STATISTICAL ANALYSIS PLAN

(Short) study title:	A Phase 2 multi-center, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of T-817MA in patients with mild cognitive impairment due to Alzheimer's Disease or mild Alzheimer's Disease
Name of the sponsor:	FUJIFILM Toyama Chemical Co., Ltd.
Protocol identification:	T817MAEU201
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VERSION HISTORY

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4.0	22-May-2023	Updated final version for sign-off. Clarification on effect size calculation. Amended protocol changes included. Adding topline and changing table/graph numbers to a more logical order. Added several clarifications for variable selection for presentations.

APPROVAL PAGE

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

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22 MAY 2023

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22. May. 2023

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LIST OF ABBREVIATIONS

AChE	Acetylcholinesterase
AD	Alzheimer's disease
ADAS-cog	Alzheimer's disease assessment scale-cognitive subscale
AE	Adverse Event
A-IADL-Q	Amsterdam Instrumental Activity of Daily Living Questionnaire
Aß1-40	Amyloid β1-40
Aß1-42	Amyloid β1-42
ApoE	ε4 allele of Apolipoprotein E
BDRM	Blinded Data Review Meeting
CDR-sb	Clinical Dementia Rating Scale Sum of Boxes
CFC	Cognitive Functional Composite
CFT	Category Fluency Test
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
EDC	Electronic Data Capture
EEG	Electroencephalogram
GFAP	glial fibrillary acidic protein
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IWRS	Interactive Web Response System
LFT	Letter Fluency Test
LSMeans	Least Squares Means
MAR	Missing At Random
MCI	Mild Cognitive Impairment
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-treat
MMRM	Mixed Model for Repeated Measures
MMSE	Mini Mental State Examination
MNAR	Missing Not At Random
MRI	Magnetic Resonance Imaging
NFL	Neurofilament Light
PK	Pharmacokinetics
PP	Per Protocol
PT	Preferred Term
p-tau181	Tau protein phosphorylated at threonine 181
p-tau217	Tau protein phosphorylated at threonine 217
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error

SOC	System Organ Class
TBV	Total Brain Volume
TEAE	Treatment Emergent Adverse Event
T-817MA	Used interchangeably as Study drug and Active drug product; a maleate salt of T-817 [chemical name: 1-{3-[2-(1-benzothiophen-5-yl)ethoxy]propyl} azetidin-3-ol maleate]
vMRI	Volumetric Magnetic Resonance Imaging
Amsterdam UMC	Amsterdam University Medical Center
WAIS-IV-DS	Wechsler Adult Intelligence Scale - 4th Edition - Digit Span
WAIS-IV-DSST	Wechsler Adult Intelligence Scale - 4th Edition - Digit Symbol Substitution Test
WHO	World Health Organisation
YKL-40	chitinase-3-like protein 1, a secreted glycoprotein formed of three N-terminal amino acids, being tyrosine (Y), lysine (K) and leucine (L).

1 GENERAL

The objective of the Statistical Analysis Plan is to ensure the credibility of all study findings by means of a predefined data analysis plan. This plan assumes familiarity with the study protocol and its amendments and will provide further details of the summaries and analyses planned therein. This Statistical Analysis Plan will be finalized via signatory prior to treatment unblinding.
A separate Pharmacokinetic Analysis Plan will describe the analysis and reporting of the pharmacokinetic (PK) results for this study.

2 STUDY INFORMATION

2.1 Study Objective(s)

2.1.1 Primary Objective

The primary objective is to evaluate the neuroprotective effect of T-817MA on Tau protein phosphorylated at threonine 181 (p-tau181) in Cerebrospinal fluid (CSF) compared with placebo, in patients with a diagnosis of Mild Cognitive Impairment (MCI) due to Alzheimer's disease (AD) or mild AD, according to the National Institute on Aging - Alzheimer Association (NIA-AA) criteria with a Mini Mental Status Examination (MMSE) score of 24 to 30 (inclusive), and Amyloid β1-42 (Aß1-42) and p-tau181 abnormality in CSF (≤1000 pg/ml for Aβ1-42, ≥19 pg/ml for p-tau181) or (p-tau181/Aβ1-42 ratio >0.020 for patients with p-tau181 ≥19 pg/ml and 1000<Aβ1-42<1700 pg/ml).

2.1.2 Secondary Objectives

To evaluate in patients on T-817MA and placebo:

- Cognitive function measured by the Clinical Dementia Rating Scale Sum of Boxes (CDR-sb) and Cognitive Functional Composite (CFC)
- AD-related biomarkers in CSF (Tau protein phosphorylated at threonine 217 [p-tau217], total tau, Aβ1-40, Aβ1-42, neurofilament light [NFL], neurogranin, YKL-40 and Aβ1-42/Aβ1-40 ratio) and in plasma (Aβ1-40, Aβ1-42, and NFL, glial fibrillary acidic protein [GFAP], p-tau181, p-tau217 and Aβ1-42/Aβ1-40 ratio)
- Imaging analysis using volumetric magnetic resonance imaging (vMRI)
- Alpha/theta ratio of the electroencephalogram (EEG)

To evaluate the safety of T-817MA by clinical laboratory tests and AEs

To evaluate the pharmacokinetics of T-817MA in plasma and CSF.

3 STUDY DESIGN

3.1 Sample size determination

In Study US202, T-817MA 448 mg statistically significantly decreased CSF p-tau181 compared with placebo (see Table 1).

Table 1. Change from Baseline in CSF p-tau181 (Study US202)

			Change from Baseline to Week 52		
Parameter	Arm	N	Mean	SE	P-value
p-Tau181	Placebo	18	**0.29**	2.64	-
(pg/mL)	224 mg	17	**-3.94**	2.72	0.269
	448 mg	24	**-7.30**	2.28	0.034

Abbreviations: N = number; SE = standard error

The CSF samples from Study US202 were delivered to the laboratory of Amsterdam UMC (the central laboratory for CSF assay for this study) and assayed for p-tau181 again to see reproducibility (see Table 2).

Table 2. Change from Baseline in CSF p-tau181 (re-assay of the samples from Study US202 at Amsterdam UMC) (in-house data)

			Change from Baseline to Week 52			
			Raw		Adjusted	
Parameter	Arm	N	Mean	SD	Mean	Difference
p-Tau181	Placebo	18	**-0.94**	4.31	-0.99	
(pg/mL)	224 mg	18	**-1.41**	4.94	-1.32	**-0.32**
	448 mg	24	**-3.40**	4.77	-3.43	**-2.43**

Abbreviations: Max = maximum; Min = minimum; SD = standard deviation

Based on the mean change and SD in T-817MA 448 mg and Placebo group in Table 2, 61 patients/group will provide 80% power at a significance level of alpha=0.05 using the t-test. The proposed sample size is 200 patients, with 100 patients in both the active and the placebo group assuming 40% drop out at Week 78.

