FUJIFILM Toyama Chemical Co.,Ltd.

CLINICAL STUDY PROTOCOL

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

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1. SYNOPSIS

PROTOCOL 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
INDICATION	Mild cognitive impairment (MCI) due to Alzheimer's disease (AD) and mild AD.
OBJECTIVES	Primary objective: 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 MCI due to AD or mild AD. 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 the Cognitive Functional Composite (CFC). • AD-related biomarkers in CSF and plasma • 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 adverse events (AEs). To evaluate the pharmacokinetics of T-817MA in plasma and CSF.
PRIMARY ENDPOINT	The change in the CSF p-tau181 from Baseline to Week 78.
SECONDARY ENDPOINTS	• The change in the CSF p-tau181 from Baseline to Week 52 • The change in AD-related biomarkers in CSF (p-tau217, total tau, Aβ1-42, Aβ1-40, neurofilament light [NFL], neurogranin, YKL-40 and Aβ1-42/Aβ1-40 ratio) from Baseline to Weeks 52 and 78 • The change in AD-related biomarkers in plasma (Aβ1-42, Aβ1-40, NFL, glial fibrillary acidic protein [GFAP], p-tau181, p-tau217 and Aβ1-42/Aβ1-40 ratio) from Baseline to Weeks 52 and 78 • The change in cognitive function assessed by CDR-sb and the CFC from Baseline to Weeks 28, 52 and 78

SECONDARY ENDPOINTS (CONTINUED)	• The change in brain volume (total brain volume (TBV), ventricular volume and hippocampal volume) and cortical thickness measured by vMRI from Baseline to Weeks 52 and 78 • The change in alpha/theta ratio measured by the EEG from Baseline to Weeks 52 and 78 • Safety as assessed by the occurrence of AEs, clinical laboratory tests, vital signs, physical examinations, ECGs • Population pharmacokinetics (PPK) analysis of T-817MA with assessment of maximum plasma concentration (C_{max}), minimum plasma concentration (C_{min}), and area under the plasma concentration-time curve during a dosage interval (AUC_{tau}) at steady-state. • The ratio of T-817 levels in CSF to plasma (CSF/plasma)
STUDY DESIGN	This is a Phase 2 proof of concept (PoC), multi-center, randomized, double-blind, placebo-controlled, parallel group study to assess the effect of T-817MA on CSF biomarkers including p-tau181 compared with placebo in high-risk individuals with MCI due to AD or mild AD. A screening visit at clinical sites will be followed by central review of screening. At Baseline, patients who have passed the central review will be randomized to placebo or T-817MA 448 mg in a 1:1 ratio. Patients will be seen at Week 4, 16, 28, 40, 52, 65, and 78. A final follow-up visit will be conducted at Week 82. Safety evaluations will be carried out at each visit. Patients will undergo lumbar puncture at Screening and at Weeks 52 and 78 to evaluate CSF biomarkers. CSF samples taken at Weeks 52 and 78 will additionally be used to perform PK analysis. The vMRI scans of the brain will be done at Screening and Weeks 52 and 78. The EEG will be done at Baseline and Weeks 52 and 78. Cognitive and memory function will be assessed at Screening, at Baseline and at Weeks 28, 52 and 78. Blood collection for PPK assessments will be done at Weeks 16, 28, 40 and 65, and for plasma biomarkers at Baseline, Weeks 52 and 78.
SAMPLE SIZE	The sample size determination for this study is based on the results of the biomarker assay in CSF samples from the previous phase 2 study targeting mild to moderate AD (Study US202) by Amsterdam UMC, location VUmc, the central biomarker laboratory for the current study. The mean p-tau181 level in CSF samples from the T-817MA 448 mg group was 2.43 pg/mL lower than in the placebo group. A sample size of 61 patients per group provides 80% power at a significance level of alpha = 0.05, using the t-test. 100 patients per group (total 200 patients) will be enrolled assuming about 40% premature discontinuation.

KEY ELIGIBILITY CRITERIA	Inclusion: • Female of non-childbearing potential or male, ages 50 to 80 years (inclusive) • MCI due to AD or mild AD per NIA-AA diagnostic criteria (Jack et al., 2018), with MMSE 24 to 30 (inclusive) • CSF results at Screening consistent with the presence of Aß42 and p-tau181 abnormality (≤1000 pg/ml for Aß42, ≥19 pg/ml for p-tau181) or (p-tau181/Aß42 ratio >0.020 for patients with p-tau181 ≥19 pg/ml and 1000<Aß42<1700 pg/ml). • Taking stable dose of AChE inhibitor (donepezil, galantamine or rivastigmine) at least for 3 months prior to randomization, or not taking any AChE inhibitors. Exclusion: • MRI of the brain within the previous 2 years that showed pathology that would be inconsistent with a diagnosis of AD • Taking memantine • Any contraindications to lumbar puncture • Any contraindications to MRI
DRUG DOSAGE AND FORMULATION	T-817MA (448 mg/day) or matching placebo. The T-817MA group will be started at 224 mg for 4 weeks, and then increased to 448 mg. The study medication will be taken orally once daily. Film-coated tablets of 224 mg T-817MA or placebo will be dispensed in blister packs.
ROUTE OF ADMINISTRATION	Oral
TREATMENT DURATION	Duration of treatment is 78 weeks. There is a screening period between 1 and 8 weeks prior to randomization and a 4-week post-treatment observation period. 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.
COVID-19 APPENDIX	To prepare for possible new waves of COVID-19 or other infections in the participating countries and to minimize its effect on sites, patient safety and scientific integrity of the study data, this appendix describes how to conduct the study in case a new wave of COVID-19 or other infection occurs. On-site visits, if possible, are strongly preferred. The decision to schedule an on-site visit, a remote visit or a home visit is up to the discretion of the Principal Investigator.

1.1 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.

