Blood Pressure: < 90 mmHg, > 140 mmHg, > 160 mmHg
- Diastolic Blood Pressure: < 50 mmHg, > 90 mmHg, > 100 mmHg
- Pulse Rate: <60 bpm, >100 bpm
- Body Weight: decrease of ≥ 7% from baseline or increase of ≥ 7% from baseline.
- Temperature: > 38.0 °C, < 36.0 °C

All observed data will be listed.

5.10.4 ECG

ECG outcome results collected as normal/abnormal will be presented descriptively using frequency counts and percentages per treatment group, using protocol visits.

All observed data will be listed.

5.10.5 Volumetric Brain MRI

Data on MRI signal changes (ARIA-E, ARIA-H and infarcts) will not be analyzed (see Section 6).

5.10.6 C-SSRS

A summary of C-SSRS will be produced displaying the number of participants (and percentage) experiencing Any suicidality, Any suicidal ideation, Any suicidal behavior, and Any self-injurious behavior without suicidal intent.

- Any suicidal ideation: “yes” answer to any of the 5 suicidal ideation C-SSRS questions:
    - Suicidal Ideation - Wish to be Dead (Y/N)
    - Suicidal Ideation - Non-Specific Active Suicidal Thoughts (Y/N)
    - Suicidal Ideation Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act (Y/N)
    - Suicidal Ideation Active Suicidal Ideation with Some Intent to Act, without Specific Plan (Y/N)
    - Suicidal Ideation - Active Suicidal Ideation with Specific Plan and Intent (Y/N)
- Any suicidal behavior: “yes” answer to any of the 5 suicidal behavior C-SSRS questions
    - Suicidal Behavior - Actual Attempt (Y/N)
    - Suicidal Behavior - Interrupted Attempt (Y/N)
    - Suicidal Behavior - Aborted Attempt (Y/N)
    - Suicidal Behavior - Preparatory Acts or Behavior (Y/N)
    - Suicidal Behavior - Suicidal Behavior (Y/N)
- Any suicidality: “yes” answer to any of the 10 suicidal ideation and behavior C-SSRS questions, as indicated in the bullet points above.
- Any self-injurious behavior without suicidal intent: “yes” answer to the following suicidal behavior C-SSRS question

- Suicidal Behavior - Has subject engaged in Non-Suicidal Self-Injurious Behavior? (Y/N)

Two separate tables will be produced:
- One summarizing data for the questionnaire collected at screening (C-SSRS Baseline)
- One summarizing data for the questionnaire collected at subsequent time points (C-SSRS Since Last Visit)

All observed data will be listed.

5.10.7 Prior and concomitant medication

The use of concomitant medication will be listed for all participants: included will be the medication generic name (Drug Name), WHO coding information (ATC code), dose, route of administration, start and stop date, frequency and reason for administration, as well as information if given for an AE. Differentiation will be made between prior and concomitant medication, by creating two separate listings.

A comedication with a stop date prior to start of study treatment is considered to be prior, and all other medications are considered concomitant.

5.10.8 Physical examination

General physical examination data will be listed.

5.11 Scheduled visits, Dosing and Treatment Compliance

5.11.1 Visit dates

A listing with actual visit dates (and times, if applicable) will be presented.

5.11.2 Dosing, exposure and treatment compliance

Relevant dosing information, scheduled and actual dosing dates/times, treatment compliance information and treatment duration will be listed for each participant as collected in the database.

Descriptive statistics of the duration of exposure and for compliance will be provided for the SAF per actual treatment group (See Section 5.1.1). These variables will be derived as follows:

- Duration of exposure (weeks) will be derived from EDC “Exposure as collected” form data as: (date of last exposure – date of first exposure + 1)/7. In case of missing date of last exposure, the study discontinuation date will be used.
- Compliance (%) will be calculated as ratio between the sum of the number of tablets taken (EDC variable: DATAKEN) during the course of the study over the sum of the tablets expected during the course of the study (EDC variable: DANUMEXP). Compliance will be based on the available drug accountability data in EDC, with no imputation. Of note, the EDC accountability dataset replicates the same number of tablets taken and expected for each drug kit record associated with a visit, therefore only one of those records per visit will have to be considered for the derivation of compliance.