3.2 Schedule of Activities

Stage of Study	Screening	Baseline[16,17]	Treatment							Post-treatment
Week	-8 to -1	-1 to 0	4±1	16±1	28±1	40±1	52±1	65±1	78±1	82±1
Visit[1]	V1	V2	V3	V4	V5	V6	V7	V8	V9 or Premature discontinuation[2]	V10
Informed consent	X									
Demographics / Medical history[3]	X									
Inclusion / Exclusion criteria	X	X								
MMSE (score 24-30 is inclusion criterion)	X									
Physical examination[4]	X		(X)	(X)	X	(X)	X	(X)	X	(X)
Vital signs[5]	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
12-lead ECG[6]	X		(X)	(X)	X	(X)	X	(X)	X	(X)
Hematology, chemistry, urinalysis	X		X	X	X	X	X	X	X	X
Blood draw for ApoE genotyping		X								
Blood draw for biomarkers		X					X		X	
Blood draw for PPK[7]				X	X	X		X		
CFC[8,9]	X	X			X		X		X	
CDR-sb[9]	X	X			X		X		X	
EEG		X[10]					X		X	
vMRI[11]	X						X		X	
Lumbar puncture for CSF[12]	X						X		X	
Randomization[13]		X								
Study drug dispense		X[14]	X	X	X	X	X	X		
Eligibility check to be performed by the Central Review Medical Monitor[15]	X									

Schedule of Activities (continued)

1. Procedures can be separated within the visit window.
2. Visit also to be conducted in case of premature discontinuation. If patient is discontinued earlier than Week 28 visit or after Week 52, EEG, vMRI and Lumbar puncture are not necessary.
3. Includes education and smoking habits
4. Includes neurological examination. To be done at Weeks 4, 16, 40, 65 and 82, only if clinically indicated.
5. Includes heart rate, blood pressure and weight (and height at screening only)
6. To be done at Weeks 4, 16, 40, 65 and 82, if clinically indicated.
7. Plasma PPK samples taken 1-6 hours *after* the last dose at Weeks 16 and 40, and *before* dosing at Weeks 28 and 65.
8. The CFC assessment comprises: ADAS-cog, A-IADL-Q, CFT, LFT, WAIS-IV-DS and WAIS-IV-DSST
9. The Screening CFC and CDR-sb must be performed at least 14 days prior to the Baseline CFC and CDR-sb in order to minimize learning effects.
10. Every effort must be taken by sites to ensure the Baseline EEG is approved prior to first administration of study medication. Note that the quality check of the Baseline EEG may take up to 2 business days after submission of the EEG file.
11. The vMRI assessment is to be done before or more than 3 days after CSF sampling.
12. CSF sample must be taken between 11AM and 2PM. Samples collected at Weeks 52 and 78 will additionally be used for PK analysis
13. Randomization must be done at the last day of the baseline procedures.
14. First intake of study medication after completion of all procedures listed at Baseline.
15. Once the eligibility of a patient is confirmed by the Investigator at the end of the Screening period, up to 5 business days must be allowed for the eligibility check by the Central Review Medical Monitor (CRMM).
16. The Baseline visit can be performed once all Screening procedures (including the eligibility check by the CRMM) are completed. A 1-week visit window prior to randomization applies to the Baseline visit procedures
17. Randomization can be done once all Baseline visit procedures have been completed and must be performed within 56 days of the first screening assessment.

Abbreviations: ADAS-cog: Alzheimer's Disease Assessment Scale-Cognitive subscale; A-IADL-Q: Amsterdam Instrumental Activity of Daily Living Questionnaire; ApoE: ε4 allele of apolipoprotein E; CDR-sb: Clinical Dementia Rating Scale Sum of Boxes; CFC: Cognitive Functional Composite; CFT: Category Fluency Test; CSF: cerebrospinal fluid; ECG: electrocardiogram, EEG: electroencephalogram; LFT: Letter Fluency Test; MMSE: Mini Mental State Examination; PPK: population pharmacokinetics; vMRI: volumetric magnetic resonance imaging. WAIS-IV-DS: Wechsler Adult Intelligence Scale - 4th Edition - Digit Span; WAIS-IV-DSST: Wechsler Adult Intelligence Scale - 4th Edition - Digit Symbol Substitution Test.

4 RANDOMIZATION AND UNBLINDING PROCEDURES

4.1 Randomization

The investigator will use the EDC system to enter screening information on each patient. Patients will be randomized at Baseline using Interactive Web Response System (IWRS) in EDC, after screening is completed and it is determined by central review that the patient is eligible for the study. For those patients who qualify, the system will issue a medication kit number.

Each patient will be randomly allocated in a 1:1 ratio into 1 of the 2 groups: treatment with 448 mg T-817MA or placebo. A randomization schedule will be generated and incorporated into EDC and the treatment group will be assigned when the site activates the patient. A centralized eligibility evaluation procedure will be applied for each patient. A stratified permuted block randomization procedure will be used. Country and MMSE at Screening will be stratification factors (MMSE score strata being Low [24-26] and High [27-30]).

4.2 Blinding

This is a double-blind controlled trial. Treatments will be blinded to the patients and study personnel throughout the study. Treatment blind will be maintained by use of matching placebo medication. In order to preserve blinding, a minimal number of study personnel that support the Independent Data Monitoring Committee (IDMC) will have access to the randomization table and treatment assignments before the study is complete.

Only in the case of an emergency, when knowledge of the patient's allocation is essential for the clinical management or welfare of the patient, may the investigator unblind a patient's treatment assignment without any prior approval. Unblinding needs to be performed via the IWRS or by phone. Unblinding at the study site for any other reason will be considered a protocol deviation. In all the cases, breaking the blind must be reported, documenting the date, the site personnel exposed to the treatment assignment, and the reason why the blind was broken.

Circumstances leading to emergency unblinding are very rare. Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a patient who presents an emergency condition.

Study medication must be discontinued after emergency unblinding. The patient should be followed-up as appropriate, depending on the reasons for discontinuation of the study.

In addition, as needed to meet regulatory reporting requirements on a country by country basis, designated personnel may be unblinded to treatment status of individual patients. In this circumstance, and if there were no other concerns, neither the sponsor nor the clinical site staff are unblinded to treatment status.

5 STUDY ENDPOINTS

5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change in the CSF p-tau181 from Baseline to Week 78 in the mITT group. The difference in this endpoint between the T-817MA group and the placebo group will be assessed and used for statistical analysis.

5.2 Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints are listed below. For all endpoints, the differences in changes from Baseline in the mITT group between the T-817MA group and the placebo group will be calculated for the timepoints indicated and used for the statistical analysis.

1. The change in cognitive function assessed by CDR-sb and CFC from Baseline to Weeks 28, 52 and 78.
2. The change in the CSF p-tau181 from Baseline to Week 52 in the mITT group
3. The change in the CSF biomarkers p-tau217, total tau, Aβ1-40, Aβ1-42, NFL, neurogranin, YKL-40 and Aβ1-42/Aβ1-40 ratio from Baseline to Weeks 52 and 78.
4. The change in plasma biomarkers Aβ1-40, Aβ1-42, and NFL, GFAP, p-tau181, p-tau217 and Aβ1-42/Aβ1-40 ratio from Baseline to Weeks 52 and 78.
5. The change in Total Brain Volume (TBV), ventricular volume and hippocampal volume and cortical thickness measured by vMRI from Baseline to Weeks 52 and 78
6. The change in alpha/theta ratio measured by the EEG from Baseline to Weeks 52 and 78

5.3 Safety endpoints

1. Occurrence of AEs
2. Physical examinations
3. Vital signs (heart rate, blood pressure and weight)
4. 12-lead (Electrocardiogram) ECG
5. Clinical laboratory tests: hematology, serum biochemistry and urinalysis

6 ANALYSIS POPULATIONS AND GENERAL STATISTICAL PROCEDURES

6.1 Definition of Analysis populations

Analysis populations are defined as follows:

- The Safety population will include all randomized patients who took at least one dose of the study medication.
- The modified Intent-to-Treat (mITT) population will include all randomized patients who took at least one dose of the study medication and who have at least one efficacy evaluation following Baseline.
- The Per Protocol (PP) population will include all mITT patients who did not have any significant protocol deviations.