TABLE OF CONTENTS

1. SYNOPSIS 3
1.1 SCHEDULE OF ACTIVITIES 6
List of Abbreviations 10
2. INTRODUCTION 12
2.1 BACKGROUND 12
2.2 PRECLINICAL PHARMACOLOGY AND PHARMACOKINETICS 12
2.3 SAFETY PHARMACOLOGY AND TOXICOLOGY 13
2.4 CLINICAL EXPERIENCE 13
2.5 RATIONALE FOR THE CURRENT STUDY 14
2.6 POTENTIAL RISKS AND BENEFITS ASSOCIATED WITH THIS STUDY 14
3. OBJECTIVES 15
3.1 PRIMARY OBJECTIVE 15
3.2 SECONDARY OBJECTIVES 15
4. ETHICS AND REGULATORY CONSIDERATIONS 15
4.1 ETHICS AND REGULATIONS 15
4.2 COMPETENT REGULATORY AUTHORITY AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE 15
4.3 INFORMED CONSENT 16
5. RATIONALE FOR STUDY DESIGN 16
5.1 DOSE SELECTION 17
5.2 LENGTH OF STUDY 17
5.3 PATIENT SELECTION 17
5.4 PLACEBO CONTROL 17
5.5 RATIONALE FOR ENDPOINTS 17
6. STUDY DESIGN 18
7. STUDY DRUG AND CONCOMITANT MEDICATIONS 19
7.1 STUDY MEDICATION 19
7.2 CODING AND PACKING 19
7.3 BLINDING 20
7.4 RANDOMIZATION AND MEDICATION ORDERING SYSTEM 20
7.5 LABELING 20
7.6 DOSAGE REGIMEN 20
7.7 DRUG ACCOUNTABILITY 21
7.8 TREATMENT OF OVERDOSAGE 21
7.9 CONCOMITANT MEDICATION 21
7.9.1 Concomitant AD Medication 21
7.9.2 Prohibited Concomitant Medications 21
7.9.3 Permitted Concomitant Medications 22
8. PATIENT SELECTION 23
8.1 INCLUSION CRITERIA 23
8.2 EXCLUSION CRITERIA 24
9. STUDY PROCEDURES 25
9.1 STUDY VISITS 25
9.1.1 Screening (between 7 and 56 days prior to randomization) 25
9.1.2 Baseline Visit (Week 0, from -7 days to randomization) 27
9.1.3 Week 4 (± 7 days) 27
9.1.4 Week 16 (± 7 days) 28
9.1.5 Week 28 (± 7 days) 28
9.1.6 Week 40 (± 7 days) 28
9.1.7 Week 52 (± 7 days) 29
9.1.8 Week 65 (± 7 days) 29
9.1.9 Week 78 (± 7 days)/End of Treatment or Premature Discontinuation 30
9.1.10 Week 82 (± 7 days)/Follow-up 31
9.1.11 Rescreening 31
9.2 CSF AND PLASMA BIOMARKER ASSESSMENTS 31
9.3 LABORATORY SAFETY ASSESSMENTS 32

9.4 PHARMACOKINETIC ASSESSMENTS....32
9.5 GENOTYPING....32
9.6 vMRI ASSESSMENTS....32
9.7 EEG ASSESSMENTS....33
9.8 DISEASE SCALES....33
10. PREMATURE DISCONTINUATION/WITHDRAWAL PROCEDURES....33
11. EFFICACY, SAFETY, and OTHER EVALUATIONS....34
11.1 ASSESSMENT OF EFFICACY....34
11.1.1 Assessments Used for the Primary Endpoint....34
11.1.2 Assessments related to Secondary Endpoints....34
11.2 ASSESSMENT OF SAFETY....35
11.3 ASSESSMENT OF PHARMACOKINETICS....35
12. DEFINITION OF ADVERSE EVENT....35
12.1 EVALUATION AND REPORTING OF ADVERSE EVENTS....36
12.2 ASSESSMENT OF ADVERSE EVENTS....36
12.3 SERIOUS ADVERSE EVENTS....37
12.4 SERIOUS ADVERSE EVENT REPORTING REQUIREMENTS....38
12.5 OVERDOSE REPORTING REQUIREMENTS....38
12.6 CLINICAL LABORATORY ABNORMALITIES AND OTHER ABNORMAL ASSESSMENTS....39
12.7 PREGNANCY AND BREAST FEEDING....39
13. STATISTICAL METHODS....39
13.1 SAMPLE SIZE DETERMINATION....39
13.2 RANDOMIZATION AND STRATIFICATION....40
13.3 PROTOCOL DEVIATIONS, DATA BLIND REVIEW, AND UNBLINDING....40
13.4 ANALYSIS POPULATIONS....40
13.5 EFFICACY ENDPOINTS....40
13.5.1 Primary Efficacy Endpoint....40
13.5.2 Secondary Efficacy Endpoints....40
13.6 SAFETY ENDPOINTS....41
13.7 STATISTICAL METHODS....41
13.7.1 Efficacy Analysis....41
13.7.2 Safety Analysis....41
13.8 POPULATION PHARMACOKINETIC ANALYSIS....42
13.9 INTERIM ANALYSES....42
14. RECORDING AND COLLECTION OF DATA....42
14.1 CASE REPORT FORM....42
14.2 STUDY FILES AND PATIENT SOURCE DOCUMENTS....43
14.3 MONITORING....43
14.4 AUDIT....43
14.5 RETENTION OF DATA....43
14.6 REPORTING OF STUDY RESULTS....44
14.7 QUALITY ASSURANCE/ QUALITY CONTROL....44
15. PUBLICATION POLICY....44
16. REFERENCES....44
17. APPENDIX 1: STUDY-SPECIFIC INSTRUCTIONS IN CASE OF RESTRICTIONS TO REGULAR STUDY CONDUCT DUE TO COVID-19 OR OTHER INFECTIONS....46
17.1 BACKGROUND....46
17.2 HOME / REMOTE STUDY VISITS....46
17.3 DISPENSING OF STUDY MEDICATION....47
17.4 TIMING OF OBTAINING SAFETY INFORMATION (COLLECTION AND FOLLOW-UP OF [S]AE, LABORATORY ASSESSMENTS, PHYSICAL EXAMINATION, VITAL SIGNS, ECG)....48
17.5 TIMING OF LUMBAR PUNCTURE, MRI, EEG, COGNITIVE TESTS PROCEDURES AND COLLECTION OF BIOMARKERS AND PK SAMPLES....48
17.6 DISCONTINUATIONS....49

LIST OF ABBREVIATIONS

Aß	Amyloid ß
AChE	Acetylcholinesterase
AD	Alzheimer's disease
ADAS-cog	Alzheimer's disease assessment scale-cognitive subscale
ADCS-CGIC	Alzheimer's Disease Cooperative Study- Clinical Global Impressions of Change
AE	Adverse Event
A-IADL-Q	Amsterdam Instrumental Activity of Daily Living Questionnaire
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
Amsterdam UMC	Amsterdam University Medical Center
ApoE	ε4 allele of Apolipoprotein E
ASCII	American Standard Code for Information Interchange
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BUN	Blood Urea Nitrogen
CA	Competent Authority
CDR-sb	Clinical Dementia Rating Scale Sum of Boxes
CFC	Cognitive Functional Composite
CFT	Category Fluency Test
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
COVID-19	Coronavirus disease 2019
CrCl	Creatinine clearance
CRMM	Central Review Medical Monitor
CRO	Contract Research Organization
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome 450
DDI	Drug-drug Interaction
DRP	Data Review Plan
DSM 5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ECG	Electrocardiogram
EDC	Electronic Data Capture
EEA	European Economic Area
EEG	Electroencephalogram
EU	European Union
FT3	Free Triiodothyronine
FT4	Free Thyroxine
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GFAP	Glial Fibrillary Acidic Protein
GMP	Good Manufacturing Practice
γ-GT	γ-glutamyltransferase
HDL	High Density Lipoprotein

ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LFT	Letter Fluency Test
MAP-2	Microtubule-Associated Protein 2
MCI	Mild Cognitive Impairment
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-treat
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
NFL	Neurofilament Light
NIA-AA	National Institute of Aging-Alzheimer's Association
PI	Principal investigator
PK	Pharmacokinetic
PoC	Proof of Concept
PP	Per Protocol
PPK	Population pharmacokinetics
QD	Quaque Die (once per day)
RBC	Red blood cell count
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOP	Standard Operating Procedure
TBV	Total Brain Volume
TC	Total cholesterol
TG	Triglyceride
TSH	Thyroid stimulating hormone
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]
ULN	Upper Limit of Normal
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
WHO	World Health Organization
WOCBP	Women of childbearing potential

2. INTRODUCTION

A comprehensive review of T-817MA is contained in the most recent Investigator's Brochure [Investigator's Brochure on T-817MA] supplied by the sponsor, FUJIFILM Toyama Chemical Co., Ltd.

2.1 Background

Alzheimer disease's (AD), first characterized in 1907 by Alois Alzheimer, is a neurodegenerative disease characterized by progressive impairment in memory and cognitive function and is a major concern as a cause of dementia in our aging society [Dipiro et al., 1996]. According to the 2013 Dementia in Europe Yearbook, almost 9 million people in Europe are affected, corresponding to 1.5% of the population, while in the United States almost 6 million people are afflicted with this disease and in excess of 450,000 cases are diagnosed every year. Affecting twice as many females as males, AD is thought to be mainly due to genetic factors, however, several environmental factors are known to contribute to its evolution [Alzheimer Europe, 2013; Alzheimer's Association, 2018]. Dementia is also the leading cause of disability in persons aged 60 years and older, and its direct and indirect costs are very high [WHO, 2003; Langa et al., 2001]. It has been discovered that pathological changes such as amyloid β (Aβ) and tau protein accumulation in the brain and neurodegeneration precedes memory and functional impairment of AD [Buchhave et al., 2012]. Therefore, mild cognitive impairment (MCI) (i.e. patients complain about their memory without impairment of daily activities) due to AD and early AD is becoming a target of potential disease-modifying drugs.

T-817MA is a low molecular weight compound, which has protective effects against various types of neuronal damage (Aβ, reactive oxygen species etc.), being developed by FUJIFILM Toyama Chemical Co., Ltd. It could therefore be a valuable therapeutic option in MCI due to AD and mild AD and should be more fully developed to investigate its safety and efficacy.

2.2 Preclinical Pharmacology and Pharmacokinetics

Nonclinical pharmacology studies using in vitro and in vivo models have shown that T-817MA acts on both neurons and glial cells, resulting in neuroprotection and preservation of neural network.

Preservation of neurons/neuronal processes against Aß-induced degeneration
Cortical neurons from rat embryos were cocultured with mixed culture of astrocytes and microglia for 8–9 days. The cocultures were exposed to various concentrations of T-817MA (0, 0.01, 0.1, 1.0 µmol/L) and 10 µmol/L Aß1-42 for 48 hours. Enzyme immunoassay for dendritic protein, microtubule-associated protein 2 (MAP-2), revealed that T-817MA at concentrations of 0.1 and 1.0 µmol/L significantly inhibited a reduction in MAP-2 immunoreactivity by the exposure to Aß. This result indicates that T-817MA has a dose-dependent neuroprotective effect against Aß-induced degeneration of neurites in a condition including astrocytes and microglia.

Protective effects on neurons
Cortical neurons from rat embryos were cultured and exposed to hydrogen peroxide with pre-treatment of various concentrations of T-817MA (0, 0.01, 0.1, 1.0 µmol/L). The hydrogen peroxide-induced cell death and decrease in glutathione content were prevented by T-817MA at concentrations of 0.1 and 1.0 µmol/L. These results indicate that T-817MA has a direct neuroprotective effect on neurons via preservation of intracellular anti-oxidative capacity.

Effects on microglial cells
Chronic activation of microglial cells is indicated to be involved in the development of AD pathology. Recent studies showed that T-817MA acts on microglial cells and accelerates phagocytosis of Aß, a homeostatic function of microglial cells. This result indicates that T-817MA might affect AD pathology by modulating microglial function.

Synaptic preservation in the hippocampus of tauopathy model mice
The efficacy of T-817MA was investigated in transgenic mice expressing P301L mutant tau protein. T-817MA was administered ad libitum via drinking water dissolved at concentrations of 0.21 and 0.7 mg/mL from the age of 12 weeks to 43 weeks. Mice were tested in the Y-maze task and by histological evaluation. T-817MA improved the impairment of spatial memory in the Y-maze test. In histological observation, T-817MA prevented the reduction of synaptophysin immunoreactive terminal density in dentate gyrus of transgenic mice. This study suggests that T-817MA has therapeutic potential for neurodegenerative disorders including tau pathology.

Nonclinical pharmacokinetics and metabolism
Absorption (^{14}C-labelled T-817) in rats was more than 97%. Bioavailability in rats was 11% to 39% with dose increment from 2.8 to 28 mg/kg single dose. The metabolite profiles in plasma and urine were similar among rats, monkeys and humans. CYP2D6 was mainly involved in the oxidative metabolism for T-817. More than 80% of the administered T-817 was recovered in urine or feces within 24 hours in rats. In urine, bile and feces, unchanged T-817 was detected as the trace amount (<1% of dose). Protein binding in human, mouse, rat, rabbit, dog and monkey serum were 65% to 82%. The cerebrum, a pharmacological target of T-817, had a tissue to plasma concentration ratio (Kp) value of 2.44 (15 minutes) and 7.47 (1 hour) in rats, suggesting good penetration of T-817 into the cerebrum.

2.3 Safety Pharmacology and Toxicology

T-817MA has been extensively studied in rodent and non-rodent toxicology tests and a profile of potential risk to humans has emerged.

T-817MA is lethal to mice, rats and monkeys if given in high enough doses (700 or 1400 mg/kg single dose to mice or rats, 420 mg/kg/day for 28 days to rats and 420 mg/kg single dose or 140 mg/kg/day for 28 days to monkeys). Convulsion and respiratory depression appeared to be the most consistent potential cause of death across studies.