6 CHANGES FROM PROTOCOL

Although Health Status is mentioned as an endpoint, it is intended as a comprehensive set of safety outputs (AE, laboratory, combined with demographics) which are already provided separately. Therefore, there is not specific analysis mentioned for Health Status in this SAP.

The assays of the following CSF disease-relevant biomarkers that were foreseen in the protocol are no longer available to the study at the time the trial ends and their analysis is not included in this SAP: sTREM2, SNAP24, and VILIP 1.

While Plasma PK and estimated TO will be analyzed, the analysis of PK and QC in CSF samples will be confirmed by the Sponsor depending on the results observed from the primary and secondary endpoints analysis.

The following measures related to secondary objectives of Phase 2B will not be evaluated via central reading but only through adverse events analysis: imaging abnormalities on brain MRIs as determined by the site Principal Investigator (PI) with a local reading, including Amyloid-Related Imaging Abnormalities Related to Hemosiderin Deposits (ARIA-H), Amyloid-Related Imaging Abnormalities Related to Underlying Vasogenic Edema (ARIA-E), infarcts.

Human leukocyte antigen (HLA) genotype results will not be evaluated in relationship with the SAE frequency.

It has been clarified that the safety and tolerability endpoint of frequency and severity of abnormalities on physical examination is to be assessed as frequency of AEs by the relevant SOC abnormalities on physical examinations.

The ITT population is briefly mentioned in the protocol section 12.4, but not anywhere used for any statistical analysis. Therefore, this population is not included in the SAP.

Similarly for the PP population: this is briefly mentioned in the protocol (section 6.9.2), but not anywhere used for any statistical analysis. Therefore, this population is not included in the SAP.

The protocol accidently mentions a baseline * visit interaction term to be included in the statistical models. This is therefore not included in the SAP.

Exploratory analyses of eGFR, Bun, and Creatinine have been included in the SAP following the results observed in VIVIAD study.

The ADNI Battery Composite (ABC) score was specified as the sum of the standardized test values (Z-scores) for 9 measures from the ADNI battery. We will instead use the mean of the standardized test values, as described in Section 8.1.1.

7 DATA RECEIPT

All data will be received from ADCS, per transfer agreement(s). Part of the datasets will be received in SDTM-like format and will be used for further creation of analysis datasets. SAS analysis datasets will be programmed for the production of tables, listings and figures. No CDISC standard datasets are required.

8 TECHNICAL DETAILS

8.1 Programming conventions

Durations will be programmed as stated in the respective analysis sections.

Computations/derivations for efficacy endpoints are as follows:

8.1.1 ABC score

The ADNI Battery Composite (ABC) score will be calculated from the following 9 measures from the ADNI Neuropsychological Test Battery:

ADNI Battery Composite (ABC)				
Subtest #	**Scale**	**Item**	**EDC Variable**	**Worst Possible Score**
01	AVLT - Immediate	Sum of Trials 1-5	AVL0216 + AVL0216A + AVL0216C + AVL0216D + AVL0216E	0
02	AVLT - Delay	Delayed word recall	AVL0216T	0
03	Number Span Forward	Total Correct	NSTF108	0
04	Number Span Backward	Total Correct	NSTB108	0
05	Category Fluency	Mean of Total Correct for Animals and Vegetables	(QSCF0301 + QSCF0304)/2	0
06	Trail Making Test A	Time to Completion	TMT0101	150
07	Trail Making Test B	Time to Completion	TMT0104	300
08	DSST	Total Score	DSST0101	0
09	Boston Naming Test	Total Correct	BNT0133	0

Each test will be scored so that higher is better (i.e. the negative value will be taken for Trail Making A and B, where higher values indicate worse performance).

For each subtest, standardized scores (Z-scores) will be calculated using the overall mean and standard deviation of all participants in the mITT at baseline as reference. For each participant and each test, the test score will be standardized by subtracting the overall baseline mean and dividing by the baseline standard deviation of the specific measure.

The ABC score for each participant will be the mean of the standardized subtest values.

Calculating the ABC score when there are missing data

Missing total scores for subtest measures from the ADNI Neuropsychological Test Battery are designated by the rater as missing for the following reasons:

- Participant Unable for Cognitive Reasons
- Participant Unable for Other Reasons (Physical, auditory, etc.)
- Participant/Study Partner Refused
- Oversight
- Related to COVID-19
- Other Reason
- Unknown

When total scores for subtest measures are missing because the participant was unable to complete the task for cognitive reasons (first bullet point above), the worst possible score for the measure will be assigned.

