NOVARTIS

Clinical Development

LCZ696/Entresto®

CLCZ696B2320 / NCT02884206

A multicenter, randomized, double-blind, active-controlled study to evaluate the effects of LCZ696 compared to valsartan on cognitive function in patients with chronic heart failure and preserved ejection fraction

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
1-Nov-2016	Prior to FPFV	Creation of final version	N/A - First version	NA
31-Jan-2018	After protocol amendment V02	Incorporate updates in protocol amendments V01 and V02 into SAP	Amendment Version 02	1. Sections 2.5 and 2.6: Protocol amendment V01&V02 updated the inclusion/exclusion criteria in terms of cerebrovascular disease burden at screening. However, this is an important prognostic factor of cognitive functions. Therefore, the statistical analyses of primary and secondary objectives are updated to include this factor in the analyses. Appendix 5.4 and Table 5-3 are added to explain how cerebrovascular disease burden score is calculated. 2. Minor text edits to make contents clear, including correction of typo(s). (1) Section 2.1.1: Randomized treatment epoch added as alias double-blind phase; (2) Section 2.2: Appendix 5-3 instead of 5-5; (3) Section 2.10: 2.12 instead of 3.13; (4) Section 2.11: Pet imaging substudy instead of Full analysis set; [redacted] (7) Appendix 5.2: minor updates. 3. Update subgroup categories in Section 2.2.1 : (1) Add new countries in the region subgroup;

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				(2) Update APOE4 category; (3) Add baseline cerebrovascular disease burden subgroup due to protocol amendment. (4) In Table 2.1: MMSE at randomization is used to define subgroup in order to be consistent with MMSE randomization stratification factor. 4. Section 2.3.2: correct APOE4 summary at randomization baseline instead of screening. 5. Section 2.3.3: remove dementia from protocol solicited medical history summary to be consistent with CRF. Remove medical history (MH) by subgroup summary. MH is only summarized by treatment group. 6. Section 2.4.1: update formula to be more clear and consistent with Paragon. 7. Section 2.4.2: (1) Update ATC WHO Drug version; (2) Category "HF medications" removed to be consistent with Perspective CRF; (3) AD/CI Concomitant medications at randomization summary removed due to randomized patients should not be on these medications. 8. Section 2.5.1: (1) formula and text are updated to make it more clear in terms of missing values. (2) Typo "DECT" is corrected to "DET". 9. Removed "Assessments at unscheduled visit remapped to the missing scheduled visit

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				assessments within a pre-specified window" due to no such unsheduled assessment. (1) Section 2.6.3; (2) Section 2.7.1.1; [redacted] 10. Section 2.7.1.1: Add sensitivity analysis for randomization stratification factor "baseline amyloid status". Qualitative (Visual) assessment method is used to determine the status (positive/negative) and is controlled as a factor in the SUVr analysis ANCOVA model. The baseline amyloid status based on quantitative SUVr cutoff will replace the qualitative baseline amyloid status in the analysis. 11. Table 2-6 is updated (1) to be consistent with data collection; (2) SBP 100 mmHg cutoff for HFpEF. 12. Sensitivity for mis-stratification of age and MMSE are added for analyses related primary and secondary objectives. 13. Section 2.7.4: [redacted] (2) Update text related to Liver enzymes to be consistent with LCZ696 program analysis.
20-May-2021	May-2021	1. To amendTable 5-1: the protocol deviations leading to exclusion of subjects from analyses for		1. Table 5-1 in Appendix 5.3 (1) Remove 3 deviations from the table: INCL03, TRT06, TRT08; (2) Update 2 deviation ID: OTH03 to OTH09, OTH11 to OTH08.

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		the following reasons: (1) APOE4 is covered under study consent, therefore INC03 is not applicable. In addition, TRT06 and TRT08 is removed due to no such PD existed; (2) Deviation ID is updated.		
		2. To address missing assessments due to Covid-19 pandemic.		2. Additional analyses are added to address assessments scheduled to be taken place on/after 1-Mar-2020 but are missing due to potential COVID pandemic impact: (1) Allow wider assessment window for SUVr assessments in PET sub-study, [redacted] The added analyses are provided in Sections 2.7.1.1 and 2.12.1, respectively. (2) An indicator variable, IND_{miss}, if patient had a missing assessment(s) on/after 1-Mar-2020 is created separately for the following endpoints: CogState GCCS, cortical composite SUVr, [redacted] Additional supportive analysis with IND_{miss} and IND_{miss}-by-treatment fixed-effect factors are added to the analyses described in Sections 2.5.3, 2.7.1.1, and 2.12.1 for CogState GCCS,

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				[redacted] and cortical composite SUVr, respectively to assess if there is a shift in the change from baseline for those who have missing assessment(s) during COVID-19 pandemic.
		3. To address possible non-convergence issue for MMRM ANCOVA model.		3. If convergence is not achieved for MMRM ANCOVA models, unstructured (UN) covariance matrix used in MMRM model will be replaced by compound symmetry (CS) in order to achieve model convergence. If covergence issue remains, cerebrovascular disease burden variable will be further removed in order to achieve model convergence. Changes are made in the following sections: (1) Section 2.5.2 for primary analysis; (2) Section 2.5.5 for sensitivity analysis of primary analysis; (3) Sections 2.7.1 and 2.7.1.1 for SUVr analyses;
		4. Per-protocol set 2 and PET substudy set		[redacted] 4. (1) Per-protocol set 2 and PET substudy set is added in Section 2.2; (2) One supportive analysis based on PPS2 is added in Section 2.5.4 and Table 2-3. (3) Wordings related to non-missing baseline in PET substudy set is added in Sections 2.7.1 and 2.12.1.
		5. Minor wording edits. Protocol amendment 2.0 is in effect when this SAP amendment takes place.		5. Minor wording edits: (1) One abbreviation Alzheimer's disease (AD) is added to the list. (2) Section 2.4.1: (1) handling of overlapping start and end dates when calculating exposure duration; (2)

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				replace by visit with overall compliance summary during randomized treatment epoch; (3) Section 2.4.2: update the version of NovDTD that will be used in CSR. (4) Section 2.5.1: Z_{CPAL} is among the negative sign tasks in the standardized Z scores; (5) Section 2.5.2: visit-by-baseline GCCS; (6) Table 2-3 and 2-4: MNAR acronym footnote; (7) Section 2.5.5: treatment-by-visit. (8) Sections 2.7.1 and 2.7.1.1: analyses will be performed in the Safety set who participate in the PET image substudy "and with non-missing baseline". (9) Section 2.7.2.1: update the version of case retrieval strategy that will be used in CSR. [redacted]
10-Jun-2022	10-Jun-2022	1. Update Cohen's D calculation with 95% confidence interval		Cohen's D and corresponding 95% CI calculations are updated in Section 2.5.2. Reference Cumming and Finch 2001 is added.
		2. Additional imputation details are provided for tipping point analysis of missng GCCS		SAS programming details are provided for imputing missing GCCS in tipping point analysis of Section 2.5.5.
		3. Changes are made in the model assumption in the joint model approach of GCCS sensitivity analysis to be consistent with original paper (Vonesh et al 2006)		(1) Covariance matrix of measurement error $e_i(t)$ in joint model approach of Section 2.5.5 is updated to diagonal matrix with common variance σ_e^2 on the diagonal elements and no correlations between time points.

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				(2) Section 2.5.5 Joint Model approach: A constant baseline hazard function over time is used in the time to starting AD or CI related medications due to limited such events over study duration. An exponential regression instead of Cox proportional hazard is fitted.
		4. Due to very limited patients with positive baseline amyloid status and convergence issue, the imputation model used in change from baseline in SUVr is updated.		Section 2.7.1: (1) There are very limited patients with positive baseline amyloid status, and imputation cannot be done for this stratum. Therefore, baseline amyloid status is included in the imputation model as factor instead. (2) SAS proc MCMC programing detail is provided.
		5. Details are added in safety related sections after dry run review.		Section 2.7.2: (1) specify analysis set for run-in epoch and double-blind randomized treatment epoch. [redacted] Section 2.7.3: Remove "confirmed by adjudication committee" because death is not adjudicated. [redacted]
		6. Visits numbers are updated in plasma Aβ1-40 to be consistent with		Section 2.11: Week 13, 52, 104 and Week 156 are the post-baseline scheduled visits for plasma Aβ1-40 assessments.

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		protocol assessment schedule Table 6-1.		Analysis set for plasma Aβ1-40 is PET substudy set with non-missing baseline.
		7. Updates related to protocol deviations impacting analysis sets		(1) Deviation ID OTH02 in Table 5-1: Site has been closed down for GCP reasons are not excluded from Safety set (SAF). (2) Per clinical review: EXCL01, EXCL13, EXCL23, EXCL24, EXCL25, EXCL26, EXCL27, TRT07 are removed, and OTH21 is added in Table 5-1. (3) Table 5-2 is updated to be aligned with Table 5-1.
		8. Additional statement for different endpoints PET substudy set		Section 2.2: Separate flag will be create for different endpoint due to non-missing baseline condition for PET substudy set
		9. Remove subgroup analysis for disposition related summary, add 3 subgroups for CogState GCCS, minor update to NYHA category, and remove Central America from Latin America definition		Table 2-1: (1) CTT reviewed and decided to remove the subgroup analyses of disposition from CSR; (2) Randomization baseline SBP <=140 and >140 mmHg subgroup, Age < 65 and >= 65 subgroup, and diabetes mellitus status at screening (Yes, No) subgroup are added for CogState GCCS endpoint; (3) subgroup categories of NYHA class at randomization are: I/II versus III/IV; (4) update Latin America to remove "including Central America" because no Central America countries participated in the study.
		10. Remove by-visit from average daily dose summary, remove one obsolete phrase, and update categories for summary. Add 2 class of HF and CV medications.		Section 2.4.1: (1) Average daily dose summary is calculated for randomized treatment epoch, not by visit; (2) Categories for summary are updated per dry run review comment. Section 2.4.2: Add SGLT2 class.
		11. Remove supportive analyses added in SAP Amendment V 3.0 that		Almost all randomized patients have at least one missing assessment during COVID-19

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		assess if there is a shift in change from baseline for those who have missing assessment(s) during COVID-19 pandemic. 12. (1) Shift table of SUVr positive/negative based on PET scan is removed since PET visual assessment of positive/negative is done only once at randomization; (2) correct analysis set used in SUVr supportive analysis; (3) Add one more supportive analysis for SUVr endpoint.		pandemic for CogState GCCS (Section 2.5.3), SUVr (Section 2.7.1.1), [redacted] endpoints, therefore, the analyses are not meaningful and removed. Section 2.7.1.1: (1) Shift table of SUVr positive/negative based on PET scan is removed since PET visual assessment of positive/negative is done only once at randomization; (2) PET substudy set instead of safety set is used SUVr supportive analysis; (3) Supportive analysis of SUVr analysis excluding patients with no post-baseline SUVr assessments from analysis.
		[redacted]		
30-Jun-2022	Before DBL	Handling of data collected on/after withdrawal of informed consent in the statistical analyses Protocol amendment 2.0 is in effect when this SAP amendment takes place.		Handling of biological data and non-biological data collected on or after withdrawal of informed consent in statistical analyses are provided in Section 2.1.

Table of contents

List of abbreviations

AD	Alzheimer's Disease
AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
CCB	CogState Cognitive Battery
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
IVR	Interactive Voice Response
IWR	Interactive Web Response
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

The statistical analysis plan (SAP) describes the detailed methodology and implementation of the planned statistical analyses outlined in the study protocol for CLCZ696B2320. The analyses performed following the SAP below will be used for clinical study reporting purposes. It is important to note that this version of statistical analysis plan details the statistical methodology for the analyses planned and agreed in the CLCZ696B2320 protocol (protocol version 02).

1.1 Study design

This study is a multi-center, randomized, double-blind, parallel group, active-controlled trial designed to evaluate the overall effect of LCZ696 compared to valsartan on cognitive function as assessed by a comprehensive cognitive battery in patients with HFpEF. The study population will consist of patients ≥60 years of age with chronic symptomatic HF (NYHA class II-IV) and a left ventricular ejection fraction (LVEF) >40%.