In repeated dose studies in rats and monkeys, several changes were observed at high doses such as suppression of weight gain, vomiting, salivation, effects on the kidneys and thyroid, and others. However, all of the observed drug-related changes in those studies showed evidence of reversibility upon cessation of dosing.

T-817MA was negative in the Ames test, bone-marrow micronucleus test in mice, and in vivo/in vitro DNA repair test in rats. T-817MA was positive in an in vitro chromosomal aberration study in Chinese Hamster Lung cells at the highest and cytotoxic dose with metabolic activation, and an in vitro gene mutation study in mouse lymphoma cells at 56 μg/mL or more without metabolic activation, and 210 μg/mL with metabolic activation.

Two reproductive toxicology studies in rats and 1 study in rabbits have been completed. In the rat embryo-fetal development study, external malformations such as anasarca, local edema and cleft palate, and visceral variations were observed in fetuses in the 280 mg/kg group along with a decreased weight gain in dams.

In the rat fertility and early embryonic development study, a low fertility index was noted in the 280 mg/kg group.

In the rabbit embryo-fetal development study, 3/18 dams aborted and a significant increase in skeletal variations was observed in the 420 mg/kg group.

2.4 Clinical Experience

Three single ascending dose studies, one food-effect study, one mass balance study, five multiple ascending dose studies, one bioavailability/food-effect study, four drug-drug interaction (DDI) studies, one PK study in subjects with hepatic impairment and one thorough QT/QTc study have been completed. In these studies, subjects have tolerated doses up to 896 mg of T-817MA for 2 weeks. Consumption of a high fat meal did not affect the

bioavailability of 112 mg T-817MA in Study US102, however C_{max} of T-817 was slightly affected by foods in Study JP104. The primary route of elimination of T-817MA and its metabolites was via the urine (84% of administered radioactivity), while the fecal route is a minor route of elimination (10% of administered radioactivity). The urine excretion ratio of T-817 was less than 3%. Assessment of DDIs between T-817MA and paroxetine (CYP2D6 inhibitor), caffeine (CYP1A2 substrate), omeprazole (CYP2C19 substrate), metoprolol (CYP2D6 substrate), midazolam (CYP3A4 substrate), bupropion (CYP2B6 substrate), repaglinide (CYP2C8 substrate), warfarin (CYP2C9 substrate) or galantamine revealed weak DDIs with paroxetine, caffeine, omeprazole or repaglinide, and a moderate DDI with metoprolol. Subjects who have mild and moderate hepatic impairment have tolerated single doses of T-817MA 448 mg. T-817MA at supratherapeutic doses (896 mg) did not cause clinically relevant QTc prolongation.

Three Phase 2, multi-center, randomized, double-blind, placebo-controlled 52-week clinical studies were conducted in patients with mild to moderate AD (Study US201, Study JP201, Study US202). In Study US201, a total of 373 patients was randomly assigned to T-817MA 224 mg once per day (QD) or placebo QD. The primary efficacy endpoint was change from Baseline in the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog). T-817MA patients performed better on the ADAS-cog test than placebo patients. Although the changes were not statistically significant, an efficacy trend was consistent throughout the treatment period. In Study JP201, a total of 271 patients were randomly assigned to T-817MA 224 mg QD, 448 mg QD or placebo QD. The primary efficacy analyses for change from Baseline in the ADAS-cog (Japanese version) showed no significant differences between T-817MA and placebo. In Study US202, a total of 482 patients were randomly assigned to T-817MA 224 mg QD, 448 mg QD or placebo QD. The primary efficacy analyses for change from Baseline in the ADAS-cog and Alzheimer's Disease Cooperative Study – Clinical Global Impressions of Change (ADCS-CGIC) showed no significant differences between T-817MA and placebo. However, the differences versus placebo in change from Baseline in p-Tau and total Tau in cerebrospinal fluid (CSF) were significant for T-817MA 448 mg.

Overall, T-817MA at repeated doses of 224 mg or 448 mg for up to 52 weeks with donepezil or rivastigmine transdermal system, with or without memantine, was well-tolerated in these Phase 2 studies. The most frequently occurring drug-related adverse events (AEs) were gastrointestinal disorders including diarrhea and nausea. Most AEs were mild or moderate in severity.

2.5 Rationale for the current Study

In Study US202, dose-dependent decreases in both p-tau and total tau in CSF were observed and the differences between 448 mg of T-817MA and placebo were statistically significant. The data may suggest a neuroprotective effect of T-817MA against tau-related AD pathology. T-817MA may show benefit by modifying pathology of tau-related diseases (tauopathies) such as MCI due to AD or early AD, because tau-related pathological changes of AD are known to precede memory and functional impairment. However, this observation was an exploratory result derived from a part of the enrolled patients (less than 20 per group).
This study is a proof of concept study to investigate the neuroprotective effect of T-817MA in patients with MCI due to AD or mild AD based on p-tau as the primary endpoint.

2.6 Potential Risks and Benefits Associated With This Study

Risks associated with study participation are the potential for adverse reactions to the study medication, concomitant medications, invasive study assessments like blood draws and lumbar puncture, and risks related to the process of undergoing brain MRI scans, and neuropsychological testing.

The most common adverse events associated with T-817MA seen in clinical studies conducted thus far are similar in study populations of healthy adults and patients with AD. They are headache, diarrhea, nausea, decreased appetite and dizziness. The adverse reaction most often deemed related to T-817MA is diarrhea. Administration of one daily dose of 448 mg T-817MA,

as will be done in this study, has been generally safe and well-tolerated.

Patients participating in this study may experience an improvement in their AD symptoms, even though such improvement cannot be predicted with any certainty. This study is expected to benefit the AD community by furthering the development of a new therapy and providing more information to those studying potential treatments for AD.

More specific information is contained in the Investigator's Brochure.

3. OBJECTIVES

3.1 Primary Objective

The primary objective is to evaluate the neuroprotective effect of T-817MA on Tau protein phosphorylated at threonine 181 (p-tau181) in CSF compared with placebo, in patients with a diagnosis of MCI due to AD or mild AD, according to the National Institute on Aging - Alzheimer Association (NIA-AA) criteria [Jack et al., 2018], with a Mini Mental Status Examination (MMSE) score of 24 to 30 (inclusive), and Aß1-42 and p-tau181 abnormality in CSF (≤1000 pg/ml for Aß1-42, ≥19 pg/ml for p-tau181) **or** (p-tau181/Aß1-42 ratio >0.020 for patients with p-tau181 ≥19 pg/ml **and** 1000<Aß1-42<1700 pg/ml).

3.2 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 Aß1-42/Aß1-40 ratio) and in plasma (Aβ1-40, Aβ1-42, NFL, glial fibrillary acidic protein [GFAP], p-tau181, p-tau217 and Aß1-42/Aß1-40 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.