Additionally, for Trail Making Test B, if the Reason Not Done is 'TMT Part A not completed within max time,' then the worst possible score (300) is assigned for Trail Making Test B.

Total scores for subtest measures that are missing for any other reason will be treated as missing in calculating the ABC score, and they will not contribute to the mean average Z-score.
The ABC score for each participant will be calculated as the overall average Z-score of the completed subtests. If more than 2 of the 9 ADNI battery subtests are missing, or if AVLT Immediate Recall (Subitem # 01) is missing, then the ABC score will be missing.

8.1.2 **CDR-SB**

The CDR-SB is calculated as the sum of the ratings (box scores) for the 6 domains evaluated by the CDR (Memory; Orientation; Judgement & Problem Solving; Community Affairs; Home & Hobbies; Personal Care). Impairment in each of the 6 domains is scored between 0 and 3 (0 none, 0.5 questionable, 1 mild, 2 moderate, and 3 severe), leading to a CDR-SB between 0 and 18; higher scores indicate greater impairment.

CDR-SB score derived in the CRF form will be used for analysis. If any of the 6 ratings (box scores) is missing, the CDR-SB is considered missing.

CDR Global score provided in CRF form will only be presented in listings.

8.1.3 **ADCOMS**

ADCOMS is calculated as a weighted composite outcome comprised of the 6 box scores from the CDR; four subtests from the ADAS-Cog; and two subtests from the MMSE (see table below). The composite score[5] is determined as the linear combination of the individual scale items using the corresponding PLS coefficients as weighting factors as listed in the table below. The range of ADCOMS is between 0 and 1.97; higher scores indicate greater impairment. If any of the individual subtest is missing, then the composite score will be missing as well.

Sub-test #	Scale	Item	EDC Variable	Worst Possible Score	PLS coefficient
01	ADAS-13	Delayed word recall	ADCDRL4	10	0.008

[5] Wang J, Logovinsky V, Hendrix SB,et al. *ADCOMS: a composite clinical outcome for prodromal Alzheimer's disease trials*. J Neurol Neurosurg Psychiatry 2016;87:993–999.

Sub-test #	Scale	Item	EDC Variable	Worst Possible Score	PLS coefficient
02	ADAS-13	Orientation	ADCOR	8	0.017
03	ADAS-13	Word recognition	ADCRGT	12	0.004
04	ADAS-13	Word finding difficulty	ADCDIF	5	0.016
05	MMSE	Orientation time	= (MMS101A+MMS101B+ MMS101C+MMS101AD MMS101E)	0	0.042
06	MMSE	Drawing	MMS111	0	0.038
07	CDR	Personal care	CDR0106	3	0.054
08	CDR	Community affairs	CDR0104	3	0.109
09	CDR	Home and hobbies	CDR0105	3	0.089
10	CDR	Judgement and problem solving	CDR0103	3	0.069
11	CDR	Memory	CDR0101	3	0.059
12	CDR	Orientation	CDR0102	3	0.078

The formula for ADCOMS composite score is as follows, using the factors as indicated in the table above:

ADCOMS Item01 * 0.008 + Item02 * 0.017 + Item03 * 0.004 + Item04 * 0.016 + (5 Item05) * 0.042 + (1 Item06) * 0.038 + Item07 * 0.054 + Item08 * 0.109 + Item09 * 0.089 + Item10 * 0.069 + Item11 * 0.059 + Item12 * 0.078.

8.1.4 **ADAS-Cog-13**

The ADAS-Cog total score is calculated by summing the scores of the 13 component subtests of the ADAS-Cog. ADAS-Cog-13 total score is derived in the CRF form per guidelines[6]. Total score derived in the CRF form (ADCTOT) will be used for analysis.