6.2 Protocol deviations

Protocol deviations resulting in exclusion of the PP population, will be determined at the time of the evaluability assessment, the time between the database soft lock and hard lock before unblinding during a Blinded Data Review Meeting (BDRM).

Possible protocol deviations that lead to exclusion from the PP include, but are not limited to:

- Violation of Inclusion/Exclusion criteria, GCP, Laws and regulations
- Non-compliance to Investigational product i.e., Low drug compliance, misrandomization.
- Prohibited /concomitant medication i.e., Use of prohibited medications
- COVID-19 impact: i.e., Low compliance with assessment schedule
- Other: i.e., Unblinding of treatment

Classification of deviations from the protocol as minor or major, and decisions regarding exclusion of patients and/or patient data from the statistical analyses, will be decided on a case-by-case basis without knowledge of the treatment assigned and before the database lock (blind data review). After database lock, the study statistician will request the treatment codes, the study will be unblinded, and the statistical analysis will be conducted.

Major protocol deviations are defined to be those deviations that could potentially bias the conclusions of the study. Minor deviations are defined to be those deviations not deemed major.

The protocol deviations summary will present the number and percentage of subjects with each deviation category and specific deviation term within each treatment group and overall. In this summary, the total number of protocol deviations and number of subjects with at least one protocol deviation will be tabulated by treatment group and overall.

6.3 Blinded Data Review Meeting

The patients will be classified to the various analysis populations during the BDRM. The BDRM will be held prior to unblinding.

Invitees to this meeting are the data manager, the clinical project manager, medical monitor/clinical expert, sponsor representative and the study statistician, but more roles can be invited if considered necessary. Input to this meeting will be supplied by the involved data

management provider in advance of the meeting: a blinded list of all protocol deviations (including missing and outlier data), with specific detailing and description regarding the deviation. Specific information will be provided where it concerns COVID-related protocol deviations.

The goal of this meeting is to reach consensus on minor and major protocol deviations. In case of a deviation impacting the primary or main secondary endpoints, the specific patient will be excluded from the PP population.

The decisions taken during the meeting will be documented by the project manager (or a delegate as agreed) and sent for review to all parties involved as soon as possible after the meeting, but before database lock. If all parties involved agree, then the document is finalized, signed by all attendees, and stored before database lock by the project manager. After the document is signed and the data are locked, the study is unblinded by the study statistician.

6.4 Application of Analysis Populations

The primary population for efficacy analysis is the mITT population. Analysis of primary and secondary efficacy endpoints will be performed in the mITT and PP populations. The Safety population will be used for analyses of safety endpoints.

When analyzing the mITT and PP population, the analysis will be according to the "as randomized" principle. For the Safety population patients will be analyzed "as treated".

6.5 General Statistical Procedures

All analyses described in this plan are considered *a priori* analyses in that they have been defined prior to breaking the study blind. All other analyses, if any, defined subsequent to breaking the study blind will be considered *post hoc* analyses and will be applied using exploratory methodology. All *post hoc* analyses will be identified as such in the Clinical Study Report.

Descriptive statistics for continuous variables will include number of subjects (n), arithmetic mean, standard deviation (SD), median, minimum, maximum and first and third quartile limits unless otherwise noted. Frequency and percentage will be calculated for categorical variables. Unless stated otherwise, all summary tables will present descriptive statistics and/or frequencies either by treatment or overall, and all data listings will be sorted by subject number.

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

Before applying a statistical analysis model, the CSF biomarker p-tau181 will be converted using a natural logarithm. For other CSF biomarkers the distribution will be checked prior to unblinding and, if considered necessary, the same conversion will be applied. Statistical analysis results will be converted back for any tabular or graphical presentations by applying the exponential function.

The primary efficacy hypothesis is that treatment with T-817MA will result in a statistically significant change in the CSF biomarker p-tau181 relative to the placebo group at Week 78 in the mITT population. The analysis will test the null hypothesis of no difference between the two treatment groups at the 0.05 level.

Change from baseline is calculated by subtracting the baseline score from the observed value at any subsequent visit. For both safety and efficacy summaries, the last pre-randomization measurement is defined as the baseline value. Early termination assessments and visits that occurred too early or too late will be included with the closest scheduled post-baseline visit that includes the efficacy assessment, based on number of days since Day 1. The end of the visit window will not be used for the week 78 visit. This convention results in sequential visit windows so that no data is excluded from analysis. If an early termination visit and a regular visit (other than baseline) both fall within the same visit window, any non-missing efficacy assessments will be averaged and a worst-case approach will be used for safety data.

Analysis visit windows of efficacy endpoints:

Analysis Visit	Baseline[a]	Week 28	Week 52	Week 78
AD related CSF biomarkers	Day -84 to 0	--	Day 190 to 455	Day 456 or after
vMRI parameters	Day -224 to 0	-	Day 190 to 455	
AD related plasma biomarkers, EEG parameters	Day -56 to 0	--	Day 190 to 455	
CFC and CDR-sb	Day -7 to 0	Day 1 to 280	Day 281 to 455	

[a] Baseline will be the last available value before study medication intake within the analysis visit window for efficacy, and this could include Day 1

Analysis visit windows of safety endpoints:

Analysis Visit	Baseline[a]	Week 4	Week 16	Week 28	Week 40	Week 52	Week 65	Week 78	Week 82/Post-Treatment[b]
Vital signs	Day -56 to 0	Day 1 to 63	Day 64 to 147	Day 148 to 231	Day 232 to 315	Day 316 to 406	Day 407 to 504	Day 505 to 553	Post-treatment[b]
ECG	Day -56 to 0			Day 1 to 280		Day 281 to 455		Day 456 to 553	Post-treatment[b]
Hematology, Chemistry, Urinalysis	Day -56 to 0	Day 1 to 63	Day 64 to 147	Day 148 to 231	Day 232 to 315	Day 316 to 406	Day 407 to 504	Day 505 to 553	Post-treatment[b]
Adverse events		a treatment emergent adverse event (TEAE) is defined as an adverse event that appears during or after study treatment.							

[b] Baseline will be the last available value before study medication intake within the analysis window for safety
[b] Post-treatment is defined as a vital signs, physical examination, laboratory, ECG assessment after the day of last study medication intake+ 8 days.

The worst case approach is detailed as follows:

Lab:

- When two observations fall within the same window, the "worst case" should be kept as the value for that visit. The "worst case" is the value that is the furthest out of range (below the low range value or above the high range value), or the value that is closest to the boundary.
- When determining how far out of range each value the standardized range values (LB.LBSTNRLO and LB.LBSTNRHI) will be used for each observation.
- If the observations tie for distance outside of the window (e.g. the first value is one below the low range value and the second value in the window is one above the high range) then the first recorded value will be kept (earliest based on date).