As per the study design (Figure 1-1), patients with signed informed consent first undergo a screening epoch, followed by a treatment run-in epoch before entering the randomized double-blind treatment epoch.

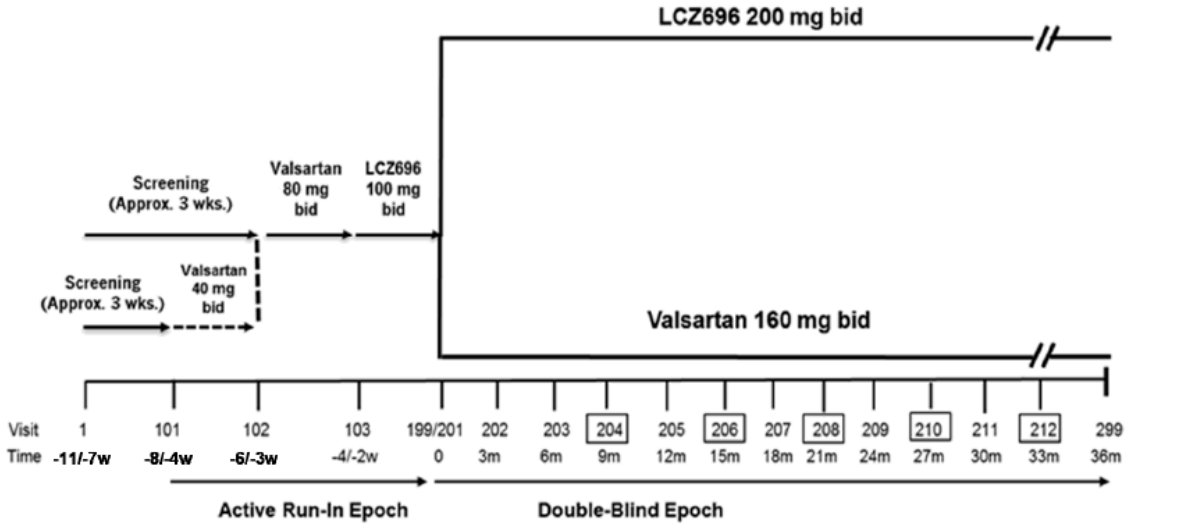
Screening epoch

Patients with signed study informed consent will undergo a screening epoch of approximately 3 weeks duration used to assess their eligibility to participate in the trial based on protocol specified inclusion/ exclusion criteria.

Single-blind treatment run-in epoch

Eligible patients enter a single-blind treatment run-in epoch which is designed to assess patient's tolerability to study drug, and to determine patients who are likely to stay on study drug for the duration of the trial. During the treatment run-in epoch, each patient undergoes Valsartan 80 mg bid treatment and followed by LCZ696 100 mg bid treatment over 3-8 weeks duration. Patients who have been on a prior dose of ACEi or ARB medication lower than the total daily doses mentioned in Table 1-1, should start on Valsartan 40 mg bid for 1-2 weeks before up-titrating to Valsartan 80 mg bid. However, at the investigator's discretion, those patients who are on ACEi or ARB medication at equivalent to the total daily doses mentioned in Table 1-1, can enter Valsartan 40 mg bid treatment run-in before starting Valsartan 80 mg bid.

Figure 1-1 Study Design



For those patients who are on ACEi or ARB medication at equivalent to or above the minimum daily dose at Visit 1, the investigator may also consider initiating treatment with valsartan 40 mg b.i.d. and can enter the treatment run-in period at Visit 101.

After Visit 203, alternating clinic and telephone contact visits will occur every 3 months until trial ends.

Indicates telephone contact visit

bid – twice daily dosing

Table 1-1 Minimum pre-study total daily doses of commonly used ACEis and ARBs allowing patients to begin the treatment run-in epoch with valsartan 80 mg bid

ACEI	Dose	ARB	Dose
Benazepril	20 mg	Azilsartan	40 mg
Captopril	100 mg	Candesartan	16 mg
Cilazapril	2.5 mg	Eprosartan	400 mg
Enalapril	10 mg	Irbesartan	150 mg
Fosinopril	20 mg	Losartan	50 mg
Imidapril	10 mg	Olmesartan	10 mg
Lisinopril	10 mg	Telmisartan	40 mg
Moxepril	7.5 mg	Valsartan	160 mg
Perindopril	4 mg		
Quinapril	20 mg		
Ramipril	5 mg		
Trandolapril	2 mg		
Zofenopril	30 mg		

Randomized treatment epoch

At the end of treatment run-in, patients who meet the protocol specified safety criteria as assessed by central or local laboratories and tolerate LCZ696 100 mg bid for at least 2 weeks are eligible for randomization. Patients will be randomized in a 1:1 fashion to either LCZ696 200 mg bid or valsartan 160 mg bid. The randomization will be stratified based on age (< 75, ≥ 75 years), MMSE score (< 28, ≥ 28), and baseline brain amyloid status (unknown, amyloid positive, amyloid negative).

With an expected screening and run-in failure rate of approximately 40%, it is estimated that approximately 870 patients will be screened at more than 150 centers worldwide to randomize approximately 520 patients. A subset of about 430 randomized patients will be enrolled in the amyloid PET imaging substudy.

There is no formal interim analysis planned for efficacy. Interim safety data will be reviewed by an external Data Monitoring Committee (DMC) regularly as specified in the DMC charter. The final analysis is planned to be executed at the completion of all planned assessments for last randomized patient.

1.2 Study objectives and endpoints

Table 1-2 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary To evaluate the effects of LCZ696 compared to valsartan on cognitive function over 3 years in patients with HFpEF as assessed by the CogState cognitive assessment battery.	Change from baseline to 3 years in the CogState Global Cognitive Composite Score (GCCS)	Section 2.5
Secondary To evaluate the effect of LCZ696 compared to valsartan on β-amyloid deposition in the brain in a subset of patients using amyloid positron emission tomography (PET) imaging over 3 years	Change from baseline in a cortical composite SUVr (standardized uptake value ratio) at 3 years	Section 2.7.1
To evaluate the effects of LCZ696 compared to valsartan on individual cognitive domains (memory, executive function, and attention) as assessed by the individual components of the CogState battery over 3 years	Change from baseline in individual cognitive domains (memory, executive function, and attention) as assessed by the individual components of the cognitive assessment battery at 3 years	Section 2.6
To compare LCZ696 to valsartan in evaluating changes in instrumental activities of daily living (IADL) as assessed with Functional Activity Questionnaire (FAQ) over 3 years	Change from baseline in the summary score of the instrumental activities of daily living (IADL) as assessed with Functional Activity Questionnaire (FAQ) at 3 years	Section 2.6

Objective	Endpoint	Analysis
Exploratory		
[redacted]		

Objective	Endpoint	Analysis
[redacted]		

2 Statistical methods

The following section contain important information on detailed statistical methodology used for analysis and reporting purposes.

2.1 Data analysis general information

Data will be analyzed by Novartis Biostatistics and Statistical Reporting personnel according to the statistical analysis section 9.1 of the study protocol using SAS 9.4 or higher, unless otherwise specified. Further details on planned statistical analyses will be presented in the following sections and will be documented in the CSR Appendix 16.1.9, as applicable.

In general, the continuous variables will be summarized descriptively by presenting n, mean, SD, median, quartiles, minimum and maximum while categorical variables will be summarized by presenting count and percentage of patients in each category. For categorical variable summaries, an additional category 'Missing' will be presented if there are missing values for that variable.

There is no planned interim efficacy analysis but safety data will be reviewed by an external DMC regularly as specified in the DMC charter. The relevant DMC analyses, to be presented at each DMC meeting, will be described in a separate DMC analysis plan and will be executed by an external independent statistician and independent programmers privileged to access unblinded clinical trial data.

Withdrawal of informed consent

Withdrawal of informed consent is defined in study protocol Section 5.6.3 as when a patient:

- Does not want to participate in the study anymore, and
- Does not want any further visits or assessments, and
- Does not want any further study related contacts, and
- Does not allow analysis of already obtained biologic material.

The biological material includes [redacted] blood sample for plasma beta-amyloid, APOE4 genotyping, [redacted] sample. The data related to the biologic material collected on/after the date of the withdrawal of informed consent will be excluded from analyses. Other non-biological data collected after the date of withdrawal of informed consent will be excluded from analyses.

2.1.1 General definitions

Study treatment or drug

In future sections through this document, 'study treatment' or 'study drug' will be used to refer to investigational therapy assigned to a patient in a specific study phase. For instance, for run-in phase, study treatment refers to valsartan in the valsartan run-in phase, and LCZ696 in the LCZ run-in phase. For the double-blind treatment phase, study treatment refers to LCZ696 or valsartan as assigned to a patient at randomization.

Single-blind run-in phase (Treatment run-in epoch)

The single-blind run-in phase (or treatment run-in epoch) is defined as the period between the start of the study drug (in general it should be Visit 101 or Visit 102) and the time prior to randomization (Visit 201). The run-in phase will be divided further into the valsartan run-in phase and the LCZ696 run-in phase.

The start of the valsartan run-in phase is the date when the patient receives the first run-in dose of valsartan. In principle, the day before a patient receives the first dose of LCZ696 (any dose level) will be the end of the valsartan run-in phase and the day patient receives the first run-in dose of LCZ696 will be the start day for the LCZ696 run-in phase for that patient. If the date of the start day of receiving LCZ696 is missing, then the date of Visit 103, which is the protocol specified run-in drug switching day, will be used as the start date for the LCZ696 run-in phase. If the date of the last dose of valsartan run-in medication falls on the same day of the first dose of LCZ696 run-in medication, this day will be considered the end of the valsartan run-in phase and the following day will be considered as the start of the LCZ696 run-in phase. In general, the LCZ696 run-in phase ends when the patient receives the randomization drug. For run-in failure patients, the LCZ696 run-in phase ends on the date patient failed run-in. During these two run-in phases, patients will be on the run-in medications in a single blind manner.

Randomized treatment phase

The randomized treatment phase begins at the time of randomization (Visit 201) and ends with the last study drug intake or last study visit date, whichever is earlier. During the randomized treatment phase, patients will return for scheduled clinic visits. For all related safety analyses randomized treatment starts with the first intake of randomized, double-blind study drug. Temporary discontinuation of the study drug will not be counted as randomized treatment phase discontinuation.

Post-randomized treatment phase

The post-randomized treatment phase (usually after unscheduled, permanent study drug discontinuation) begins after last study drug intake + 1 day and ends up on the date of end of study visit (Visit 299).

Double-blind (DB) phase (Randomized treatment epoch)

The double-blind randomized phase starts with the randomization visit (visit 201) and ends with the end of study visit (visit 299). Hence, this combines the randomized treatment phase and post-randomized treatment phase.

Study Day

Study day is determined as number of days relative to the randomization visit (Visit 201) which is considered as day 1 unless other specified.

Baseline

For the analysis purpose, baseline for run-in phase and baseline for double blind phase are identified separately as below.

Baseline for run-in phase

The treatment run-in baseline is defined as the last available measurement prior to starting valsartan run-in treatment or at time of Visit 101 or Visit 102, whichever is earlier. They usually are collected at screening (Visit 1).

Baseline for double blind phase

Baseline for double blind phase is defined depending on the parameter of interest. In general, the baseline for double blind phase is defined as the measurement obtained at the randomization visit date (visit 201/ Day 1). Any missing baseline value due to missing value for parameters designed to be assessed at randomization will be imputed by the most recent measurement (scheduled/ unscheduled) taken prior to randomization.

For the parameters which are not scheduled to be assessed at randomization (height, NT-pro-BNP), the baseline is defined as the measurement obtained at an earlier visit (scheduled or unscheduled) which was closest to Day 1.

On-treatment data

In all the analyses planned in this document, on-treatment data refer to data collected while patients are on-study-medication (regardless of treatment interruption) or within a specified window after final study drug intake date based on the endpoint of interest.

- For cortical SUVr [redacted] based endpoints, data collected within 6 months after final study drug intake date will be considered as on-treatment data.
- For all other primary, secondary and exploratory endpoints, data collected within 3 months after final study drug intake date will be considered as on-treatment data.