ADAS-Cog-13				
Subtest #	**Scale**	**Subtest Name**	**Worst Score**	**EDC Variable**
01	ADAS-13	Immediate Word Recall	10	ADCRL
02	ADAS-13	Commands	5	ADCCMD
03	ADAS-13	Constructional Praxis	5	ADCCP
04	ADAS-13	Delayed Word Recall	10	ADCDRL4
05	ADAS-13	Naming	5	ADCOF
06	ADAS-13	Ideational Praxis	5	ADCIP
07	ADAS-13	Orientation	8	ADCOR
08	ADAS-13	Word Recognition	12	ADCRGT
09	ADAS-13	Remembering Test Instructions	5	ADCRI
10	ADAS-13	Comprehension (Examiner Rating)	5	ADCCMP
11	ADAS-13	Word Finding (Examiner Rating)	5	ADCDIF

[6] Administration and Scoring Manual Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog) 10/10/13 (Manual Update: 7/22/2021

ADAS-Cog-13				
Subtest #	**Scale**	**Subtest Name**	**Worst Score**	**EDC Variable**
12	ADAS-13	Spoken Language (Examiner Rating)	5	ADCSL
13	ADAS-13	Number Cancellation	5	ADCNC
Total Score	ADAS-13	ADAS-Cog Total Score	85	ADCTOT

Calculating the ADAS-Cog-13 Total Score when ADCTOT is missing

If a participant is unable to complete any of the ten performance subtests (Word Recall; Delayed Word Recall; Commands; Constructional Praxis; Naming; Ideational Praxis; Orientation; Word Recognition; Number Cancellation; Remembering Word Recognition Test Instructions), the rater codes the reason for incompletion using the following options:

- Not done for reasons other than physical or cognitive
- Participant refused
- Participant unable to complete for physical reasons
- Participant unable to complete for cognitive reasons

When total scores for performance subtest measures are missing because the participant is unable to complete the task for cognitive reasons, the worst possible score for the measure will be assigned. Total scores for performance subtest measures that are missing for any other reason will be treated as missing.

Because Remembering Test Instructions is scored solely based on performance on Word Recognition, if Word Recognition was not completed for any reason, then Remembering Test Instructions must also be scored as not completed.

For the ADAS-Cog Total Score

- The total score is the sum of scores obtained on the 13 subscales (10 performance subtests and 3 examiner ratings).
- If more than two subscales (either performance subtest or examiner ratings) are missing, or if both the Word Recall and Word Recognition subtests are missing, then the ADAS-Cog total score will be missing. Otherwise, the total score will be based on the sum of the scores from the non-missing subscales multiplied (prorated) by the ratio (max ADAS-cog Total Score of 85/max total possible from non-missing subscales).

  For example, if the Word Recall performance subtest, which ranges from 0-10 (maximum 10), is missing, and another subtest Commands, which ranges from a score of 0-5 (maximum 5) is also missing, then the total ADAS-cog score will be calculated as the sum from the 11 non-missing subscales multiplied by the ratio (85/(85 (10 + 5)) 85/55 1.55, the resulting prorated total score will be rounded up to the nearest integer.

8.1.5 **ADAS-Cog-Exec**

ADAS-Cog-Exec is a cognitive composite outcome comprised of measures from the ADAS-Cog-13; CDR; and measures of executive function from the ADNI neuropsychological test battery (see table below).

When a subtest of the ADAS-Cog-Exec composite is missing and the examiner indicated it is missing "for cognitive reasons", the worst possible score is assigned for that item prior to constructing the ADAS-Cog-Exec score. Additionally, for Trail Making Test B, if the Reason Not Done is 'TMT Part A not completed within max time,' then the worst possible score (300) is assigned for Trail Making Test B. Subtest scores that are missing for any other reason will be treated as missing. If any subtest of the ADAS-Cog-Exec is missing, then the ADAS-Cog-Exec composite score will be missing.

Each component test score is z-score normed on baseline data (subtracting out the mean of baseline scores, and dividing by the standard deviation of baseline scores for all study participants in the mITT) before applying the weights. Finally, scores on component tests for which larger values indicate more impairment (i.e., ADAS-Cog-13 subtests; CDR box scores; Trail-Making A and B time to completion) are transformed so that higher scores indicate better performance for all component subtests. This is achieved by multiplying the component scores by -1 as indicated in the formula for the ADAS-Cog-Exec below.