VS:

The "worst case" is determined in the same way as for lab (see above), according to the following reference ranges defined by WHO and/or American Heart Association.
Heart rate: 60 - 100 bpm
Systolic blood pressure: 100 - 140 mmHg
Diastolic blood pressure: 60 - 90 mmHg
BMI (for weight): 18.5 - 25.0

For weight, BMI needs to be calculated first to determine the "worst case". A BMI <18.5 or >=25 is outside of the normal weight range. The worst value is the weight that contributes to the BMI that is furthest outside of this range. When calculating BMI, use the height recorded at the screening visit.

EG:
Worst-case of ECG is when "clinically significant ECG abnormality" is Yes. If all records are the same (i.e. all no or all yes) for all clinically significant ECG abnormalities, then the first recorded value will be kept (earliest based on date).

Percentages are based on the number of subjects in each treatment group and overall in the given population for medical history, prior and concomitant medications and AE summary tables. For all other tables, percentages are based on the number of subjects with non-missing data in each treatment group and overall for the given population.

6.6 Procedures for Handling Missing Data

Patients who drop out will have all available post-baseline data included in the analysis. The primary analysis mixed model is based on an assumption of Missing at Random (MAR) and is designed to handle right censored data for subjects who drop out of the study: this analysis is described in the primary analysis section of this SAP.
One additional analysis will be performed as sensitivity analysis in this study for the primary endpoint. The Missing not At Random (MNAR) sensitivity analysis will use a subject's last observed value. At each subsequent (missing) visit, a value will be imputed such that for all treatment groups the imputed z-score will be assigned relative to the placebo group mean and standard deviation of completers at each visit. This analysis is to estimate the treatment effect expected if active subjects continued to the end of the study with no treatment (or a placebo treatment). After imputation for the sensitivity analyses, the estimated change from baseline between active and placebo group will be assessed by fitting the primary analysis model including covariates and random effect as described in section 8.1. For variables collected post-baseline at week 52 and 78 only: this analysis can only be performed for missing values at Week 78, using the values of Week 52 as last observed value. In case of also missing Week 52 values, no imputation is possible with this approach.
For variables collected post-baseline at week 28, 52 and 78 (cognition):

- if both Weeks 52 and 78 are missing, Week 28 will be used with the imputation approach.
- if Week 78 is observed, and Week 28 and/or Week 52 is missing it will be treated as missing in the analysis and no imputation will be performed.
- if only Week 52 is observed, Week 52 will be used to impute Week 78, and no imputation will be performed for Week 28.

Using the most conservative approach, missing/incomplete information related to AEs will be handled as listed below, to indicate an AE as being treatment emergent or presented having a

certain intensity/causality. Note that the imputed dates or intensity/causality will not appear in data listings, but only in descriptive statistics tables (where applicable).

- In case of (partially) missing onset dates, the AE will be handled as follows:
  - If full start date is available, and on or after first dosing date in each period, the AE is considered treatment emergent.
  - In case full stop date is available and prior to first dosing date in each period, the AE is considered prior.
  - If the day part of the start date is missing:
    - The AE is considered treatment emergent if the month and year of the start date are the same or after the month and the year of the first dosing date.
  - If the day and month part of the start date are missing:
    - The AE is considered treatment emergent if the year of the start date is the same or after the year of the first dosing date.
  - In case the start date is completely missing:
    - If stop date is fully available and on or after the first dosing date, the AE is considered treatment emergent.
    - If the stop date is partially missing, but the month and year (or year alone in case of missing month) are after the month and year (or year alone) of the first dosing date, the AE is considered treatment emergent.
  - In case full start date and full stop date are missing, the AE is considered treatment emergent.

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

Regarding prior/concomitant medication, a similar approach will be followed for partially missing dates, as described above for AEs. If a comedication is started prior to study treatment and continued during study, this is considered concomitant.

For any other missing dates (e.g., date of diagnosis etc.), the following imputations will be done for presentations of descriptive statistics and statistical analyses:

- If the day part is missing, then day will be set to the 15th day of the month.
- If both day part and month part are missing, then day and month will be set to 15 June, unless the year of diagnosis and year of visit 1 (Screening) are the same and visit 1 is before June 15: then the diagnosis date will be set to January 1st of that year.

Missing data could also occur as a consequence of COVID-19 pandemic restrictions. Study specific instructions are described in the protocol, to prohibit missing visits. With the possible approaches, it is assumed that data collection at home/remote visits is of similar quality as data collection during on-site visits. Any missing data will be handled as described in the statistical analysis section and the sensitivity analysis.

6.7 Interim Analysis

As an interim analysis, study continuation is to be assessed by IDMC based on interim efficacy and safety data of 100 patients who have completed treatment for 52 weeks. Since the discontinuation by efficacy superiority is not planned, correction for inflation of the Type I error following the interim analyses is not deemed necessary.

The following stopping rules apply:

- Mean of the change in the CSF p-tau181 from Baseline to Week 52 in the T-817MA group is less than in the Placebo group.
- Critical subject safety issues are identified in the T-817MA group compared to the Placebo group.

Further details for the interim analyses by IDMC will be specified in the IDMC charter and interim analysis plan.

7 SUBJECT DISPOSITION, DEMOGRAPHICS AND BASELINE CHARACERISTICS

7.1 Subject Enrollment

Subject enrollment will be summarized by treatment and country for all populations. The number of subjects overall and at each country for each analysis population will be presented. Study timelines will also be summarized by treatment and overall, for all randomized patients. This summary will include the earliest and latest screening and dosing dates among subjects within each treatment group and overall. It will also list the last patient and the date of his/her last visit within each treatment group and overall. Study duration will be presented in weeks and will be calculated using the following formula:

$$\frac{(Latest\ Week\ 82\ Visit\ Date - Earliest\ Screening\ Date + 1)}{7}$$

where visit 82 is the last known visit date for the patient and can also indicate an early withdrawal visit (Week 78 or Week 82).

Enrollment information will be provided in a data listing by subject.

7.2 Subject disposition

Subject disposition will be summarized overall and by treatment group for all populations. The number and percentage of subjects completing the study and discontinuing from the study will be presented by treatment and overall and by reason for termination in a table.
Cumulative discontinuation rates will be calculated using the Kaplan-Meier method for all reasons combined and for the various reasons separately. Censoring will be at study completion, the last available day of follow-up for patients that discontinue the study early, or death (if occurring). Treatment groups will be compared using a log-rank test.
For both the disposition table and the KM plots, study duration as presented in 7.1 will be used.

Subject disposition will be provided in a data listing by subject.

7.3 Drug exposure

Duration of exposure is defined as the total time a subject is exposed to any study drug. The duration of exposure in weeks will be calculated as follows:

$$\frac{(Last\ Dose\ Date - First\ Dose\ Date + 1)}{7}$$

Extent of exposure to study drug will also be characterized by calculating the cumulative number of milligrams taken by subjects. The duration and extent of exposure to study drug will be summarized by treatment group for both the safety and mITT populations.

The duration of exposure will be summarized by exposure category in weeks (less than or equal to 4 weeks, 4-12 weeks, 12-24 weeks, 24-52 weeks, 52-78 weeks). The extent of exposure will be summarized by number of 112 mg tablets administered with 4 or 5 categorical breakouts determined by distribution of the data. N and percentage of subjects in each population will be displayed. The duration and extent of exposure to study drug will be summarized using descriptive statistics.