2.2 Analysis sets

The following analysis sets will be used for the statistical analyses:

- **Screened set (SCR)** – All patients who signed the informed consent. The screened set includes only unique screened patients, i.e., in the case of re-screened patients only the chronologically last screening data is counted.
- **Enrolled set (ENR) (run-in phase)** – All patients who received at least one dose of run-in study drug.
- **Valsartan run-in set (VRS)** – All patients who are in the ENR and received at least one dose of run-in valsartan.
- **LCZ696 run-in set (LRS)** – All patients who are in the ENR and received at least one dose of run-in LCZ696.

- **Randomized set (RAN)** – All patients who received a randomization number, regardless of receiving trial medication.
- **Full analysis set (FAS)** – it consists of all randomized patients with the exception of those patients who have not been qualified for randomization and have not received study drug, but have been inadvertently randomized into the study. Following the intent-to-treat principle, patients will be analyzed according to the treatment to which they were assigned at randomization.
- **Safety set (SAF)** – it consists of all randomized patients who received at least one dose of study drug. Patients will be analyzed according to the treatment actually received. The safety population will be used for the analyses of safety variables.
- **Per-protocol set (PPS)** – it is a subset of the FAS which will consist of the patients who meet the following conditions:
  - No major deviations from the protocol procedures in the randomized treatment epoch
  - Have been exposed to study medication for at least 30 months and have 80% compliance on study medication.
- **Per-protocol set 2 (PPS2):** it is defined same as PPS except for the second condition being patients whose study medication exposure (in months) multiplied by compliance on study treatment is at least 24 or above.
- **PET substudy set (PET)** – it consists of SAF patients who participate in PET substudy and have non-missing baseline assessment. Separate flags will be created for different endpoints.

Appendix 5-3 presents a sample of study specific protocol deviations that lead to exclusion from analysis sets in the study. The final list may be different from this and will be signed off before DB lock.

2.2.1 Subgroup of interest

Subgroups will be formed to explore the consistency of treatment effects and safety profiling on selected parameters between the subgroups and the overall population.

In general, subgroups will be defined based on baseline information. In this study, since we have a run-in phase to test patients' tolerability to the study drugs before they can enter the double blind phase, we have defined two baselines (Section 2.1): the run-in baseline and the double-blind baseline. Subgroups will be formed using one of these baselines according to their analysis purposes.

In Table 2-1, we have listed all subgroups defined for this study and the ways to derive them. Subset of these subgroups will be used depending on the parameter under consideration. Also note that only important parameters or variables in these analyses will have subgroup analyses. The details about the parameters having subgroup analyses will be presented in the corresponding sections as appropriate. Also, additional subgroups may be formed later for regional or country-wide analyses.

Table 2-1 Specification of subgroups

Subgroup	Method of derivation	Background & Demographics / Exposure	Efficacy	Safety
Age groups: (<65 vs. ≥65 years)	Screening (derived)		X (CogState GCCS)	
Age groups: (<75 vs. ≥75 years)	Screening (derived)	X	X	X
Gender (male/female)	Screening	X	X	X
Region*	Derived (pooled countries or country), using Screening data	X	X	X
Education level (<12, >=12 years)	Derived using screening data		X	X
Baseline MMSE cut-off (<28, ≥28)	Derived using MMSE at randomization	X	X	X
Baseline LVEF cut-off (<50%, ≥50%)	Screening		X	X
Baseline NYHA class (I/II and III/IV)	Derived using randomization data for DB phase and screening data for run-in phase		X	X
APOE4 allele status** (+/+, -/+, -/-)	Randomization		X	X (Dementia related AE summaries)
Baseline brain amyloid status (unknown, positive, negative)	Randomization	X	X	X
Baseline cerebrovascular disease burden***	Screening	X	X	X (Dementia related AE summaries)
Baseline diabetes mellitus (Yes, No)	Screening		X (CogState GCCS)	
SBP status (<=140, >140 mmHg)	Randomization		X (CogState GCCS)	

* ***North America:*** *USA, Canada*

Latin America: *Argentina*

Western Europe: *Belgium, France, Germany, Italy, Spain, Switzerland, UK, Netherland*

Central Europe: *Bulgaria, Croatia, Lithuania, Russia, Turkey, Poland*

Asia Pacific and Others: *Australia, Korea, Taiwan*

** *APOE4 allele status: "+" means e4 is present ; "-" means e4 is absent.*

*** *Cerebrovascular disease burden score will be assigned to each patient and subgroup will be formed based on the grouping of the scores. See Appendix* Table 5-3 *for the scoring.*

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Based on the screened set (SCR), the number and percentage of patients successfully screened will be presented. In addition, the primary reasons for screen failures will be summarized by presenting number and percentage of patients that screen fail by category. For patients who are screened more than once, the information from the last screening will be used in the summary. The number and percentage of subjects enrolled, completed, and failed in run-in will be summarized for the valsartan run-in and LCZ696 run-in separately. The reasons for run-in failures will be provided for all patients in the enrolled set (ENR). The same information for the valsartan run-in set (VRS) and LCZ696 run-in set (LRS) will also be summarized.

The number of subjects randomized (RAN) and number of randomized subjects included in each of the analysis sets will be presented by treatment group. The number and percentage as well as the reasons that subjects had been excluded from the RAN will be summarized by treatment group. The number and percentage of randomized subjects who completed the study, who discontinued the study and the reasons for discontinuation will be presented for each treatment group.

The number and percentage of subjects with protocol deviations as well as the criteria leading to exclusion from analysis sets will be presented in separate tables for the RAN. Furthermore, the number of subjects enrolled and randomized per region and per country will be presented descriptively for the ENR and the FAS, respectively. All the disposition data will also be listed at a patient level.

In addition, the number and percentage of subjects in the PET imaging sub-study who completed the study, who discontinued the study and the reasons for discontinuation will be presented for each treatment group.

2.3.2 Demographic and baseline characteristics

For the run-in phase, summary statistics will be provided by total number of patients based on the enrolled set (ENR) for background and demographic characteristics, disease characteristics, and cardiovascular risk factors for the run-in phase baseline (Screening visit), including the following parameters:

- **Continuous variables**: Age (in years), weight (in Kg), height (in cm), body mass index (BMI, in kg/m^2), education level (number of years), number of years of continuous employment, number of HF hospitalizations in last 12 months, Ejection fraction (in %), NT-pro-BNP, systolic blood pressure (in mmHg), diastolic blood pressure (in mmHg), pulse (in bpm), MMSE overall summary score

- **Categorical variables**: Age group (<65 years vs. ≥65 years; <75 years vs. ≥75 years), sex, race, ethnicity, country, region, education level (<12, ≥12years), category of prior CV medication, prior HF hospitalization (yes/no), NYHA class, NT-pro-BNP, and MMSE category (<28, ≥28).

BMI will be calculated as weight (kg) / height^2 (m^2) from the collected height and weight at Visit 1 (Screening Visit).

Similarly, for the double-blind phase, summary statistics will be provided by randomized treatment group and overall based on the Safety set for the above mentioned parameters in addition to: APOE4 allele status, baseline SUVr value, amyloid status (positive/negative) [redacted] at baseline.

Demographic and baseline characteristics will be similarly summarized for patients in the SAF who participated in the PET imaging sub-study.

2.3.3 Medical history

Any condition entered on the relevant medical history / current medical conditions CRF will be coded using the most updated version of MedDRA dictionary. Medical history includes:

- Cardiovascular disease history
- Heart Failure history
- Other protocol solicited medical history, including neurological disease history (e.g. cognitive impairment, depression)

which are collected at Visit 1 (Screening visit). The number and percentage of subjects with each medical condition will be provided by treatment group and system of organ class for the ENR set and for the Safety set (SAF). Similar analyses for medical history will be summarized for patients in the SAF who participated in the PET imaging sub-study.

Analysis of patients' disposition, demographic and baseline characteristics for the double-blind phase will be summarized for the following subgroups:

- Age group (<75 vs. ≥75 years)
- Gender (male/female)
- Region
- Baseline brain amyloid status (unknown, positive, negative)
- Baseline MMSE cut-off (<28, ≥28)
- Baseline cerebrovascular disease burden

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The duration of run-in treatment exposure will be calculated separately for Valsartan run-in period and LCZ696 run-in period.

The valsartan run-in period (as defined in section 2.1.1), starts at the date when the patient receives the first dose of run-in valsartan and ends at the day prior to receiving LCZ696 or when the patient discontinued, whichever comes first. The LCZ696 run-in starts at the date when the patient receives the first dose of run-in LCZ696 and ends at the day prior to randomization or when the patient discontinued, whichever comes first. Accordingly, the duration of treatment exposure in each run-in treatment phase is calculated as –

- Overall valsartan run-in treatment exposure (days) = min(date patient received the 1st dose of run-in LCZ696-1, date when patient failed during run-in, date patient died during run-in) – date patient received the 1st dose of run-in valsartan +1
- Overall LCZ696 run-in treatment exposure (days) = min(date of randomization-1, date when patient failed during run-in after 1st dose of LCZ696, date patient died after 1st run-in dose of LCZ696 during run-in) – date patient received the 1st dose of run-in LCZ696+1

As specified in section 2.1.1, if the date of the last dose of valsartan run-in medication falls on the same day of the first dose of LCZ696 run-in medication, this day will be considered the end of the valsartan run-in phase and the following day will be considered as the start of the LCZ696 run-in phase. In this situation, the above exposure algorithms need to be adjusted accordingly.

Duration of valsartan run-in treatment exposure will be summarized for all patients in VRS by presenting summary statistics (n, mean, standard deviation, min, Q1, median, Q3, max). Treatment exposure data for valsartan run-in will also be summarized by presenting frequency and percentage of patients with following duration categories-

- 0 Days
- <=1 Week
- >1-2Weeks
- > 2Weeks

Similarly, duration of LCZ696 run-in treatment exposure will be summarized for all patients in LRS by presenting summary statistics (n, mean, standard deviation, min, Q1, median, Q3, max) and also by presenting frequency and percentage of patients with following duration categories-

- 0 Days
- <=1 Week
- >1-2 Weeks
- >2-4 Weeks
- >4 Weeks

Treatment exposure during the double-blind Epoch

The duration of the double-blind treatment exposure for a patient, regardless of temporary interruptions of usage of the study drug, is defined as date of last study drug intake – first study drug intake date + 1.

Table 2-2 Study drug dose levels during randomized treatment epoch

Dose level	LCZ696 Treatment arm	Valsartan Treatment arm
3	200 mg bid	160 mg bid

Dose level	LCZ696 Treatment arm	Valsartan Treatment arm
2	100 mg bid	80 mg bid
1	50 mg bid	40 mg bid

Duration of overall double-blind treatment exposure will be summarized descriptively by treatment group (i.e. n, mean, standard deviation, min, Q1, median, Q3, max) and the number (percentage) of patients with following by duration categories will also be provided:

- <=6 months
- >6 months - 12 months
- >12 months - 18 months
- >18 months - 24 months
- >24 months - 30 months
- >30 months

Duration of treatment exposure in double-blind period will be summarized by dose levels permitted for titration in each treatment arm according to Table 2-2.

Overall patient-years on-treatment and average patient-year on-treatment will be reported by each treatment group.

- Overall patient-years on-treatment = Sum of duration of treatment exposure (in days) from all patients / 365.25
- Average patient-years on-treatment = Overall patient-years on-treatment / Number of patients randomized to the treatment

Duration of overall double-blind treatment exposure excluding treatment interruptions, computed as date of last study drug intake – first study drug intake date + 1 – *number of days of treatment interruption,* will also be summarized descriptively and by duration categories as above. For overlapping start date of current dose level and end date of previous dose level, "+0.5" day will be used instead of "+1" day.

Average daily dose for each patient during double-blind period will be summarized by treatment group, by providing summary statistics (i.e. n, mean, standard deviation, min, Q1, median, Q3, max). Average daily dose for each patient is calculated as:

$$\frac{\sum_{i=0}^{3}(\text{Number of days on dose level } 'i')x(\text{Dose level } 'i')x2}{\sum_{i=0}^{3}(\text{Number of days on dose level } 'i')}$$

The number and percentage of patients at each dose level (Table 2-2) will be summarized by visit and treatment group as well.