Sub-test #	Scale	Item	Worst Possible Score	EDC Variable	Estimated weight
01	ADAS-13	Immediate word recall	10	ADCRL	0.2330
02	ADAS-13	Delayed word recall	10	ADCDRL4	0.0735
03	ADAS-13	Orientation	8	ADCOR	0.1088
04	ADAS-13	Number Cancellation	5	ADCNC	-0.2436
05	Trail Making Test A	Time to Completion	150	TMT0101	0.0586
06	Trail Making Test B	Time to Completion	300	TMT0104	0.1080
07	DSST	Number Correct	0	DSST0101	-0.0577
08	Category Fluency	Mean of Total Correct for Animals and Vegetables	0	= (QSCF0301 + QSCF0304)/2	0.1602
09	CDR	Memory	3	CDR0101	0.1043
10	CDR	Orientation	3	CDR0102	0.3012
11	CDR	Judgement & Prob Solving	3	CDR0103	0.1030

ADAS-Cog-Exec (-1 * z-scored Item01 * 0.2330) + (-1 * z-scored Item02 * 0.0735) + (-1 * z-scored Item03 * 0.1088) + (-1 * z-scored Item04 * -0.2436) + (-1 * z-scored Item05 * 0.0586) + (-1 * z-scored Item06 * 0.1080) + (z-scored Item07 * -0.0577) + (z-scored Item08 * 0.1602) + (-1 * z-scored Item09 * 0.1043) + (-1 * z-scored Item10 * 0.3012) + (-1 * z-scored Item11 * 0.1030).

8.1.6 FAQ

The total score derived in the CRF form [FAQ0111] will be used for analysis. If any item on the FAQ is missing, the FAQ total score is missing.

8.1.7 NPI

The total score derived in the CRF form [NPI1TOT] will be used for analysis. If any item on the NPI is missing, the NPI total score is missing.

8.1.8 MMSE

The total score derived in the CRF form [MMS112] will be used for analysis. If any item on the MMSE is missing, the MMSE total score is missing.

8.1.9 MoCA

The total score derived in the CRF form [MOCA109] will be used for analysis. If any item on the MoCA is missing, the MoCA total score is missing.

8.1.10 CFC2

The Cognitive Functional Composite-2 (CFC2)[7] is a novel composite outcome measure of cognition and everyday function that was developed to optimize detection of change in early AD. CFC2 is comprised of the following measures:

CFC2 (Cognitive Functional Composite 2)				
Subtest #	**Scale**	**Item**	**Worst Possible Score**	**EDC Variable**
01	ADAS-13	Immediate word recall	10	ADCRL
02	ADAS-13	Delayed word recall	10	ADCDRL4
03	ADAS-13	Orientation	8	ADCOR
04	CDR	Memory	3	CDR0101
05	CDR	Orientation	3	CDR0102
06	CDR	Judgement & Prob Solving	3	CDR0103
07	FAQ	Total Score	30	FAQ0111

Scores for all component subtests are transformed so that higher scores indicate better performance. To this aim, all subitem scores will be multiplied by -1.

The CFC2 score is then calculated as the sum of the transformed raw scores for the component subtests. If any of the 7 subtests of CFC2 is missing, CFC2 will be missing.

8.1.11 C-SSRS

C-SSRS questionnaire data are collected in CRF. No scores are planned to be derived for analysis.

[7] Raghavan N, Samtani MN, Farnum M, Yang E, Novak G, Grundman M, Narayan V, DiBernardo A; Alzheimer's Disease Neuroimaging Initiative. The ADAS-Cog revisited: novel composite scales based on ADAS-Cog to improve efficiency in MCI and early AD trials. Alzheimers Dement. 2013 Feb;9(1 Suppl):S21-31. doi: 10.1016/j.jalz.2012.05.2187. Epub 2012 Nov 2.

8.1.12 eGFR

eGFR data provided within safety laboratory parameters are calculated by the laboratory using the 2021 CKD-EPI refit equation.
Additional eGFR endpoint data will be estimated for analysis by means of the MDRD formula[8]: 186 [serum creatinine (mg/dl)]$^{-}$ ^{54} (age)$^{-0\ 203}$ (0.742 if female). The serum creatinine value will be multiplied by 0.0113, if provided by the lab in (umol/L) units, instead of (mg/dL). The age of the patient at the sampling timepoints will be calculated as follows:
[Sample collection year] [Year of birth]; if derived age is less than the age at screening then impute age at screening.