4. ETHICS AND REGULATORY CONSIDERATIONS

4.1 Ethics and Regulations

This study will be conducted in compliance with the current version of the Declaration of Helsinki, the principles outlined in the ICH Tripartite Guideline for Good Clinical Practice (GCP), the General Data Protection Regulation (GDPR) (Regulation (EU) 2016/679) and all applicable local and international laws and regulations.

Study personnel involved in conducting this study will be qualified by education, training and experience to perform their respective task(s) in accordance with GCP.

4.2 Competent Regulatory Authority and Institutional Review Board/Independent Ethics Committee

For EU/EEA member states, the sponsor in collaboration with the investigators will submit to the competent regulatory authorities (CA) and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) the protocol and any accompanying materials including ones provided to the patient (such as patient information sheets or descriptions of the study used to obtain informed consent as well as any recruitment materials or compensation given to the patient).

Approval from the CA and committee(s) must be obtained before starting the study and should be documented in a letter to the investigator specifying the date on which the committee(s) met and granted the approval.

Any modifications made to the protocol and accompanying material after receipt of the CA and IRB/IEC approval must be re-submitted by the sponsor in the EEA member states in accordance with local procedures and regulatory requirements.

The study will not commence at any site until written approval for investigational product release and approval to enroll is obtained from the sponsor.

Protocol and informed consent form amendments can be made only with the prior approval of the sponsor. The investigator may not implement any protocol deviation without prior notification to the sponsor and prior review and documented approval of the IRB/IEC, except where necessary to eliminate an immediate hazard to study patients, or when change(s) involve only logistical or administrative aspects of the trial, i.e. change of monitor(s) or telephone number(s) (ICH 4.5.2). The investigator shall notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site, in accordance with local procedures.

4.3 Informed Consent

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, GDPR, and applicable local regulations. The sponsor, in collaboration with the CRO and investigators, will prepare the Informed Consent Form (ICF) and provide the documents to IRB/IEC for approval. The ICF must be in a language fully comprehensible to the prospective patients and study partners. Patients and study partners will be given ample opportunity to inquire about the details of the study. Prior to a patient's participation in the trial, the written ICF should be signed and personally dated by the patient and by the person who conducted the informed consent discussion. Patients must be provided a copy of the signed ICF. Study Partners will also sign the study partner ICF prior to study participation and receive a copy.

Copies of the signed ICF will be given to the patient and his/her study partner and the original will be maintained with the patient's records. If new safety information results in significant changes in the risk/benefit assessment, the ICF will be reviewed and updated if necessary. All patients should be informed of the new information and give their signed consent to continue the study.

No study-specific procedure will be undertaken on an individual patient until that patient has given written informed consent to take part in the study.

It will be made clear to each potential patient that informed consent may be withdrawn at any time without the need to give a reason and that such withdrawal will not compromise the relationship between the patient and the investigator nor the patient's future treatment.

The consent for storage will include consent to access stored data, biological samples, and imaging data for secondary analyses. Banked samples in this study concern CSF and plasma for biomarker determinations (Section 9.2), plasma and CSF for pharmacokinetics (Section 9.4), and DNA used for ε4 allele of Apolipoprotein E (ApoE) (Section 9.5). Consent forms will specify that DNA and biomarker samples not specified in the protocol are for research purposes only; the tests on the DNA and biomarker samples not specified in the protocol are not diagnostic in nature and patients will not receive results. MRI scan findings of clinical significance, determined by the site radiologist, can be shared with patients per site clinician discretion.

5. RATIONALE FOR STUDY DESIGN

This Phase 2 study is designed as a proof of concept study to evaluate the neuroprotective effect of T-817MA on CSF biomarkers, notably p-tau, compared with placebo, in patients with a diagnosis of MCI due to AD or mild AD, according to the NIA-AA criteria, with a MMSE score

of 24 to 30 and Aß1-42 and p-tau abnormality in CSF (≤1000 pg/ml for Aß1-42, ≥19 pg/ml for p-tau181) **or** (p-tau181/Aß1-42 ratio >0.020 for patients with p-tau181 ≥19 pg/ml **and** 1000<Aß1-42<1700 pg/ml). This study will also assess the effects of T-817MA on cognitive and functional tests (CDR-sb and CFC), imaging (vMRI), EEG parameters (alpha/theta ratio) and plasma biomarkers and as such will provide important information needed to design the Phase 3 pivotal study.

5.1 Dose Selection

In Study US202, T-817MA dose-dependently decreased p-tau and total tau in CSF and the difference between 448 mg and placebo was statistically significant.

T-817MA 448 mg achieves a plasma drug level that sufficiently covers efficacious level in various *in vivo* models.

Mean CSF drug levels in patients administered with T-817MA 448 mg was 57.76 ng/mL which approximately corresponds to 0.2 μmol/L. While it is not clear if timings of the samplings were around T_{max}, the concentration is within the range that showed neuroprotective effect *in vitro* (0.1 - 1 μmol/L).

5.2 Length of Study

The 78-week treatment period was chosen referring to clinical studies with other disease modifying drugs in patients with MCI due to AD, being a sufficiently long period to observe changes in brain volume and cognitive function, in addition to change in the CSF biomarkers. Considering there is a screening period of between 1 and 8 weeks prior to randomization and a 4-week post-treatment observation period, the overall duration of patient participation can be up to 90 weeks.

5.3 Patient Selection

A dose-dependent and significant decrease of both p-tau and total tau in CSF samples was observed in Study US202. The data may suggest a neuroprotective effect of T-817MA against AD pathology, in view of the discovery that pathological changes such as Aβ and tau accumulation in the brain and neurodegeneration precede memory and functional impairment of AD. Neuroprotective drugs may show benefit by modifying earlier stages of the disease such as MCI due to AD or early AD, because pathological change of AD precedes memory and functional impairment. Therefore, patients with MCI due to AD and mild AD were chosen as patient population for this study.

5.4 Placebo Control

The trial will be conducted in a randomized, double-blind, placebo-controlled fashion in order to control for known and unknown biases.

5.5 Rationale for Endpoints

It was reported that p-tau and total tau in CSF, that reflect the hyperphosphorylation state of tau and neurodegeneration, increase during progression from MCI to AD. In Study US202, both CSF p-tau and total tau dose-dependently and significantly decreased in patients administered with T-817MA. Since the p-tau is a more specific pathological marker for AD than total tau, CSF p-tau181 was chosen as the primary endpoint to investigate effect of T-817MA on neurodegeneration occurring during the disease progression.

In addition, p-tau217, total tau, Aß1-42, Aß1-40, NFL, neurogranin, YKL-40 and Aß1-42/Aß1-40 ratio in CSF and Aß1-42, Aß1-40, NFL, GFAP, p-tau181, p-tau217 and Aß1-42/Aß1-40 ratio in plasma will be evaluated as markers for tangle formation, amyloid deposition in the brain, neurodegeneration, synaptic damage and inflammatory process driven by glia cells.