Apart from the above analyses, dose administration records for double-blind period will also be listed at a patient level for the patients in safety set with reasons for changing dose.

Number and percentage of patients with treatment interruption and permanent treatment discontinuations will be provided by reason for treatment interruption or discontinuation. Time from randomization to permanent study treatment discontinuation will be summarized by treatment group by providing Kaplan-Meier estimate of cumulative rate of permanent treatment discontinuation.

Compliance with respect to protocol specified study treatment will be summarized based on the site reported compliance for by actually received treatment group and overall during randomized treatment epoch for all patients in Safety set (SAF)

All these analyses pertaining to treatment exposure during double-blind period will be carried out for all patients in Safety set (SAF). Compliance summary will also be provided for patients in Full Analysis set (FAS).

Summaries of duration of treatment exposure in the double-blind phase will also be provided separately for subjects included in the PET imaging substudy.

2.4.2 Prior, concomitant and post therapies

Medications will be identified using Novartis Drug and Therapy Dictionary, NovDTD which is a modified Novartis internal version WHO Drug Dictionary Enhanced (DDE) including Anatomical Therapeutic Chemical (ATC) code. The latest version at the time of database lock will be used.

For the run-in phase, the run-in concomitant medication information will be summarized based on the ENR.

Prior and run-in concomitant medications taken at any time between the screening visit and the randomization visit will be summarized in sequential format by treatment of valsartan for the VRS and LCZ696 for the LRS based on the latest version of the dictionary. Medications will be presented in alphabetical order, by ATC codes and grouped by *anatomical main group* (the 1st level of the ATC codes). Tables will show the overall number and percentage of patients receiving at least one drug of a particular ATC code and at least one drug in a particular anatomical main group.

Prior medications are defined as drugs taken prior to first dose of run-in study medication. Any medication given at least once between the day of first dose of run-in study medication and the last day prior to randomization visit will be a **run-in concomitant medication**, including those which were started pre-screening and continued into the run-in phase. Prior or run-in concomitant medication will be identified based on recorded or imputed start and end dates of taking medication. The rules for imputing incomplete (start and end) dates are described in Section 5.

The concomitant medication information for the double blind phase will be summarized based on the SAF.

Concomitant medications taken at any time since the randomization visit will be summarized by treatment group based on the latest version of the dictionary. As before, medications will be presented in alphabetical order, by ATC codes and grouped by anatomical main group (the 1st level of the ATC codes). Tables will also show the overall number and percentage of subjects receiving at least one drug of a particular ATC code and at least one drug in a particular anatomical main group.

Any medication given at least once between the day of first dose of randomized study medication and the last day of study visit will be a double-blind concomitant medication, including those which were started pre-randomization visit and continued into the double blind treatment phase.

Heart Failure and CV medications

The following important classes of concomitant heart failure and CV medications administered during run-in and during double blind phase will be summarized separately in a similar way as described above.

- ARBs
- ACE inhibitors
- Renin inhibitors
- Diuretics
- Beta blockers
- Aldosterone antagonists
- Cardiac glycosides (Digoxin/digitalis glycoside)
- Calcium antagonists
- Other vasodilators
- Oral anticoagulants
- Antiarrhythmic agents
- Aspirin
- Other antiplatelet agents
- Statins
- Nitrates
- Other lipid lowering agents
- SGLT2

Medications for treating AD or cognitive impairment

Concomitant use of AD or cognitive impairment related medication will be summarized by treatment group separately for patients newly starting such medications during post-randomization phase. Treatments for AD or cognitive impairment include:

- Glutamate receptor antagonists (memantine)
- Cholinesterase inhibitors (donepezil, galantamine, and rivastigmine).

The classes of medications criteria searching the heart failure, CV medications and AD or cognitive impairment medications will be defined in a separate EXCEL sheet with ATC preferred term and WHO drug code. This EXCEL sheet will be stored in CREDI at the RAP level after the content is agreed to by the Global Program Medical Director (GPMD) and prior to CDBL

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary variable is the change from baseline (baseline definition as in section 2.1.1) to 3 years in the CogState Global Cognitive Composite Score (GCCS). The CogState cognitive test battery includes the following seven tasks:

1. **Detection Test (DET)** – Assesses psychomotor function using the speed (milliseconds) of correct responses in a simple reaction time paradigm
2. **Identification Test (IDT)** – Assesses visual attention using the speed (milliseconds) of correct responses in a simple reaction time paradigm
3. **Continuous Paired Associate Learning (CPAL)** – Assesses visual episodic memory measuring accuracy of performance by the number of errors made over 6 learning trials
4. **One back (ONB)** - Assesses working memory using the speed (milliseconds) of correct responses in a n-back paradigm
5. **International Shopping List Test (ISLT)** – Assesses verbal learning using the accuracy (number of words recalled correctly) of recall in a verbal list learning paradigm
6. **International Shopping List Test – delayed recall (ISLT-DR)** - Assesses verbal memory using the accuracy (number of words recalled correctly) of delayed recall in a verbal list learning paradigm
7. **Groton Maze learning Test (GMLT)** – Assesses executive function using the number of total errors (number of error responses over 5 trials) in a hidden pathway maze learning paradigm

Standardized z-scores for each outcome measure and visit will be calculated using the sample baseline mean and standard deviation of individual tasks as follows:

- $Z_{DET} = -$ (Log10(DET) – baseline mean of log10(DET))/SD of log10(baseline DET),
- $Z_{IDT} = -$ (Log10(IDT) – baseline mean of log10(IDT))/SD of log10(baseline IDT),
- $Z_{CPAL} = -$ (CPAL total errors – baseline mean of CPAL total errors/SD of baseline CPAL total errors),
- $Z_{ONB} = -$ (Log10(ONB) – baseline mean of log10(ONB))/SD of log10(baseline ONB),
- Z_{ISLT} = (ISLT – baseline mean of ISLT))/SD of baseline ISLT,
- $Z_{ISLT\text{-}DR}$ = (ISLT-DR) – baseline mean of ISLT-DR))/SD of baseline ISLT-DR,
- $Z_{GMLT} = -$ (GMLT – baseline mean of GMLT))/SD of baseline GMLT

Note that negative sign is included in the calculation for tasks where increasing values indicate worsening performance (i.e., Z_{DET}, Z_{IDT}, Z_{CPAL}, Z_{ONB} and Z_{GMLT}) so that for all standardized change scores negative values indicate a decline from baseline while positive scores indicate improvement from baseline.

These seven individual z-scores are then combined to generate the GCCS:

CogState GCCS = average of (Z_{DET}, Z_{IDT}, Z_{CPAL}, Z_{ONB}, Z_{ISLT}, $Z_{ISLT\text{-}DR}$, Z_{GMLT})

The composite score will be computed if at least five of the seven tests are completed and the five tests provide an assessment of the three cognitive domains as defined below being assessed. That is, a composite score requires that each cognitive domain be measured by at least one cognitive test.

In addition to the GCCS, composite scores for three main subdomains memory, attention and psychomotor function will also be generated by combining the standardized change from baseline scores for individual tests from the CCB using the following formulae:

- Composite score of memory tests = average of (ZCPAL, ZISLT, ZISLT-DR)
- Composite score of executive function tests = average of (ZONB, ZGMLT)
- Composite score of attention tests = average of (ZDET, ZIDT)

Each composite score will be the average of the non-missing individual test z-scores.

2.5.2 Statistical hypothesis, model, and method of analysis

The change from baseline in the GCCS of CogState test battery will be analyzed using a repeated measures analysis of covariance (ANCOVA) model in which treatment, age stratification factor, MMSE stratification factor, education level, APOE4 status (carrier vs. non-carrier), baseline cerebrovascular disease burden, visit (Weeks 26, 52, 78, 104, 130 and Week 156) and treatment-by-visit interaction are included as fixed-effect factors and baseline GCCS and visit-by-baseline GCCS interaction as covariates, with a common unstructured covariance matrix among visits between treatment groups. The adjusted mean changes at 3 years (Week 156) within each treatment, the difference in mean changes at 3 years (Week 156) between the two treatments, and its 95% confidence interval obtained from the above model will be presented. In addition, the treatment difference (LCZ696-valsartan) in mean changes from baseline to 3 years will also be expressed based on a standardized effect size (Cohen's d) with a 2-sided 95% confidence interval. The Cohen's d will be estimated by using the adjusted between-treatment mean difference, divided by the estimated pooled standard deviation. The estimated standard deviation for the mean difference is:

$$SD = \left(\frac{1}{n_1} + \frac{1}{n_2}\right)^{1/2} \hat{\sigma}$$

where n1 and n2 are the number of patients within each treatment group and $\hat{\sigma}$ is the pooled standard deviation of the within treatment group adjusted mean change. Cohen's d can be re-written in terms of t value of the estimated between treatment group difference based on the adjusted mean changes from the model mentioned above:

$$t = \frac{\widehat{\mu_1} - \widehat{\mu_2}}{SD} = \frac{\widehat{\mu_1} - \widehat{\mu_2}}{\left(\frac{1}{n_1} + \frac{1}{n_2}\right)^{\frac{1}{2}} \hat{\sigma}}$$

$$\hat{d} = \frac{\widehat{\mu_1} - \widehat{\mu_2}}{\hat{\sigma}} = \left(\frac{1}{n_1} + \frac{1}{n_2}\right)^{\frac{1}{2}} \times t$$

Confidence interval (CI) of Cohen's d is based on 95% CI of the noncentrality parameter of t value divided by the square root of the degrees of freedom from the estimated between treatment group adjusted mean change (Cumming and Finch 2001). The analysis is based on a direct likelihood method with an assumption of missing at random (MAR) for the missing data mechanism.

As the primary analysis, the repeated measure ANCOVA model will be performed in the Safety set including 'on-treatment' data (section 2.1.1) collected prior to the start of treatments for AD or cognitive impairment. The Cohen's d based on the adjusted difference in mean changes at 3

years (Week 156) between two treatments and its 95% confidence interval from this model will be used to draw the main conclusion for the primary objective. As defined in section 2.1.1, on-treatment data refer to cognitive test data collected while patients are on-study-medication (regardless of treatment interruption) or within three months after final study drug intake date.

When above mentioned model does not converge, the primary analysis model will be modified by replacing the common unstructured covariance matrix with a compound symmetry covariance matrix between treatment groups and provide above mentioned estimates. If convergence issue remains after implementing the compound symmetry covariance matrix, the model will be simplified by removing baseline cerebrovascular disease burden as explanatory factor from the model.

2.5.3 Handling of missing values/censoring/discontinuations

The repeated measure ANCOVA modeling as described in the previous section is based on a direct likelihood method with an assumption of missing at random for the missing data mechanism. That means, missing data, including those from dropouts, will be implicitly predicted based on similar patients. By similar we mean patients with similar baseline covariates, measurement histories and who were randomized to the same treatment arm. Various analyses to assess the sensitivity of the primary analysis results to the MAR assumption are described in section 2.5.5.

Data collected more than three months after patients permanent discontinuation of the study medication will be excluded from analyses in both the Safety and PPS analyses. In addition, data collected after patients starting treatments for AD or cognitive impairment will be excluded from "on-treatment" analyses.

Patients with no post-baseline assessments available will be excluded from the primary analysis. However, these patients will contribute to the imputation model for the missing GCCS scores in the sensitivity analyses.