7.4 Treatment compliance

Relevant dosing information, scheduled and actual dosing dates, and treatment compliance information, defined as the ratio of the number of doses taken and number of planned doses to be taken times 100% will be listed for each subject and summarized using descriptive statistics.

7.5 Subject Demographic and Baseline Disease Data

Subjects will be described using demographic information and baseline characteristics recorded during the screening phase.

Demographic information to be assessed is age, gender, racial group, ethnicity, smoking status, tobacco use, smoking duration, duration of education, height, weight and body mass index (BMI). Subject demographics will be summarized by treatment for the safety, mITT and PP populations.

Gender, age group (≥75, <75), racial group, smoking status (smoker vs. non-smoker) and other categorical questions will be summarized using the number and percentage of subjects with a particular attribute. The denominators for calculating the percentages will be the number of subjects in each treatment for the safety, mITT, and PP populations. Age, weight, height and other numeric responses will be summarized using descriptive statistics.

Baseline disease characteristics will be provided in a separate summary table, and will display Diagnosis, Time since diagnosis (per diagnosis), baseline MMSE group (Low [24-26], High [27-30]), apoE4s homozygote status, AChE) inhibitors Use (AChE inhibitor use vs. no AChE inhibitor use), and baseline efficacy variables will be summarized using descriptive statistics or number and percentage of subjects by treatment for the safety, mITT and PP populations. Time since diagnosis (weeks) is defined as follows:

$$\frac{(\textit{Date of First Dosing} - \textit{Date of diagnosis of MCI})}{7}$$

Date of diagnosis of MCI for patients is collected as date of diagnosis from DM page in the EDC.

Demographics and baseline disease characteristics will be provided in a data listing by subject.

7.6 Medical History

Medical history will be provided in a data listing by subject.

7.7 Prior and Concomitant Medication

Medication summaries will present the number and percentage of subjects taking medications for the safety population per coded term (i.e. standardized medication name). Summaries will be presented for prior (end date of medication use prior to Day 1) and concomitant (start date of medication use on Day 1 or later) medication use, if applicable.

Specific similar tables will be created for AD medication.

All summaries will present the number and percentage of subjects by treatment.

Prior, concomitant and AD medication will be provided in a data listing by subject.

8 EFFICACY EVALUATIONS

8.1 Statistical analysis primary and secondary endpoints

Analysis of primary and secondary efficacy endpoints (see Section 5.1 and 5.2) will be performed on the mITT, and PP populations. For each endpoint, the analyses will test the null hypotheses of no difference between the two treatment groups using a Mixed-effect Model for Repeated Measures (MMRM). A MMRM including various interaction terms (see Section 8.1.3) will be performed on the mITT population.

Countries will be pooled to ensure that countries as used in the primary and secondary analysis will have a sufficient and comparable number of patients such that the adjustment of country in the analyses will not put undue emphasis on small countries. This will be done by define a “small country” to be a country with 5 or less patients and pool all the “small countries”. If there is only one small country, this country is pooled with the country with the smallest number of patients.

Unscheduled measurements will be excluded from analysis if they lie outside the analysis window for all visits, and only presented in listings.

8.1.1 Primary analysis

The primary efficacy hypothesis is that treatment with T-817MA will result in a statistically significant change in CSF biomarker p-tau181 value relative to the placebo group at Week 78 in the mITT population based on a MMRM analysis using the week 52 and 78 (time) change from baseline data. The analysis will test the statistical hypothesis of no difference in the estimated change from baseline by Least Squares Means (LS Means) between the two treatment groups at week 78.

Before applying a statistical analysis model, the CSF biomarker p-tau181 will be converted using a natural logarithm. Statistical analysis results will be converted back for any tabular or graphical presentations by applying the exponential function.

SAS PROC MIXED will be used to fit an MMRM with the value of change from baseline p-tau181 as the response variable and the following covariates and fixed effects:

- Baseline MMSE (stratification factor): two levels: Low [24-26]/High [27-30]
- Country (stratification factor, random): >2 different categories

- Age at baseline as a covariable
- Baseline p-tau181 as a covariable
- Time (ordered categorical value): Week 52 and Week 78
- Treatment (2 levels): T817MA and Placebo
- Subjid: each patient in the mITT
- Time*Treatment interaction
- ApoE4 status (APOECT4; 2 levels): carrier and non-carrier

```
PROC MIXED;
CLASS Subjid BASMMSE Country Time Treatment APOECT4;
MODEL CHG_ptau=BASMMSE Age Basptau APOECT4 Time Treatment
Time*Treatment/ddfm=kenwardroger;
REPEATED Time/subject=Subjid type=un;
LSMEANS Treatment*Time/slice=Time adjdfe=row diff cl;
RANDOM int/subject=Country;
RUN;
```

The covariance structure for the repeated measures in this model will be unstructured (UN). If UN does not converge for the model, Country will be switched from a random to a fixed factor, if convergence is still not achieved, the MMRM model will be simplified to allow convergence using a first-order heterogenous autoregressive covariance structure (ARH(1)).

Effect of Treatment and Time on p-tau181 will be investigated by the main effects Treatment, Time and Time*Treatment interaction after fitting all covariates in the model. The presence of a Time*Treatment indicates a difference between the 2 treatment groups over time. Therefore, for each timepoint (week 52 and 78) the effect size compared to placebo will be estimated through the LS means based on the model including all covariates, and presented with its 95% confidence interval, taking into account the necessary back-transformation. Effect size will be calculated by taking the difference of LSMEANS and dividing by the standard deviation (i.e. the standard error of the estimated difference multiplied by the square root of the degrees of freedom).

In addition, a standardized effect size based upon Cohen's D will be displayed for treatment comparisons. Cohen's D will be calculated for each timepoint using the following equation, where t1=active treatment (T817MA) and t2=reference treatment (Placebo):

$$\text{Cohen's } D = \frac{M_{t1} - M_{t2}}{Pooled\ SD}.$$

where the pooled standard deviation (pooled SD) is the standard deviation for both treatment groups, determined using the estimated Variance/Covariance matrix from the model.

8.1.2 Secondary analysis

A MMRM will be fitted for each secondary efficacy endpoint using a similar procedure as described for the primary efficacy parameter. This analysis will assess whether or not there is a difference in estimated change from baseline values between treatment groups and placebo at 78 weeks and explore intermediate time points using LS means estimates from the MMRM model.

Regarding the secondary CSF biomarker endpoints: the distribution of each biomarker will be checked prior to unblinding and, if considered necessary, the relevant biomarker will be converted using a natural logarithm before applying a statistical model. Statistical analysis results will be converted back for any tabular or graphical presentations by applying the exponential function.

CFC is collected as a weighted CFC z-score and a ratio of CFC z-score/A-IADL z score. The first one will be used for the statistical analysis, the latter will only be listed. The endpoint CFC comprises of several subscores, which will be presented as well: ADAS-cog, A-IADL-Q, CFT, LFT, WAIS-IV-DS and WAIS-IV-DSST.

- Total score ADAS-cog is calculated as the sum of 3 subscores (Orientation, Word Recall, Word Recognition), and will range from 0-30. The subscores will only be listed.
- The A-IADL-Q score is collected as a T-score.
- Total score CFT and LFT consists of #correct and #incorrect. For the statistical analysis, the #correct will be used. Other variables will only be listed.
- WAIS-IV-DS is collected as WAIS-IV DIGIT SPAN BACKWARD SCORE, and this will be used for the statistical analysis. Other variables will only be listed.
- WAIS-IV-DSST is collected as WAIS-IV DIGIT SYMBOL CODING SCORE, and this will be used for the statistical analysis. Other variables will only be listed.
- For any derived total scores: if a subscore is missing, the total score will also be missing.