8.1.13 APOE

Genotyping laboratory data for APOE will be used to derive the following categorical variables:

APOE laboratory results	APOE status	E4-carrier Characteristics
E2/E3	non-carrier	
E2/E4	E4-carrier	heterozygous
E3/E3	non-carrier	
E3/E4	E4-carrier	heterozygous
E4/E4	E4-carrier	homozygous
Result Removed Due to Discrepancy Resolution	Missing	Missing

8.2 Coding

Coding of adverse events, concomitant medication and medical history will be performed by ADCS Medical Safety. Adverse events and medical history of randomized participants are coded with the MedDRA coding system (v24.1 or later). Concomitant medication is coded according to the WHO drug code (2021Q3 or later) and the ATC class code. CTCAE v5.0 will be used to grade AESI, all other AEs will be graded in Mild/Moderate/Severe as indicated in protocol Section 11.2 “Assessments of Adverse Events” for the severity assessments of AEs. Coding will be supplied as part of the data transfer, and version used are documented in the relevant Data Management documentation.

8.3 Analysis software

The statistical analysis and reporting will be done using SAS® for Windows™ version 9.4 or R software. For the analysis produced in SAS, SAS tabular output (tables and listings) will be saved in RTF format. SAS graphs will be saved in PNG format. Both will be imported into Word® and PDF supplied to ADCS and Vivoryon for further study reporting. When the sponsor wants to receive the output before the study report, then the Word® document is transferred to PDF and supplied.

8.4 Presentation of tables, listings, graphs

All output will be generated as SAS tables, graphs and listings.

All tables and listings will be created such that they fit landscape pages, following the page format and margins of the CSR template to be used. The tables for the end-of-text and listings

[8] Wu X, Qiu F, Jin X, Liu Q, Zhou J, Duan X. Evaluation of Four eGFR Calculating Formulae in Predicting Postoperative Acute Kidney Injury in Adult Patients Undergoing Open-Heart Surgery with Cardiopulmonary Bypass. Contrast Media Mol Imaging. 2022 Jul 13;2022:6929758. doi: 10.1155/2022/6929758.

for the appendix will be created using SAS with an RTF output, and font Times New Roman size 9 will be used.

For graphs, in general Swiss font will be used, and output will be as created as PNG plot. Graphs are preferably created using black, grey and white color only, to facilitate black-and-white printing. Different line patterns and symbols will be used to differentiate between classification or treatment levels. Graphs will be created such (i.e. taking into account line thickness and font size) that a smaller presentation (e.g. as two (2) per page in the clinical study report) is still clearly readable.

9 TABLES, LISTINGS, GRAPHS

9.1 General

A detailed list of tables, graphs and listings is presented, if applicable, per report section in sections 9.2, 9.3, and 9.4. Template tables and listings as well as *example* plots (as received from client or extracted from a relevant paper) will be used as a reference for creation of all output, and a separate document will be created for this. Table/graph/listing numbering will be followed, however, if the data give cause for combining or splitting tables or listings, numbering may be adapted as necessary.

9.2 In-text tables and graphs

Not applicable. In-text tables and graphs will be designed or extracted by the Medical Writer during creation of the Clinical Study Report, based on the tables and graphs created for section 14 of the CSR. These in-text tables will also use font Times New Roman.

9.3 End-of-text tables and graphs

Following ICH E3 guidelines, all tables and graphs will be presented in Section 14 of the CSR, and tables will be prepared in the order and with section number as stated.

9.4 Listings

Following ICH E3 guidelines, all listings mentioned here will be presented in Section 16.2 of the CSR, and listings will be prepared in the order and with section number as stated.

Individual listings will be prepared of all the data collected in the database, following analysis data format. No combining of data other than mentioned in this paragraph will be performed. The key variables in the listings (except a few displaying screening data) will be patient number. If applicable, study day will be presented along with the assessment dates and visit number will be listed additionally.

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PPD PPD Security Level: Email, Account Authentication (Required)	PPD Signature Adoption: Pre-selected Style Signature ID: PPD Using IP Address: PPD With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 10/28/2024 4:37:02 PM Viewed: 10/28/2024 4:48:44 PM Signed: 10/28/2024 4:49:31 PM
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