Table 2-3 Overview of missing data handling in analyses for primary endpoint

Analysis	Analysis Set	Data excluded	Missingness assumption	Analysis method	Time points included	Imputed dataset required?
Estimand: The treatment effect had all patients stayed 'on-treatment' for the 3-year planned follow-up duration (Under 'as-treated' principle)						
Primary	SAF	Off-treatment (>3 months after last dose) After start of treatment for AD or cognitive impairment	MAR	Repeated measure ANCOVA	Weeks 26, 52, 78, 104, 130 and Week 156	No
Sensitivity to Primary analysis	SAF	Off-treatment (>3 months after last dose) After start of treatment for AD or cognitive impairment	MNAR for missing data due to death, HF hosp., stroke	Tipping point analysis followed by ANCOVA	Baseline, Weeks 26, 52, 78, 104, 130 and Week 156	Yes

	SAF	Off-treatment (>3 months after last dose) After start of treatment for AD or cognitive impairment	MNAR for missing data after starting treatments for AD or cognitive impairment	Tipping point analysis followed by ANCOVA	Baseline, Weeks 26, 52, 78, 104, 130 and Week 156	Yes
	SAF	Off-treatment (>3 months after last dose) After start of treatment for AD or cognitive impairment	MNAR for missing values due to withdrawal for unknown reasons	Tipping point analysis followed by ANCOVA	Baseline, Weeks 26, 52, 78, 104, 130 and Week 156	Yes
	SAF	Off-treatment (>3 months after last dose) After start of treatment for AD or cognitive impairment	MNAR for missing data after starting treatments for AD or cognitive impairment	Jointly model longitudinal measurements and time to starting treatments for AD or cognitive impairment	Baseline, Weeks 26, 52, 78, 104, 130 and Week 156	No
Estimand: The treatment effect had all patients completed the planned follow-up of 3 years regardless of premature study drug discontinuation (under 'Intention-To-Treat' principle)						
Supportive	FAS	No	MAR	Repeated measure ANCOVA	Weeks 26, 52, 78, 104, 130 and Week 156	No
Sensitivity to supportive analysis	FAS	No	MNAR due to death, HF hosp., stroke	Tipping point analysis followed by ANCOVA	Baseline, Weeks 26, 52, 78, 104, 130 and Week 156	Yes
	FAS	No	MNAR after starting treatments for AD or cognitive impairment	Tipping point analysis followed by ANCOVA	Baseline, Weeks 26, 52, 78, 104, 130 and Week 156	Yes
Estimand: The treatment effect had all patients completed the study treatment as per protocol schedule without major protocol deviations (under 'as treated' principle)						
Supportive	PPS	Off-treatment (>3 months after last dose) After start of treatment for AD or cognitive impairment	MAR	Repeated measure ANCOVA	Weeks 26, 52, 78, 104, 130 and Week 156	No
	PPS2	Off-treatment (>3 months after last dose) After start of treatment for AD or cognitive impairment	MAR	Repeated measure ANCOVA	Weeks 26, 52, 78, 104, 130 and Week 156	No
Estimand: Measure of treatment effect of interest MAR = Missing At Random; MNAR = Missing Not At Random; MI = Multiple Imputation						

Following sections provide more detail on the specifications for supportive and sensitivity analyses on primary endpoint as outlined above.

2.5.4 Supportive analyses

In addition to the planned primary analysis in Section 2.5.2, the same repeated measure ANCOVA will be performed in the following three analysis sets as supportive analyses as described in Table 2-3:

- **Targeting treatment effect had all patients completed planned follow up of 3 years regardless of early study drug discontinuation**
  Based on FAS, including all available data (even after treatment discontinuation and after start of treatments for AD or cognitive impairment)
- **Targeting treatment effect had all patients completed the study treatment as per protocol schedule without major protocol deviations**
  Based on the per-protocol set, including 'on-treatment' data collected prior to the start of treatments for AD or cognitive impairment only.
- **Targeting treatment effect had all patients completed the study treatment as per protocol schedule without major protocol deviations and study treatment exposure and compliance defined in PPS2**
  Based on the per-protocol set 2 (PPS2), including 'on-treatment' data collected prior to the start of treatments for AD or cognitive impairment only.

Summaries of absolute values and change from baseline in the GCCS and domain-specific composite z-scores by treatment group and visit will be presented. Figures will be produced to visually show both the raw and the model-based mean global composite z-scores and mean domain-specific composite z-scores by visit over study period for each treatment group. These will be done in both the Safety and FAS with the same data inclusion rules as for the above repeated measure ANCOVA modeling in the Safety and FAS.

Analysis of primary endpoint will also be performed based on pre-defined subgroups as in Section 2.2.1 on the Safety set including 'on-treatment' data collected prior to the start of treatments for AD or cognitive impairment. The analysis will be done using a similar repeated ANCOVA model as for the primary analysis at individual subgroup level separately, while the p-values of the subgroup-by-treatment interaction will be derived from a similar model but with additional terms including the subgroup, the interaction term of subgroup-by-treatment.

2.5.5 Sensitivity analysis

The primary analysis methods are consistent under the assumption of 'missing at random (MAR)' for the missingness mechanism. Though this is deemed to be an appropriate choice for the primary analysis, this is an untestable assumption based on the observed data (CHMP, 2010, National Research Council, 2010). Indeed it is conceivable that censoring, respectively the missing data mechanism (e.g., due to death) may be informative and that the cognitive function decline in patients who died would have been steeper than estimated under the MAR assumption. Thus, the primary analysis would favor the valsartan group in the presence of a reduction in mortality in the LCZ696 group. Alternatively, patients starting medications for treatment of AD or cognitive impairment may have had a steeper decline than estimated under the MAR assumption, if they would have not started the medication.

Due to this uncertainty on the missingness mechanism, the following sensitivity analyses will be performed to investigate the sensitivity of the primary analysis results to the MAR assumption.

Tipping point analysis

First, a tipping point analysis (Permutt 2016), which falls into the class of pattern mixture models, will be performed to evaluate the MAR assumption for missing data due to death, HF hospitalization and stroke.

This sensitivity analysis assumes that missing data due to death, HF hospitalization and stroke are missing not at random (MNAR). More specifically, it assumes that missing GCCS values due to death, HF hospitalization and stroke could have been worse than those imputed under the MAR assumption. It is implemented in the following steps:

1. Multiple (e.g. 100) imputations of missing GCCS values under a MAR assumption are generated, resulting in multiple (100) complete data sets. This imputation is based on predicted GCCS values from the fitted repeated measures ANCOVA model for the GCCS values (at baseline, Weeks 26, 52, 78, 104, 130 and Week 156) with treatment, age group (<75, ≥75 years), baseline MMSE status (<28, ≥28), baseline cerebrovascular disease burden, visit and treatment-by-visit interaction as factors having fixed effects assuming a common unstructured covariance matrix among visits between treatment group. SAS proc MI FCS statement is used to impute missing values in the following sequence: factor variables in the increasing order of missing frequency, the GCCS at baseline, Weeks 26, 52, 78, 104, 130 and Week 156.
2. For each completed data set, the imputed GCCS values at a given visit for patients who died, or had a HF hospitalization or stroke since the preceding visit, a penalty factor would be applied to the imputed values to reflect that the MAR approach may have overestimated the missing values, e.g. by assuming the actual GCCS values could be a certain percentage (e.g. 5%) worse than MAR based imputations for discontinuations due to death, HF hospitalization and stroke. If the MAR-imputed GCCS value is positive, the final value will be 95% x the imputed value; if the MAR-imputed GCCS value is negative, the final value will be 105% x the imputed value.
3. The primary analysis model as described above will be fitted to the 100 completed data sets following the application of the penalty factor in step 2 which produces 100 sets of parameter estimates and associated covariance matrices.
4. These 100 sets of parameter estimates are then combined by using Rubin's rules to derive overall estimates and their confidence intervals. In a similar manner to the primary analysis, a standardized effect size estimate (Cohen's d) and 95% CI will also be reported using the pooled SD.

The analysis will be repeated for varying penalty factors in a range between 0 and 50%. It is performed using 'on-treatment' data in the SAF, as done in the primary analysis. Tipping point analyses will be performed separately to assess the sensitivity of the results to MAR assumptions under the following situations:

- for missing data due to censoring at the start of AD and cognitive impairment treatments, including on-treatment data only in the SAF
- for missing data due to withdrawal for unknown reasons, including on-treatment data only in the SAF
- for missing data due to censoring at the start of AD and cognitive impairment treatments, including all data in the FAS
- for missing data due to withdrawal for unknown reasons, including all data in the FAS

In a similar procedure, missing values due to respective reasons will be imputed assuming MNAR while assuming all other missingness mechanism to be MAR.

If model convergence issue arises in the tipping point analysis, the model in step 1 above will be modified by replacing the common unstructured covariance matrix with a compound symmetry covariance matrix between treatment groups. If convergence issue remains after implementing the compound symmetry covariance matrix, the model will be simplified by removing baseline cerebrovascular disease burden as explanatory factor from the model.

Joint model approach

To adjust for the non-ignorable missingness in the primary endpoint due to starting AD/CI related medication, a joint modeling of the primary longitudinal process and missingness mechanism will be performed using a shared parameter approach (Vonesh et al 2006). Specifically, a generalized linear mixed model (GLMM) for the longitudinal GCCS outcome and a Cox proportional hazard model for the time to starting AD/CI related medication will be fitted which share common unobserved patient-specific random effect. It is assumed that the longitudinal outcome process is independent of the time to starting AD/CI related medication conditional on the random effects.

Model for longitudinal outcomes

The repeated GCCS outcomes will be analyzed following a repeated measures ANCOVA model with treatment, age stratification factor, MMSE stratification factor, education level, baseline cerebrovascular disease burden, APOE4 status (carrier vs. non-carrier) are included as factors and baseline GCCS, assessment time (in days), assessment time by baseline GCCS and assessment time by treatment interaction as covariates having fixed effects. Further, a patient-specific random intercept and random slope (on time) is fitted to the model. In general, the model has the following mathematical form:

$$y_i(t) = m_i(t) + e_i(t)$$

$$m_i(t) = X_i^T(t)\beta + (b_{0i} + b_{1i}t)$$

where

$y_i(t)$ =GCCS outcome for i-th patient at time t (assessment time in months)

$m_i(t)$ ='True' (unobserved) patient-specific mean GCCS outcome for i-th patient at time t

$X_i(t)$ = Covariate vector having fixed effects on mean GCCS outcome for i-th patient (treatment, age stratification factor, MMSE stratification factor, education level, baseline

cerebrobascular disease burden, APOE4 status, baseline GCCS, assessment time, assessment time by baseline GCCS and assessment time by treatment)

β = Parameter vector representing fixed effects of covariate vector $X_i(t)$ on mean GCCS outcome at time t

b_{0i} =Patient-specific random intercept

b_{1i} =Patient-specific random slope on time

$e_i(t)$ = Measurement error,

Assumption:

- (b_{0i}, b_{1i})'s are assumed to be following bivariate normal distribution with mean vector 0 and unstructured covariance matrix independently for all patients
- $e_i(t)$'s are assumed to be independently normally distributed with mean vector 0 and an covariance matrix with no correlation between the time points and an common variance σ_e^2 on the diagonal elements

Model for time to starting AD or CI related medication

Time to starting AD or CI related medication from randomization will be calculated as –

- Date of starting AD or CI related medication – Randomization date +1

Patients who do not start AD or CI related medication, their data will be censored at the earlier of –

- Last known date patient took study medication
- Date of withdrawal of consent
- Date of last visit

A exponential regression is fitted to the time to starting AD or CI related medication.

$$\lambda_i(t|H_i(t), X_i) = \lambda_0 \exp(X_i^T \gamma + \alpha m_i(t))$$

where

$\lambda_i(t|H_i(t), X_i)$ =Conditional intensity function at time t for i-th patient given the covariate and history of outcomes until time t, $H_i(t)$

λ_0 =Baseline hazard function that is constant over time

γ = Parameter vector representing fixed effects of time-independent covariate vector X_i on event risk (hazard) at time t

α =Fixed effect of 'true' patient-specific mean outcome at time t

A constant function will be assumed for the baseline intensity function. over time. Assuming that the longitudinal GCCS outcome process and event process of starting AD or CI related medication are independent conditional on the random effects, the conditional likelihood is computed as multiplication of the likelihood from GCCS outcome process and event process. Parameter estimation will be done through numerically maximizing the marginal likelihood obtained from numerically integrating the conditional likelihood over the distribution of random effects.

Of note, the modeling may fail to converge yielding unreliable or no estimate for parameters if the incidence of start of AD/CI related medication are low. In such a case, restrictions may be imposed on the form of baseline intensity function to change to a parametric baseline intensity (e.g. Weibull function) which will be documented in the clinical study report section 9.7. If the model still fails to converge, the results may be excluded from the clinical study report.