For vMRI, post-baseline change in brain volume (total brain, hippocampus, lateral ventricles) is collected as ATROPHY (WHOLE BRAIN/HIPPOCAMPUS/LATERAL VENTRICLES, BILATERAL), and this variable is already presenting a change value. The variable VOLUME (WHOLE BRAIN/HIPPOCAMPUS/LATERAL VENTRICLES, BILATERAL) is the baseline value of this variable.
Other variables for vMRI to be used for the statistical analyses/presentations are as follows in the database for location and lattitude:

- total brain volume = WHOLE BRAIN, BILATERAL
- ventricular volume = LATERAL VENTRICLES, BILATERAL
- hippocampal volume = HIPPOCAMPUS, BILATERAL
- cortical thickness = CORTICAL, BILATERAL; MEDIAL TEMPORAL LOBE, BILATERAL; PRECUNEUS, BILATERAL; PREFRONTAL LOBE, BILATERAL

Remaining vMRI data will only be listed.

For the secondary EEG endpoints: in case the quality of an EEG was not approved, these data will be excluded from statistical analysis. Only quality approved EEG results will be presented. For the change in alpha/theta ration, the variable GLOBAL THETA/ALPHA RATIO will be presented in the statistical analyses. Other EEG data will only be listed.

8.1.3 Explorative analysis using MMRM Including Various Interaction Terms

The model from Section 8.1.1 will be run for the primary endpoint and CFC, CDR-sb with the addition of a specified fixed effect interaction term. Before applying a statistical analysis model, the CSF biomarker p-tau181 will be converted using a natural logarithm. Statistical analysis results will be converted back for any tabular or graphical presentations by applying the exponential function.

The following categorical items at baseline will be included, separately, in the model as a two-way interaction with treatment and a three-way interaction with time and treatment:

- Gender (female vs. male)
- Baseline Age Group (≥75 vs. <75)
- Median Age Group (≥ median vs. < median)
- Smoking status (smoker vs. non-smoker)
- Baseline MMSE Group (≥27 vs. <27)
- ε4 allele of Apolipoprotein E (APOE) 4 Status (homozygotes vs. heterozygotes vs. non-carriers)
- APOE4 Homozygote Status (homozygotes and heterozygotes vs. non-carriers);
- APOE4 Homozygote Status (homozygotes vs. heterozygotes and non-carriers);
- Acetylcholinesterase (AChE) inhibitors Use (AChE inhibitor use vs. no AChE inhibitor use)
- Time Since Diagnosis Median Split (≥ median vs. < median)

LS means and summary statistics will be provided for each level of the factor (e.g. Age≥75, Age<75) at each visit.

LS mean line plots over time will be displayed for each efficacy outcome with separate lines for each treatment.

9 SAFETY EVALUATIONS

9.1 Adverse events

A treatment emergent adverse event (TEAE) is defined as an adverse event that appears during or after study treatment.

An AE overview table will be created displaying the number of subjects (and percentage) experiencing a treatment-emergent adverse event (TEAE) and the number of TEAEs for: Any TEAE, Any mild/moderate/severe TEAE, Any related/unrelated TEAE, Any serious AE, Deaths, Any SUSAR and Any TEAE leading to study discontinuation.

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

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

In addition, for SAEs the following table will be presented:

The difference of proportion of SAEs between treatment arms, including a 95% CI using Newcombe-Wilson score method, will be presented overall and per SOC of patients experiencing an SAE.
In addition, for the frequency of SAEs overall and per SOC, the relative risk (RR) of T817MA versus placebo and associated 95% CI of the RR will be calculated using a Poisson regression

model. The model will utilize a logarithmic link to calculate RR adjusted for the time under observation. For the time under observation the duration of exposure in weeks as defined in 7.3 will be used.
Only in case of a large number of SAEs, will the above SAE presentation be made on SOC/PT level instead of per SOC: if at SOC level there are at least 5 events per treatment arm, then it will be investigated if presenting on PT level can be added.

Separate listings will be created for AEs leading to discontinuation, SAEs and deaths, if applicable.

For summary tables, an AE is considered related if the causality to the study medication is classified as either 'Definitely Related', 'Probably Related' of 'Possibly Related'. Otherwise, it will be considered unrelated for summary tables. The original description will be used in listings.

9.2 Clinical laboratory

Laboratory safety data for hematology, biochemistry and urinalysis will be summarized (n, mean, SD, median, minimum and maximum for quantitative data, or frequency and percentage for qualitative data) and listed per visit and treatment group, using protocol visits. Change from baseline will be calculated and presented as well for quantitative data, using the same summary statistics. If applicable, laboratory safety data collected as additional/unscheduled assessments (i.e. apart from those per protocol) will only be listed and will not be used in summary statistics.

Frequencies of high and low values with respect to the normal range will be displayed, as will shift tables comparing each treatment visit (Weeks 4, 16, 28, 40, 52, 65, 78 and 82) and Baseline visit by time point and treatment group. Urinalysis values will be cross-summarized at pre-dose and post-dose.

For laboratory safety data, all recorded and determined laboratory safety data will be listed. Safety laboratory parameters will be presented in the tables and listings in the same (standardized) units as supplied.

Lastly, for clinical laboratory parameters, a listing will be created presenting all data that are out of reference range on a per-subject level. The investigator judges the out-of-range values on their clinical significance, and this information will be added as well.

9.3 Vital Signs

Vital sign data consist of measurements for heart rate, systolic, diastolic blood pressure and weight. Vital signs will be summarized (n, mean, SD, median, minimum and maximum) and listed per visit and per treatment group, using protocol visits. Change from baseline will be calculated and presented as well, using the same summary statistics. If applicable, vital sign measurements collected as additional/unscheduled assessments (i.e. apart from those per protocol) will only be listed and will not be used in summary statistics.

9.4 ECG

ECG data consist of measurements for PR interval, QRS duration, QT interval, RR interval, and QTc corrected by Fridericia. ECG parameters will be summarized (n, mean, SD, median, minimum and maximum) and listed per visit and per treatment group, using protocol visits. Change from baseline will be calculated and presented as well, using the same summary statistics.

ECG outcome results collected as normal/abnormal will be presented descriptively using frequency counts and percentages per treatment group, using protocol visits. If applicable, ECG results collected as additional/unscheduled assessments (i.e. apart from those per protocol) will only be listed and will not be used in summary statistics.

9.5 Physical examination

General physical examination data will be listed.

10 CHANGES FROM PROTOCOL

No changes.

11 DATA RECEIPT

All data will be received as raw SAS files from <sponsor/vendor>, per transfer agreement. The raw SAS files will be programmed to CDISC standards (SDTM and ADaM) before programming of the tables, listings and figures is done. With regards to PK, the following process will be adhered to. As concentration data are provided in the eCRF, the CDISC package including PC domain (without other PK domains) is created and finalized by Certara. After receiving CDISC package from Certara, FFTC will perform PPK analyses using the PC domain according to the population PK analysis plan, and the results (tables, listings and figures) of the PPK analysis will be shared with Certara for CSR documentation. FFTC will update the CDISC package, including PPK files (e.g. ADPC, ADPP), SDTM RELREC and CDISC documentation, including the relevant SAS coding for these.