Cognitive function will be measured by CDR-sb and CFC that include cognitive and functional

measures and were validated for monitoring and treatment evaluation in early dementia stages of AD in order to obtain preliminary information about effect size on cognitive function to design future study.

Brain structural change is seen in normal aging, but is accelerated in neurodegenerative disease, including MCI and AD [Leung et al., 2013]. Especially, hippocampal and ventricular volume change over time from MCI to AD. MRI scans and volume calculation are included in the study to investigate the effect of T-817MA on brain atrophy. Longitudinal MRI measures of regional and whole-brain volumetric change provide a valuable complement to cognitive measures in that they are not influenced by temporary symptomatic improvements, and they provide an early index of the study drug's ability to reach the target organ and have an effect on AD-related atrophy.

An EEG will be derived at Baseline, Week 52 and Week 78 to measure global relative power in the theta band (4 – 8 Hz). Relative theta power has been regarded as the most sensitive marker of EEG oscillatory activity in early AD. First, it has highest discriminatory value in the distinction between AD and controls. Second, it is a predictive marker for future cognitive decline in amyloid-positive patients without objective cognitive disturbances. Third, in a recently completed multi-center placebo-controlled phase 2 trial in MCI due to AD / mild AD, relative theta power showed significant changes towards normal values in the treated group compared to placebo (Amsterdam UMC, Data on File). In addition, relative power in the alpha band (8 – 13 Hz), beta band (13 – 30 Hz), dominant peak frequency, alpha / theta ratio and global functional connectivity using amplitude envelope correlation (AEC, 4 – 13 Hz) will be evaluated. In addition to overall functional connectivity, several specific functional brain network markers will be explored, since previous studies indicate their sensitivity to neurodegenerative disease, and this type of EEG analysis is a specific Amsterdam UMC expertise.

The ε4 allele of apolipoprotein E (ApoE) genotype is associated with the risk and age of onset of AD. ApoE genotyping will be performed at Baseline. Results of ApoE genotyping will be used to explore for a relationship between ApoE genotype clinical course, and response to treatment.

6. STUDY DESIGN

This is a Phase 2, proof of concept, multi-center, randomized, double-blind, placebo-controlled, parallel group study with a 78-week treatment period in high-risk individuals with MCI due to AD or mild AD, to assess the effect of T-817MA on CSF biomarkers including p-tau181 as compared to placebo.

Patients will be screened at the investigative site in order to determine eligibility for the study. A central review of screening results will then be conducted and, if appropriate, permission will be granted to randomize the patient.

At Baseline, patients who have passed the central review will be randomized to one of 2 treatment groups: placebo or 448 mg T-817MA in a 1:1 allocation. A stratified permuted block randomization procedure will be used. Country and MMSE will be stratification factors.

During the first 4 weeks of treatment, two tablets per day will be administered (a daily dose of 224 mg T-817MA and placebo or placebo only); from Day 29 onwards two tablets per day will be administered (a daily dose of 448 mg or placebo).

Patients will visit the clinic with a 1-week permittable window at Weeks 4, 16, 28, 40, 52, 65, 78 and 82.

Evaluation of CSF and MRI scan of the brain for volume will be performed at Screening and Weeks 52 and 78.

Evaluation of plasma biomarkers will be performed at Baseline, Weeks 52 and 78.

Evaluation of EEG will be performed at Baseline and Weeks 52 and 78. During the Baseline visit, every effort must be taken to ensure the EEG is approved prior to the first administration of study medication.

Cognitive and memory function (CDR-sb and CFC) will be assessed at Screening, Baseline and Weeks 28, 52 and 78.

Blood collection for PPK assessments will be done at Weeks 16, 28, 40, and 65; CSF collection for PK assessments will be done at Weeks 52 and 78.

Safety evaluations, including vital signs, AEs, hematology, biochemistry and urinalysis, will be carried out at each visit. An ECG will be taken at Screening and Weeks 28, 52 and 78.

The final follow-up visit will be conducted at Week 82.

The assessments listed for Week 78 should also be performed in case of premature discontinuation.

To prepare for possible new waves of COVID-19 or other infections and to minimize its effect on sites, patient safety and scientific integrity of the study data, Appendix I describes in detail how to conduct the study.

7. STUDY DRUG AND CONCOMITANT MEDICATIONS

7.1 Study Medication

The study medication will be presented as identically-appearing, film-coated tablets each containing one of the following:

- T-817MA, 224 mg (160 mg T-817 free base)
- Placebo

Drug substance of T-817MA is manufactured by FUJIFILM Toyama Chemical Co., Ltd. Drug product and package are manufactured by a qualified IMP vendor.

The study medication will be securely stored at the study site in accordance with the conditions specified on the label, separately from other drugs. The study medication may not be used for any purpose other than this study.

7.2 Coding and Packing

Assignment of study medication kits to treatment groups will be done with an allocation ratio of 1:1 by a computer-generated random sequence, using interactive web response system (IWRS) in an electronic data capture (EDC) system.

Group 1 (448 mg QD): One 224 mg T-817MA tablet and one placebo tablet once per day for 4 weeks, followed by two 224 mg T-817MA tablets once per day for 74 weeks.

Group 2 (Placebo): Two placebo tablets once per day for 4 weeks, followed by two placebo tablets once per day for 74 weeks.

The study medication will be packaged in blister packs of 14 tablets (2 × 7). Each blister pack will be sealed in a wallet. The wallet will be sealed inside a labeled aluminum barrier pouch with desiccant disks. An appropriate number of pouches will be packed in visit-specific cartons. Additionally, each visit-specific carton will contain one extra pouch to prevent a lapse in treatment as visits may be conducted within a ± 7-day window.

Note: Each patient completing this study will take between 77 to 79 weeks of study drug, depending on scheduling of Week 78 Visit.

7.3 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 Interactive Web Response System (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.

7.4 Randomization and Medication Ordering System

The investigator will use the EDC system to enter screening information on each patient. Patients will be randomized at Baseline using 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.

7.5 Labeling

Labels will be in accordance with all applicable regulatory requirements for the labeling of active pharmaceutical ingredients and with Annex 13 of GMP. Labels will contain the drug name, protocol number, date of manufacture, storage conditions and a caution statement that the drug is for clinical investigational use only.

7.6 Dosage Regimen

The study drug will be provided as tablets in blister packs. Patients will be instructed to take two tablets once daily for 78 weeks. The first dose of study drug will be taken at the study site at the Baseline visit (V2), after pre-dosing examinations including cognitive testing. Patients will be instructed to take subsequent doses of the study drug at approximately the same time every morning.