2.5.5.1 Mis-stratification

For randomization stratification that is done incorrectly due to transciption error or inconsistent site and central reviewer readings, primary analysis described in Section 2.5.2 will be repeated using the final data entered in the clinical database, instead of the stratification factors in IVR system.

2.6 Analysis of secondary efficacy objective(s)

2.6.1 Secondary endpoints

The secondary efficacy variables are –

1. Change from baseline in individual cognitive domains (memory, executive function, and attention) as assessed by the individual components of the cognitive assessment battery at 3 years.
2. Change from baseline in the summary score of the instrumental activities of daily living (IADL) as assessed with Functional Activity Questionnaire (FAQ) at 3 years.

Composite scores for three main subdomains memory, attention and psychomotor function will also be generated by combining the standardized change from baseline scores for individual tests from the CCB using the following formulae:

- Composite score of memory tests = average of (Z_{CPAL}, Z_{ISLT}, $Z_{ISLT\text{-}DR}$)
- Composite score of executive function tests = average of (Z_{ONB}, Z_{GMLT})
- Composite score of attention tests = average of (Z_{DET}, Z_{IDT})

Each composite score will be the average of the non-missing individual test z-scores.

2.6.2 Statistical hypothesis, model, and method of analysis

For secondary efficacy variables composite z-scores by individual domain (memory, executive function and attention) and IADL, the changes from baseline to 3 years will be analyzed using the same repeated measures ANCOVA model as described in Section 2.5.2 but with baseline GCCS replaced with respective secondary variable baselines. The adjusted mean changes at 3 years (Week 156) within each treatment, the difference in mean changes at 3 years (Week 156) between two treatments, its 95% confidence interval obtained from the above model will be presented. In addition, the treatment difference (LCZ696-valsartan) in mean changes from baseline to 3 years will also be expressed in terms of a standardized effect size (Cohen's d) with a 2-sided 95% confidence interval. The Cohen's d will be estimated as in a similar manner as planned for the primary endpoint analysis (Section 2.5.2). The analysis is based on likelihood method with an assumption of missing at random for missing data, and will be performed in the Safety set including 'on-treatment' data collected prior to the start of treatments for AD or cognitive impairment. On-treatment data are those collected while patients are on-study-

medication (regardless of treatment interruption) or within three months after final study drug intake date. This analysis will be performed in the SAF.

In addition, as supportive analysis, similar repeated measure ANCOVA model will also be performed for these secondary endpoints for all data in the FAS.

Summaries of absolute values and change from baseline by treatment group and visit will be presented. Figures will be produced to visually show the endpoint values (composite z scores by cognitive domain and IADL) by visit over the study period for each treatment group.

These analyses will be done in both SAF and FAS, for 'on-treatment' data and for all data, respectively.

2.6.3 Handling of missing values/censoring/discontinuations

As in the primary analysis, the analysis methods for secondary endpoints are consistent under the assumption of 'Missing at random'.

2.6.4 Sensitivity analysis for mis-stratification

For randomization stratification that is done incorrectly due to transciption error or inconsistent site and central reviewer readings, analysis described in Section 2.6.2 will be repeated using the final data entered in the clinical database, instead of the stratification factors based on IVR system.

2.7 Safety analyses

Safety evaluations to be analyzed are listed as below:

- Change from baseline in a cortical composite SUVr (standardized uptake value ratio) at 3 years

[redacted]

2.7.1 Change from baseline in SUVr at 3 years

PET amyloid brain scans will be performed at randomization visit, at 18 months, and at end of study visit (scheduled at 3 years) for the patients participating the PET imaging sub-study and with non-missing baseline. In addition, for patients who have premature permanent discontinuation of study drug, it is planned to obtain an end-of-treatment PET scan if the next scheduled PET scan is < 6 months after treatment discontinuation. In order to make the most use of data collected from all available PET scan assessments, including the planned 'end-of-treatment' and 'end-of-study' assessments, the analysis of change from baseline (randomization) in a cortical composite SUVr at 3 years (Week 156) will be based on a model-based multiple imputation approach under the MAR (missing at random) assumption. Further sensitivity analyses will be provided to assess the robustness of the MAR assumption on the missingness

mechanism. Following table provides an overview of missing data handling for cortical composite SUVr data with corresponding assumptions on missingness.

Table 2-4 Overview of missing data handling in analysis of change from baseline in SUVr at 3 years

Analysis	Analysis Set	Data excluded	Missingness assumption	Analysis method	Time points included	Imputed dataset required?
Estimand: The treatment effect had all patients stayed 'on-treatment' for the 3-year planned follow-up duration (Under 'as-treated' principle)						
Primary	SAF (restricted to PET imaging substudy)	Off-treatment (>6 months after last dose)	MAR	MI followed by ANCOVA	Baseline, Month 18, Year 3, and all other post-BL measurements <= 6 months after last dose	Yes
Sensitivity	SAF (restricted to PET imaging substudy)	Off-treatment (>6 months after last dose) Data outside 6-months window from scheduled visit	MAR	Repeated measure ANCOVA	Month 18, Year 3	No
Sensitivity	SAF (restricted to PET imaging substudy)	Off-treatment (>6 months after last dose)	MNAR for missing due to death, HF hospitalization and stroke - tipping point anaysis	MI (tipping point anaysis) followed by ANCOVA	Baseline, Month 18, Year 3, and all other post-BL measurements <= 6 months after last dose	Yes
Estimand: Measurement of treatment effect of interest MAR = Missing At Random; MNAR = Missing Not At Random; MI = Multiple Imputation						

The imputation model will include age stratification factor, MMSE stratification factor, region, baseline cerebrovascular disease burden, APOE4 status (carrier vs non-carrier), baseline amyloid status (positive/negative) and time (when the SUVr is assessed in days) as fixed effects with random intercept and slope (time) and a common unstructured covariance. This will be done separately within each treatment. Missing values will be imputed by the predicted values following from the fitted imputation model with random effects and random errors simulated from their respective distributions. SAS proc MCMC is used to impute missing values described above.

This imputation process will first create multiple imputations of missing SUVr at 3 years under a MAR assumption, resulting in multiple complete data sets after combining the imputed missing SUVr at 3 years values with the available SUVr at 3 years (so every patient with baseline SUVr in these multiple complete data sets will have an SUVr value at 3 years). An ANCOVA model using change from baseline to 3 years in SUVr as response variable, with treatment, age stratification factor, MMSE stratification factor, region, baseline cerebrovascular disease burden, APOE4 status, baseline amyloid status as factors and baseline SUVr value and treatment-by-baseline SUVr interaction as covariates will be run on each of these multiple completed data sets. Overall results and inference, including adjusted mean change at 3 years within each treatment, the difference in mean change at 3 years between two treatments, its 95%

confidence interval, are obtained by applying Rubin's rules on the estimates obtained from the imputed/completed data sets.

If covergence issue arises, the imputation model will be modified by replacing the common unstructured covariance with a common compound symmetry covariance between treatment groups. If convergence issue remains after implementing the compound symmetry covariance matrix, the model will be simplified by removing baseline cerebrovascular disease burden as explanatory factory from the model.

2.7.1.1 Supportive analysis

Both the actual SUVr values and change from baseline values will be descriptively summarized for each treatment group by each assessment visit over study period by providing summary statistics (n, mean, SD, median, Q1, Q3, min, max). Additionally, number and percentage of patients with positive PET scan will be reported for each treatment group by each assessment visit. Available SUVr data at 'end of treatment' and 'end of study' will be summarized separately as above.

To assess the sensitivity of the primary analysis method results to the imputation model, a sensitivity analysis will be performed on the change in a cortical composite SUVr from baseline to 3 years by incorporating information from other assessments still under the assumption of MAR. The change from baseline in SUVr will be analyzed based on a repeated measures ANCOVA model in which treatment, age stratification factor, MMSE stratification factor, region, baseline cerebrovascular disease burden, APOE4 status (carrier vs. non-carrier), baseline amyloid status (positive/negative), visit (18 months, 3 years), and treatment-by-visit interaction will be included as fixed-effect factors and baseline value and baseline-by-treatment as covariates, with a common unstructured covariance matrix among visits between treatment groups. The adjusted mean changes at 3 years (Week 156) within each treatment, the difference in mean changes at 3 years (Week 156) between two treatments, its 95% confidence interval obtained from the above model will be presented. The analysis is based on likelihood method with an assumption of missing at random for missing data.

To assess the sensitivity of the primary analysis methods results to the baseline amyloid status (positive/negative) based on quantitative (numerical) cutoff instead of qualitative (visual) assessment, a sensitivity analysis will be performed using the same ANCOVA model specified in Section 2.7.1 but with the quantitative positive/negative assessment of the baseline brain amyloid status. A shift table to summarize the proportion of patients' amyloid status change over time from baseline i.e. patients transitioning from negative to positive based on quantitative assessment will also be provided by treatment group.

In addition, to assess the sensitivity of the analysis results to the MAR assumption used in the multiple imputation for primary analysis method, a tipping point analysis will be performed on the change from baseline in SUVr which assumes that missing values after death, HF hospitalization and stroke are missing not at random (MNAR). This analysis will follow the same procedure as described in section 2.5.5 for the primary endpoint, with the exception that the imputations under MAR are obtained from a regression based imputation as described in the primary analysis method of this endpoint (Section 2.7.1). The analysis will be repeated for varying penalty factors in a range between 1 and 1.6.

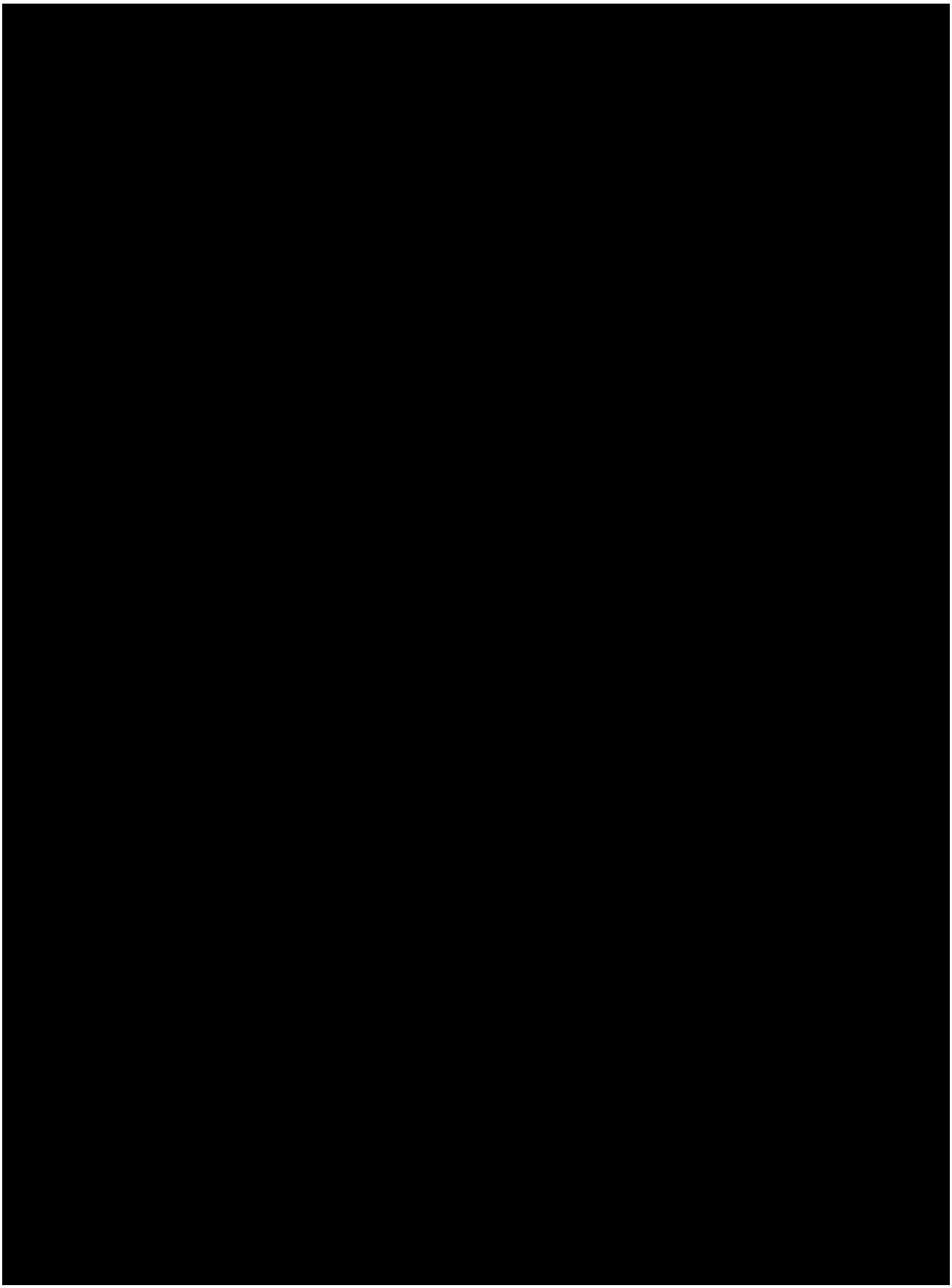
If convergence issue arises in any of above described supportive analyses, the handling approach described in Section 2.7.1 will be used to address the convergence issue.