12 TECHNICAL DETAILS

12.1 Programming conventions

BMI will be calculated in SAS as follows: weight/height^2, with weight in kg and height in meter (unit kg/m^2). Durations will be programmed as stated in the respective analysis sections. Where applicable, weight and height measurements will be converted to units cm and kg, respectively, using the following conversion factors: from inch to cm: multiply by 2.54, from lb to kg: multiply by 0.45359237.

12.2 Coding

Coding of adverse events, concomitant medication and medical history will be performed by the Data Management provider. Adverse events and medical history are coded with the MedDRA coding system using the latest version at data base lock. Concomitant medication will be coded according to the World Health Organization (WHO) drug dictionaries and the ATC class code: version WHO Drug Global (B3) 2021 Sep. CTCAE (Common Terminology Criteria for Adverse Events) version 5.00 will be used to grade adverse events.

12.3 Analysis software

The statistical analysis and reporting will be done using SAS® for Windows™ version 9.4.

SAS tabular output (tables and listings) will be saved in pdf format. Output of selected tables and listings in RTF format will be available on request. SAS graphs will be saved in PNG format.

12.4 Presentation of tables, listings, graphs

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

All tables and listings will be created such that they fit landscape pages, following the page format and margins of the Clinical Study Report (CSR) template to be used. The tables for the end-of-text and listings for the appendix will be created using SAS and Courier new fontsize 8.

13 TABLES, LISTINGS, GRAPHS

13.1 General

A detailed list of tables, graphs and listings is presented, if applicable, per report section in sections 13.2, 13.3 and 13.4. Template tables and listings as well as *example* plots (as received from client or extracted from a relevant paper) will be used as a reference for creation of all output, and a separate document will be created for this. Table/graph/listing numbering will be followed, however, if the data give cause for combining or splitting tables or listings, numbering may be adapted by the programmer as necessary.

13.2 In-text tables and graphs

In-text tables and graphs will be designed or extracted by the Medical Writer during creation of the Clinical Study Report, based on the tables and graphs created for section 14 of the CSR.

13.3 End-of-text tables and graphs

Following ICH E3 guidelines, all tables and graphs mentioned here will be presented in Section 14 of the CSR.

Type	Number	Contents	Topline
14.1 Demographic Data Summary figures and tables			
Table	14.1.1	Summary of Subject Disposition by treatment	(X)
Graph	14.1.1.1	Kaplan-Meier Plot of Time to Any Discontinuation	
Graph	14.1.1.X	Kaplan-Meier Plot of Time to << Reason>>	
Table	14.1.2	Summary of Drug Exposure (including compliance) by treatment	
Table	14.1.3	Summary of Study Duration	
Table	14.1.4	Summary of Protocol Deviations	
Table	14.1.5	Demographic Data by treatment	(X)
Table	14.1.6	Baseline Characteristics by treatment	
Table	14.1.7	Summary of Prior Medication by treatment	
Table	14.1.8	Summary of Prior AD Medication by treatment	
Table	14.1.9	Summary of Concomitant Medication by treatment	
Table	14.1.10	Summary of Concomitant AD Medication by treatment	
Table	14.1.11	Summary of Number of Treated Subjects by center	(X)
Table	14.1.12	Summary of Analysis Populations	(X)
14.2 Efficacy Data Summary figures and Tables			
Table	14.2.1.1	Descriptive Statistics of CSF p-tau181, absolute and change from baseline values by treatment and visit	X
Table	14.2.1.2	PROC MIXED statistics and LSMEANS of CSF p-tau181, change from baseline by visit	X
Graph	14.2.1.3	LSMEAN (SE) of CSF p-tau181, change from baseline by visit	X
Table	14.2.1.4	Explorative analysis of CSF p-tau181, using MMRM Including Various Interaction Terms	X

Table	14.2.1.5-14.2.1.12	Descriptive Statistics of CSF biomarkers (p-tau217, total tau, Aβ1-42, Aβ1-40, Aβ1-42/Aβ1-40 ratio, NFL, neurogranin, YKL) absolute and change from baseline values by treatment and visit	X
Table	14.2.1.13-14.2.1.20	PROC MIXED statistics and LSMEANS of CSF biomarkers (p-tau217, total tau, Aβ1-42, Aβ1-40, Aβ1-42/Aβ1-40 ratio, NFL, neurogranin, YKL), change from baseline by visit	X
Graph	14.2.1.21-14.2.28	LSMEAN (SE) of CSF biomarkers (p-tau217, total tau, Aβ1-42, Aβ1-40, Aβ1-42/Aβ1-40 ratio, NFL, neurogranin, YKL), change from baseline by visit	X
Table	14.2.2.29-14.2.35	Descriptive Statistics of plasma biomarkers (p-tau181, p-tau217, Aβ1-42, Aβ1-40, Aβ1-42/Aβ1-40 ratio, NFL, GFAP) , absolute and change from baseline values by treatment and visit	X
Table	14.2.2.36-14.2.42	PROC MIXED statistics and LSMEANS of plasma biomarkers (p-tau181, p-tau217, Aβ1-42, Aβ1-40, Aβ1-42/Aβ1-40 ratio, NFL, GFAP), change from baseline by visit	X
Graph	14.2.2.43-14.2.2.49	LSMEAN (SE) of plasma biomarkers (p-tau181, p-tau217, Aβ1-42, Aβ1-40, Aβ1-42/Aβ1-40 ratio, NFL, GFAP), change from baseline by visit	X
Table	14.2.3.1	Descriptive Statistics of total brain volume and atrophy by treatment and visit	
Table	14.2.3.2	PROC MIXED statistics and LSMEANS of total brain volume by visit	
Graph	14.2.3.3	LSMEAN (SE) of total brain volume by visit	
Table	14.2.3.4	Descriptive Statistics of ventricular volume and atrophy by treatment and visit	
Table	14.2.3.5	PROC MIXED statistics and LSMEANS of ventricular volume by visit	
Graph	14.2.3.6	LSMEAN (SE) of ventricular volume by visit	
Table	14.2.3.7	Descriptive Statistics of hippocampal volume and atrophy by treatment and visit	
Table	14.2.3.8	PROC MIXED statistics and LSMEANS of hippocampal volume by visit	
Graph	14.2.3.9	LSMEAN (SE) of hippocampal volume by visit	
Table	14.2.3.10-14.2.3.13	Descriptive Statistics of cortical thickness (cortical, bilateral; medial temporal lobe, bilateral; precuneus, bilateral; prefrontal lobe, bilateral), absolute and change from baseline values by treatment and visit	
Table	14.2.3.14-14.2.3.17	PROC MIXED statistics and LSMEANS of cortical thickness (cortical, bilateral; medial temporal lobe, bilateral; precuneus, bilateral; prefrontal lobe, bilateral), change from baseline by visit	
Graph	14.2.3.18-14.2.3.21	LSMEAN (SE) of cortical thickness (cortical, bilateral; medial temporal lobe, bilateral; precuneus, bilateral; prefrontal lobe, bilateral), change from baseline by visit	
Table	14.2.4.1	Descriptive Statistics of clinical dementia rating (sum of boxes), absolute and change from baseline values by treatment and visit	X
Table	14.2.4.2	PROC MIXED statistics and LSMEANS of clinical dementia rating (sum of boxes), change from baseline by visit	X
Graph	14.2.4.3	LSMEAN (SE) of clinical dementia rating (sum of boxes), change from baseline by visit	X