If a patient misses a dose of study drug, the dose for that day will be skipped unless it is taken within 12 hours of the patient's usual dosing time. Patients should take study drug as per the instructions of the investigator, which may include instructions on dose holiday and dose reductions. Adherence to the study drug will be assessed by delegated clinical site staff at each study visit. In case adherence to the study drug is poor (below 70%), the patient and study partner will be counseled on the importance of carefully following the dosing instructions.

After Week 4, if the patient experiences an AE for which the investigator believes a dose reduction or holiday is warranted, the investigator may halve the dose or temporarily suspend dosing (dose holiday) until such time as he/she feels it is safe to return to the assigned dose. A

dose holiday could also be used if the patient experiences an AE between Baseline to Week 4. Any dose changes must be promptly noted in the electronic Case Report Form (eCRF).

Guidance to return to the assigned dose is outlined below.

- After the AE has resolved, return to the full dose as soon as possible.
- If the AE persists, decision on the next step (continuation of half the dose or holiday, discontinuation or resumption) should be made within a month of the dose change.
- If the patient cannot return to the full dose, the patient must be discontinued.

7.7 Drug Accountability

The investigator or his/her designated representatives will dispense study drug only to patients enrolled in the study.

The investigator (or as appropriate, institution/pharmacist/individual who is designated by the investigator/institution) must maintain records of the delivery of the study medication to the trial site, the inventory at the site, the use by each patient, and the return to the drug distributor or destruction if local regulation allows.

At each visit, patients or their study partners should bring in all unused drug and empty or partially full containers (visit carton, sachets, blister cards). After conclusion of the study, each site will return to the drug distributor all unused study medication and empty or partially full containers collected from each patient or destroy unused medication and empty or partially full containers at site if local regulation allows this.

7.8 Treatment of Overdosage

Treatment of any suspected or confirmed overdose with T-817MA should be symptomatic with supportive care given as necessary on an individual basis.

For the purpose of the study, an overdose of T-817MA is defined as any dose greater than the highest daily dose included in the protocol. Overdoses should be reported as outlined in Section 12.5.

7.9 Concomitant Medication

7.9.1 Concomitant AD Medication

Patients who take an Acetylcholinesterase (AChE) inhibitor (donepezil, galantamine and rivastigmine) at a stable dose for more than 3 months before randomization can be enrolled in the study. The dose will be encouraged to be maintained throughout the study. Any dose changes of AChE inhibitor must be promptly noted in the eCRF.

Patients who do not take any AChE inhibitors can be enrolled, and are encouraged not to take any AChE inhibitors throughout the study. Starting any AChE inhibitor must be promptly noted in the eCRF.

7.9.2 Prohibited Concomitant Medications

The following concomitant medications are not permitted from screening through the end of the study. (Low doses of some prohibited medications may be allowed at the Medical Monitor's discretion):

- Other medications for AD, i.e., except for the AChE inhibitors mentioned in Section 7.9.1:
  - Memantine
  - Tacrine and huperzine A
- Tricyclic antidepressants (e.g. amitriptyline, amoxapine, clomipramine, desipramine,

doxepin, imipramine, nortriptyline, protriptyline, trimipramine)

- Monoamine oxidase inhibitors (e.g. isocarboxazid, phenelzine, tranylcypromine, selegiline, rasagiline)
- Long-acting benzodiazepines (EXCEPT short- to medium-acting benzodiazepines as described in Section 7.9.3)
- Conventional and atypical antipsychotics (EXCEPT ≤50 mg/d of quetiapine and ≤0.5 mg/d of risperidone in a stable dose 1 month prior to screening)
- Mood-stabilizing psychotropic agents (e.g. lithium salts)
- Prescription sedatives (e.g. barbiturates, methaqualone, meprobamate; EXCEPT sedating antihistamines, ramelteon, eszopiclone, zaleplon and zolpidem tartrate under the condition described in Section 7.9.3)
- Psychostimulants (e.g. amphetamines, modafinil-related compounds like armodafinil)
- L-dopa
- Dopamine agonists (e.g. apomorphine, pramipexole, ropinirole, rotigotine)
- Anticholinergics (e.g. benztropine mesylate, trihexyphenidyl HCL; EXCEPT darifenacin, trospium, oxybutynin, solifenacin and tolterodine)
- Anticonvulsant medications (EXCEPT gabapentin and pregabulin (Lyrica) for non-seizure indications, ≤50 mg/d of lamotrigine and ≤1200 mg/d of oxcarbazepine and eslicarbazepine acetate for non-seizure indications if dose ≤1200 mg/d.)
- Opiate analgesics (e.g. morphine, codeine, hydromorphone, hydrocodone, meperidine, oxycodone; EXCEPT external use e.g. transdermal fentanyl patch)
- Immunosuppressive medications (EXCEPT inhaled, topical and intra-nasal steroids)
- Chemotherapeutic agents for malignancies
- CYP2D6 substrates with narrow safety margin (e.g. thioridazine, pimozide)
- CYP2C19 substrates with narrow safety margin (e.g. S-mephenytoin)
- Anticoagulation medications (e.g. heparin, warfarin, thrombin inhibitors, Factor Xa inhibitors; a possibility cannot be ruled out that T-817MA reduces INR effect from warfarin.)

If during the clinical study the administration of a non-permitted concomitant medication becomes necessary, the Medical Monitor should be contacted to determine if the patient still can stay in the study (see Section 10).

7.9.3 Permitted Concomitant Medications

The following concomitant medications are permitted *under the following conditions*:

- The dose should be stable while on the prescribed medication.
  - Antidepressants (e.g. trazodone, vortioxetine, vilazodone, venlafaxine, des-venlafaxine, duloxetine, atomoxetine, milnacipran, l-milnacipran, sertraline, citalopram, s-citalopram) starting at least 2 months prior to Screening, except the prohibited medications as described in Section 7.9.2 like tricyclic antidepressants.
  - Beta-blockers used for cardiovascular reasons starting at least 1 week prior to Screening
- The following concomitant medications are permitted. But they should not be taken from 12 hours prior to any scheduled visits that include any cognitive tests.
  - Short to medium-acting benzodiazepines, starting at least one month prior to

Screening

- Ramelteon (up to 8 mg), eszopiclone (up to 2 mg), zaleplon (up to 5 mg) or zolpidem tartrate (≤6.25 mg controlled release (CR) and ≤10 mg immediate release tablet)
- Sedating anti-allergy medications (e.g. diphenhydramine), starting at least one month prior to Screening

- Hypnotics are permitted. But it should be discontinued during a period of 72 hours prior to EEG recording (at Baseline, Week 52 and Week 78).
- Anti-platelet medications (e.g. clopidogrel (Plavix®), dipyridamole, cilostazol, aspirin) are permitted. But it may be discontinued at the investigator's discretion around lumbar puncture.
- The following concomitant medications are permitted.
  - Medical foods; Axona®, Souvenaid®, Ensure®-like medical foods, including soy-based supplements
  - Food supplements in general
  - Vitamins in general
  - Non-sedating antihistamines
- P-glycoprotein substrates with a narrow safety margin (e.g. digoxin, colchicine-containing compounds, ranolazine) should be used with caution. T-817MA is a possible P-glycoprotein inhibitor and it may increase the blood concentration of such drugs.
- CYP2D6 substrates (e.g. metoprolol) should be used with caution. T-817MA is a CYP2D6 inhibitor and may increase the blood concentration of such drugs.