Furthermore, to assess the sensitivity of the analysis results to the randomization stratification that is done incorrectly due to transciption error or inconsistent site and central reviewer readings, analysis described in Section 2.7.1 will be repeated using the final data entered in the clinical database, instead of the stratification factors based on IVR system.

To address missing assessments due to COVID-19 pandemic, the analysis mentioned in Section 2.7.1 will be repeated using PET substudy set with a wider assessment window extending from 6 months to 9 months for assessments that are scheduled to take place starting Mar 1, 2020 and onwards. This also applies to the data excluded from analysis if assessment is done more than 9 months after last study drug intake instead of 6 months.

All analyses will be performed in patients in the Safety set who participate in the PET image substudy and with non-missing baseline, including 'on-treatment' data only. On-treatment data refer to the SUVr values obtained while patients are on-study-medication (regardless of treatment interruption), or within defined window in each supportive analysis (six months or nine months) after the final study drug intake date.

In addition, for patients who do not have any post-baseline SUVr assessments and part of the reason is due to concerns over exposure to COVID-19 by visiting the site, the analysis mentioned in Section 2.7.1 will be repeated using PET substudy set excluding patients without any post-baseline assessments, including 'on-treatment' data only (within six months after the final study drug intake date).



[redacted]

[redacted]

[redacted]

2.7.3 Deaths

Patients that died during the study period will be reported separately for run-in and double-blind treatment epochs. Deaths occurring during the double-blind treatment epoch will be summarized by actually received treatment group to present number and percentage of patients that died by overall and reason categories (CV/non-CV causes as reported by investigator). In addition, listings will be provided for patients that died during the study period with the primary reason of death.

The analysis will consider all patients in the Safety set (SAF) for reported deaths during the double-blind treatment epoch while deaths during the run-in epoch will be reported based on patients in the Enrolled set (ENR).

[redacted]

[redacted]

2.8 Pharmacokinetic endpoints

Not applicable

2.9 PD and PK/PD analyses

Not applicable.

2.10 Patient-reported outcomes

Following Patient reported outcomes (PRO) are collected by sites at respective visits.

1. Instrumental activities in daily life (IADL) as assessed through Functional activity questionnaire (FAQ)

[redacted]

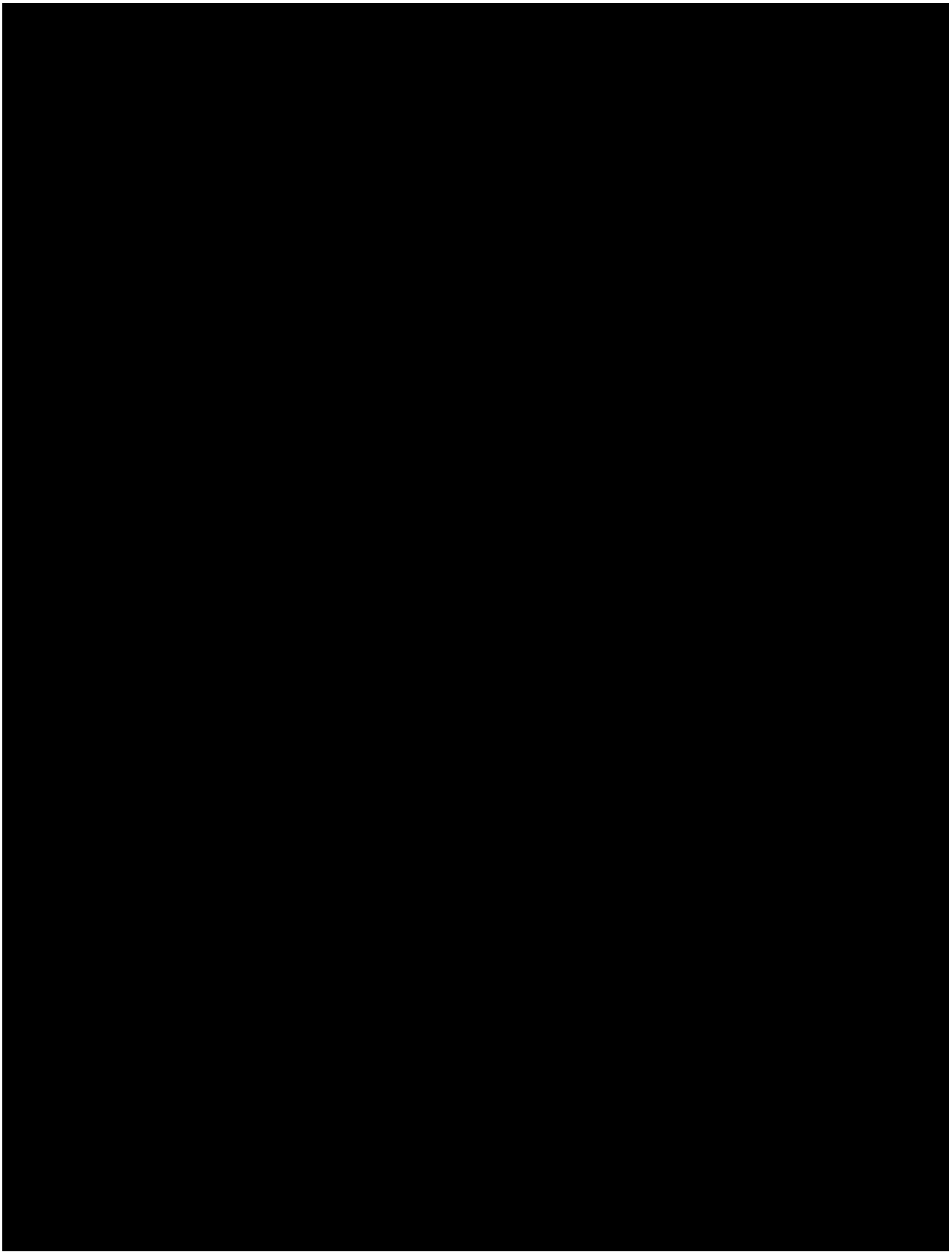
Analysis method for outcome (1) has been outlined in section 2.6.2 for secondary endpoints. The analysis methods for other outcomes will be described in Section 2.12 as part of the exploratory endpoint analyses.

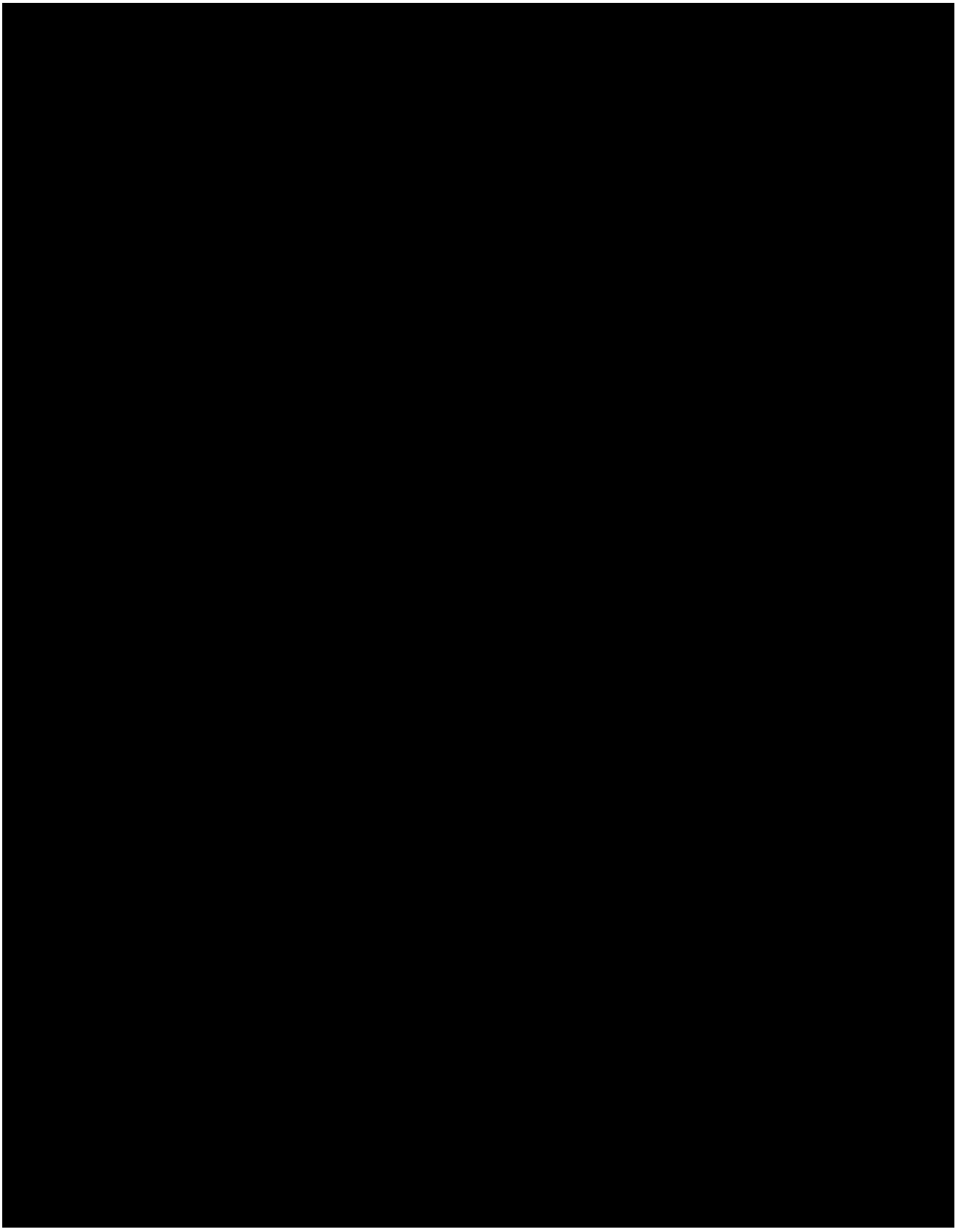
2.11 Biomarkers

For plasma Aβ1-40, the log-transformed ratio to baseline i.e. log (post-dose value/baseline) will represent the change from baseline in logarithmic change for each subject at every post-dose time point, The change from baseline to a pre-defined time-point (Weeks 13, 52, 104 and 156) in logarithmic scale will be analyzed using a repeated measures ANCOVA model in which treatment, age stratification factor, MMSE stratification factor, education level, APOE4 status (carrier vs. non-carrier), visit (Weeks 13, 52, 104 and Week 156) and treatment-by-visit interaction are included as fixed-effect factors and baseline log-transformed plasma Aβ1-40 and visit by baseline log-transformed plasma Aβ1-40 interaction as covariates, with a common unstructured covariance matrix among visits between treatment groups. The adjusted mean changes within each treatment, the difference in mean changes between the two treatments, and its 95% confidence interval obtained from the above model will be presented for all the assessment visits. All the estimates will be back-transformed to natural scale for reporting.

Descriptive summaries of absolute values and change from baseline in Aβ1-40 by treatment group and visit will be presented using summary statistics (n, mean, SD, median, minimum, maximum, Q1, Q3, geometric mean and Coefficient of Variation). Mean Aβ1-40 levels will also be graphically presented by each visit over study period for each treatment group.