Table	14.2.4.4	Explorative analysis of clinical dementia rating (sum of boxes), using MMRM Including Various Interaction Terms	X
Table	14.2.4.5	Descriptive Statistics of cognitive function composite (CFC) z-score, absolute and change from baseline values by treatment and visit	X
Table	14.2.4.6	PROC MIXED statistics and LSMEANS of cognitive function composite (CFC) z-score, change from baseline by visit	X
Graph	14.2.4.7	LSMEAN (SE) of cognitive function composite (CFC) z-score, change from baseline by visit	X
Table	14.2.4.8	Explorative analysis of CFC, using MMRM Including Various Interaction Terms	X
Table	14.2.4.9	Descriptive Statistics of total score ADAS-cog, absolute and change from baseline values by treatment and visit	
Table	14.2.4.10	PROC MIXED statistics and LSMEANS of total score ADAS-cog, change from baseline by visit	
Graph	14.2.4.11	LSMEAN (SE) of total score ADAS-cog, change from baseline by visit	
Table	14.2.4.12	Descriptive Statistics of A-IADL, absolute and change from baseline values by treatment and visit	
Table	14.2.4.13	PROC MIXED statistics and LSMEANS of A-IADL, change from baseline by visit	
Graph	14.2.4.14	LSMEAN (SE) of A-IADL, change from baseline by visit	
Table	14.2.4.15	Descriptive Statistics of CFT (#correct), absolute and change from baseline values by treatment and visit	
Table	14.2.4.16	PROC MIXED statistics and LSMEANS of CFT (#correct), change from baseline by visit	
Graph	14.2.4.17	LSMEAN (SE) of CFT (#correct), change from baseline by visit	
Table	14.2.4.18	Descriptive Statistics of LFT (#correct), absolute and change from baseline values by treatment and visit	
Table	14.2.4.19	PROC MIXED statistics and LSMEANS of LFT (#correct), change from baseline by visit	
Graph	14.2.4.20	LSMEAN (SE) of LFT (#correct), change from baseline by visit	
Table	14.2.4.21	Descriptive Statistics of WAIS-IV-DS (DSB), absolute and change from baseline values by treatment and visit	
Table	14.2.4.22	PROC MIXED statistics and LSMEANS of WAIS-IV-DS (DSB), change from baseline by visit	
Graph	14.2.4.23	LSMEAN (SE) of WAIS-IV-DS (DSB), change from baseline by visit	
Table	14.2.4.24	Descriptive Statistics of WAIS-IV-DSST (BSC), absolute and change from baseline values by treatment and visit	
Table	14.2.4.25	PROC MIXED statistics and LSMEANS of WAIS-IV-DSST (BSC), change from baseline by visit	
Graph	14.2.4.26	LSMEAN (SE) of WAIS-IV-DSST (BSC), change from baseline by visit	
Table	14.2.5.1	Descriptive Statistics of alpha/theta ratio, absolute and change from baseline values by treatment and visit	

Table	14.2.5.2	PROC MIXED statistics and LSMEANS of alpha/theta ratio, change from baseline by visit	
Graph	14.2.5.3	LSMEAN (SE) of alpha/theta ratio, change from baseline by visit	
Table	14.2.6.1	Correlation table of primary and secondary endpoints	
14.3 Safety Data Summary Tables			
Table	14.3.1.1	Overview of Adverse Events	(X)
Table	14.3.1.2	Incidence of Subjects with Treatment Emergent Adverse events by SOC and PT	(X)
Table	14.3.1.3	Incidence of Subjects with Related Treatment Emergent Adverse events by SOC and PT	
Table	14.3.1.4	Incidence of Subjects with Treatment Emergent Adverse events by severity by SOC and PT	
Table	14.3.1.5	Incidence of Subjects with Treatment Emergent Adverse Events causing discontinuation by SOC and PT	
Table	14.3.2.1	Incidence of Deaths by SOC and PT	
Table	14.3.2.2	Incidence of Subjects with Treatment Emergent Serious Adverse events by SOC and PT	
Table	14.3.2.3	Incidence of Subjects with Related Treatment Emergent Serious Adverse events by SOC and PT	
Table	14.3.2.4	Incidence of Subjects with Treatment Emergent Serious Adverse events by severity by SOC and PT	
Table	14.3.2.5	Statistics on incidence of Subjects with Treatment Emergent Serious Adverse events	
Table	14.3.3.1	Abnormal values Hematology by treatment and visit	
Table	14.3.3.2	Abnormal values Chemistry by treatment and visit	
Table	14.3.3.3	Abnormal values Urinalysis by treatment and visit	
Table	14.3.3.4	Shift tables of Hematology parameters by treatment and visit	
Table	14.3.3.5	Shift tables of Chemistry parameters by treatment and visit	
Table	14.3.4.1	Descriptive Statistics Hematology parameters by treatment and visit	
Table	14.3.4.2	Descriptive Statistics Chemistry parameters by treatment and visit	
Table	14.3.4.3	Descriptive Statistics Urinalysis parameters by treatment and visit	
Table	14.3.5.1	Descriptive Statistics of Vital Signs by treatment and visit	
Table	14.3.6.1	Descriptive Statistics of ECG parameters by treatment and visit	

X = will be part of topline results
(X) = will be added to topline results if time permits

13.4 Listings

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

Individual listings will be prepared of all the data collected in the database, following SDTM data format. The key variables in the listings (except a few displaying screening data) will be

patient number and treatment. |For lab safety, gender and age will be added. If applicable, visit number will be listed additionally. Furthermore, a listing containing study visit dates will be presented. Where applicable, screen failed subjects will be flagged in the listings.

Type	Number	Contents
Listing	16.2.1.1	Inclusion/exclusion criteria – description
Listing	16.2.1.2	Inclusion/exclusion criteria – deviations
Listing	16.2.1.3	Patient disposition
Listing	16.2.2	Protocol deviations
Listing	16.2.3	Patients Excluded from the Efficacy Analysis Population
Listing	16.2.4.1	Demographics
Listing	16.2.4.2	Baseline characteristics: MCI/Alzheimer Disease History
Listing	16.2.4.3	Medical history
Listing	16.2.5.1	Treatment exposure
Listing	16.2.5.2	Drug accountability and compliance
Listing	16.2.5.3	Study visits
Listing	16.2.6.1	CSF biomarkers
Listing	16.2.6.2	Plasma biomarkers
Listing	16.2.6.3	vMRI parameters
Listing	16.2.6.4	Cognitive function parameters
Listing	16.2.6.5	EEG parameters
Listing	16.2.7.1	Adverse events
Listing	16.2.7.2	SAEs
Listing	16.2.7.3	Deaths
Listing	16.2.7.4	AEs leading to discontinuation from the study
Listing	16.2.7.5	Vital signs
Listing	16.2.7.6	ECG
Listing	16.2.7.7	Physical Examination
Listing	16.2.7.8	Prior and concomitant medication
Listing	16.2.8.1	Laboratory safety data – haematology
Listing	16.2.8.2	Laboratory safety data – chemistry
Listing	16.2.8.3	Laboratory safety data - urinalysis