All of the above analyses will be performed for patients for whom the biomarker data is obtained in the PET imaging substudy with non-missing baseline including all data.





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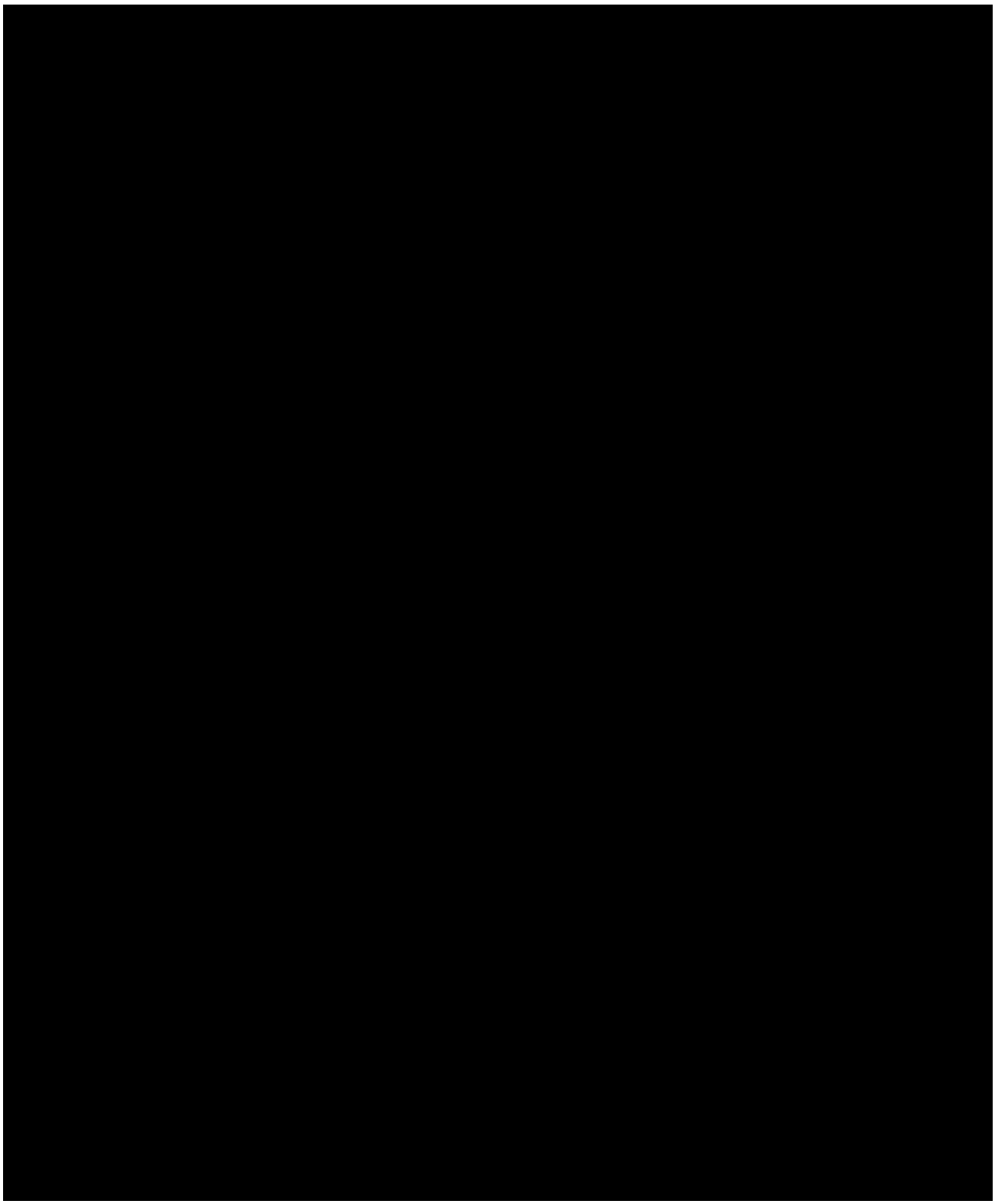

2.13 Interim analysis

There is no planned interim efficacy analysis but an external DMC will review the unblinded safety data every 6 months. The relevant analyses will be executed by a group of external

independent statisticians and independent programmers privileged to access unblinded clinical trial data.

3 Sample size calculation

It is planned to randomize a total of 520 patients for the main study and a subset of 430 randomized patients will be enrolled in the PET imaging substudy. With an assumed drop-out rate of 30%, this will result in approximately 360 randomized patients for the main study.

3.1 Sample size calculation for the primary endpoint

It is currently estimated that approximately 180 patients per group having data on 3-year planned follow up –

- Would provide at least 80% probability that the 2-sided 95% confidence interval (CI) excludes a standardized effect size (Cohen's d) of 0.3 (or greater) in change in composite z-score of the battery test over 3 years, given that there is no expected difference between two treatments.
- Would provide at least 80% probability that the 2-sided CI excludes 0 (corresponding to $p<0.05$), if the true effect size is 0.3 or greater (in either direction).

An effect size of 0.3 in Cohen's d corresponds to a margin of 0.3xSD (SD=standard deviation) on the original scale for the difference between treatments in mean global score change from baseline, and is generally considered as small (Cohen 1988). In a systematic review of studies for health-related quality of life instruments that have reported the minimally important difference (MID), it was found that for the majority of studies the MID estimates were consistently close to 0.5xSD (Norman et al 2003). In addition, socially accepted benchmarks for conditions that induce cognitive impairment such as low level alcohol intoxication within legal driving limit in most countries (0.05%) are generally associated with declines of 0.3 or higher for psychomotor speed, attention and working memory. Therefore, the sample size of the study was determined to be able to detect (or exclude) effect sizes in the magnitude of 0.3 in Cohen's d with high probability, as it appears to be an appropriate choice to guide the interpretation of the cognitive function results.

In addition, defining the magnitude of the MID using a measure of effect size, rather than a raw difference score has additional advantages:

- Expressing the magnitude of an important difference in scale free units (Cohen's d) allows models of clinically meaningful difference to be based on integration of outcomes from a broad set of studies whose characteristics are relevant to the current study (i.e. magnitude of change in cognition related to amyloid, magnitude of change occurring after heart failure, and magnitude of change related to cardiovascular disease).
- Estimates of clinically meaningful difference can be referenced to the magnitude of cognitive decline detected from studies where compounds with accepted central nervous system adverse effects, at known doses are administered to older adults (e.g. scopolamine, alprazolam).

Sample size calculation was performed using N-Query 7.0.

3.2 Sample size calculation for the PET imaging substudy

Approximately 300 complete patients (in 1:1 allocation ratio to LCZ696 and valsartan) will provide at least 80% probability that the 2-sided 95% CI excludes a between-treatment absolute difference of 0.01 (corresponding to an incremental 33% increase in LCZ696 vs. valsartan) in change from baseline in SUVr over 3 years if there is no expected difference between two treatments. This calculation is based on the assumptions that the mean change over 3 years from baseline in SUVr is 0.03 in the control group, the common standard deviation is 0.03 (estimated from ADNI data, Chen et al 2015). It is noted that the ADNI data presented in Chen's paper are by patients' cognitive status (normal, MCI, dementia) and for changes over two years. The assumptions used here are guestimates from the 2 year data in normal cognitive and MCI subjects.

An absolute difference in SUV ratio of 0.01 was considered small as it represents a value that is lower than the rate of SUVr change that distinguishes between amyloid positive and negative patients (0.026 vs. 0.011).

Sample size calculation was performed using N-Query 7.0.

3.3 Blinded sample size re-estimation

Approximately 520 patients will be randomized in order to provide overage to account for the information loss caused by an estimated 30% "drop-out" (including death, lost-to-follow-up, permanent discontinuation of study medication and start of treatments for AD or cognitive impairment) during 3 year period. In the PET imaging substudy approximately 430 patients will be randomized.

A loss of 30% of information is a crude estimate therefore it is planned to monitor the 'dropout' pattern as the trial is ongoing in order to provide a better prediction of the information loss for a given number of patients. The final number of patients randomized may be reduced if there is sufficient evidence that the information loss will be less than 30% and that the precision of the estimates of treatment effect (as described in the sample size section above), will be maintained.

4 Change to protocol specified analyses

Not applicable

5 Appendix

5.1 Imputation rules

5.1.1 AE date imputation

The missing or partially missing AE start or end dates will be handled/imputed using the Novartis ADaM Governance Board (AGB) global standard approach. Details will be provided in the study Programming Datasets Specifications (PDS) document.

5.1.2 Concomitant medication date imputation

The missing or partially missing concomitant medication start or end dates will be handled/imputed using the Novartis AGB global standard approach. Details will be provided in the study PDS document.

5.2 Statistical models

5.2.1 Primary analysis

See Section 2.5.2.

5.2.2 Key secondary analysis

Not applicable.

5.3 Rule of exclusion criteria of analysis sets

Following tables present a sample of the rules for subject classification in the analysis sets based on protocol deviation specifications (Table 5-1) and non-protocol deviation classification criteria (Table 5-2). The PDs leading to exclusion of patients from analysis sets may be updated prospectively and will be finalized before DB lock.

Table 5-1 Protocol deviations leading to exclusion of subjects

Deviation ID	Description of Deviation	Exclusion in Analyses
INCL01	No study informed consent signature.	Excluded from all analyses
INCL02	No sub-study informed consent signature.	Excluded from PET imaging sub-study related analyses only
INCL10	No adequate functioning (e.g.: intellectual, motor, visual and auditory) to complete the study assessments	Excluded from per-protocol (PP) analyses
EXCL19	MMSE score <24 at screening visit	Excluded from PP analyses
OTH21	MMSE score invalid or missing at screening visit	Excluded from PP analyses
EXCL20	Clinical diagnosis of Alzheimer's disease or other dementia syndrome or any indication for or current treatment with cholinesterase inhibitors and/or another prescription AD treatment (e.g.memantine)	Excluded from PP analyses
EXCL21	History of medical or neurological condition likely to affect the participant's cognition or Vitamin B12 or folate deficiency at screening	Excluded from PP analyses
EXCL22	Inability to perform cognitive battery or other study evaluations based on significantly impaired motor or sensory skill	Excluded from PP analyses

Deviation ID	Description of Deviation	Exclusion in Analyses
EXCL39	Patients who previously entered a LCZ696 study and had been randomized or enrolled into the active drug treatment epoch.	Excluded from PP analyses
OTH02	Site has been closed down for GCP reasons.	Excluded from analyses on FAS and PP
OTH09	Blind was broken locally	Excluded from PP analyses
OTH08	Patient was misrandomized (patient was randomized in error and no DB study medication taken).	Excluded from analyses on FAS and PP

Table 5-2 Subject classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
ENR	INCL01	
LRS	INCL01	Not in ENR; Did not take any dose of run-in LCZ696
VRS	INCL01	Not in ENR; Did not take any dose of run-in valsartan
RAN	INCL01	Not randomized
FAS	INCL01, OTH02, OTH08	Not in RAN; Mistakenly randomized and no double-blind study drug taken
PPS	INCL01, INCL10, EXCL19, EXCL20, EXCL21, EXCL22, EXCL39, OTH02, OTH08, OTH09, OTH21	Not in FAS; Less than 30 months exposure to study medication or have less than 80% compliance on study medication averaged over treatment exposure duration
PPS2	INCL01, INCL10, EXCL19, EXCL20, EXCL21, EXCL22, EXCL39, OTH02, OTH08, OTH09, OTH21	Study medication exposure (in months) multiplied by compliance on study treatment is less than 24
SAF	INCL01	No double-blind study drug taken
PET	INCL01, INCL02	

5.4 Cerebrovascular disease burden scoring

Table 5-3 Cerebrovascular disease burden scoring

Component	Criteria	Score

Lacunar infarcts	> 2	1
	≤ 2	0
Cortical or subcortical infarct	> 1 cm^3	1
	≤ 1 cm^3	0
White matter lesion	Fazekas score ≥ 3	1
	Fazekas score < 3	0
Micro haemorrhages	≥ 4	1
	< 4	0

6 Reference

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