Any concomitant medications must be recorded in the eCRF, noting the name of medication, the dose, duration, and indication.

8. PATIENT SELECTION

8.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrolment:

1. Male or female, age 50 to 80 inclusive at date of ICF signature.
2. Diagnosis by the investigator of a clinical syndrome of cognitive impairment consistent with either MCI due to AD or mild AD per NIA-AA diagnostic criteria (Jack et al., 2018), with MMSE 24 to 30 (inclusive).
3. CSF results at screening consistent with the presence of Aß1-42 and p-tau181 abnormality (≤1000 pg/ml for Aß1-42, ≥19 pg/ml for p-tau181) **or** (p-tau181/Aß1-42 ratio >0.020 for patients with p-tau181 ≥19 pg/ml and 1000<Aß1-42<1700 pg/ml).
4. A brain MRI not-inconsistent with the clinical diagnosis of MCI due to AD or mild AD
5. Receiving an AChE inhibitor (donepezil, galantamine or rivastigmine) at a stable dose for more than 3 months prior to randomization, or not receiving any AChE inhibitors.
6. Weight of ≤100 kg (220 pounds) at Screening
7. Ability (patients and their study partners) to read, speak and understand local language to ensure compliance with cognitive testing and study visit procedures
8. Living in the community (includes assisted living facilities, but excludes long-term care nursing facilities)

9. Ambulatory, or able to walk with an assistive device, such as a cane or walker
10. If male, patients must:
    a. agree he will not donate sperm during the study and until 104 days after the last dose, AND
    b. be required to use the following highly effective methods of contraception during the study and until 104 days after the last dose:
        i. Abstain from sexual intercourse OR
        ii. Use a condom during sexual intercourse with pregnant or non-pregnant women of childbearing potential (WOCBP) partner even if he is vasectomized. In addition, WOCBP partner of the male patient (except a vasectomized male) must use one of the following highly effective methods of contraception.
            - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
                - oral
                - intravaginal
                - transdermal
            - Progestogen-only hormonal contraception associated with inhibition of ovulation:
                - oral
                - injectable
                - implantable
            - Intrauterine device (IUD)
            - Intrauterine hormone-releasing system (IUS)
            - Bilateral tubal occlusion
11. If female, patients must:
    a. be post-menopausal (i.e. no menses for 12 months without an alternative medical cause) OR
    b. be permanently sterilized with methods including hysterectomy, bilateral salpingectomy and bilateral oophorectomy
12. A study partner who has regular contact with the patient for at least 10 hours per week and is able to participate in the patient's clinical assessment and complete the questionnaire about the patient's daily life at Screening, Baseline and Weeks 28, 52 and 78
13. Patient is clearly able to understand the nature, meaning and consequences of the clinical trial and its interventions and conveys his/her will to participate by personally signing the informed consent form
14. Written informed consent obtained from study partner

8.2 Exclusion Criteria

Patients meeting any of the following criteria must not be included in the study:

1. Has had an MRI of the brain within the previous 2 years that showed pathology that would be inconsistent with a diagnosis of AD
2. Use of prohibited medications, including memantine
3. Has any contraindications for MRI including claustrophobia, the presence of metal (ferromagnetic) implants, or a cardiac pacemaker that is not compatible with MRI
4. Has any contraindications to lumbar puncture
5. Pregnant or breastfeeding woman

6. Psychiatric disorder such as schizophrenia or dementia not of the Alzheimer's type according to the criteria of DSM-5
7. Other neurodegenerative diseases, including Parkinson's disease and Huntington's disease, or cerebral tumor
8. Dementia other than AD
9. History of untreated thyroid disorder, Type I diabetes, and insulin-dependent or uncontrolled Type II diabetes, as determined by the investigator (except non-insulin-controlled Type II diabetes, whose HbA1c value must be below 8.0 %). The HbA1c value should not be older than 6 months prior to screening. If no recent HbA1c value is available, then HbA1c should be assessed locally.
10. History of a seizure disorder or stroke, unless >5 years ago
11. History of alcohol abuse or dependence or drug abuse in the past 5 years
12. Uncorrected impairment of vision or hearing that would preclude the patient from taking tests or patients lacking the ability to communicate
13. Clinically significant abnormal laboratory values in the opinion of the investigator
14. Severe hepatic or severe renal impairment (e.g. bilirubin > 3 x ULN, AST/ALT > 5 x ULN, eGFR < 30 ml/min/1.73m^2 or CrCl <30 ml/min)
15. Clinically significant B12 deficiency (i.e., no macrocytosis) in the opinion of the investigator
16. Severe heart disease (history of myocardial infarction, congestive heart disease, history of unstable angina pectoris, clinically significant ECG abnormality) within 6 months prior to screening. Patients with arterial thrombosis will not be excluded if they are stable for at least 6 months prior to Screening
17. Cancer or a malignant tumor within the past 3 years, except patients who underwent potentially curative therapy with no evidence of recurrence.
18. Participation in another clinical trial for an investigational agent and having taken at least one dose of study medication, unless confirmed as having been on placebo, within 12 weeks prior to screening. (The end of a previous investigational trial is defined as the date of the last dose of an investigational agent.)
19. Participation in a previous clinical trial with T-817MA
20. Patients whom the investigator deems to be otherwise ineligible
21. Has an MRI of the brain at screening indicative of significant abnormality, including, but not limited to, prior hemorrhage or infarct, large (>1 cm) infarct, >2 lacunar infarcts outside the brain stem, severe white matter changes (Fazekas grade 3), >4 microbleeds, superficial hemosiderosis >1 cm, aneurysm, vascular malformation, subdural hematoma, hydrocephalus, space-occupying lesion (e.g, abscess or brain tumor such as meningioma).

9. STUDY PROCEDURES

9.1 Study Visits

9.1.1 Screening (between 7 and 56 days prior to randomization)

Patients who the investigator considers to be appropriate for the study, will have the study explained to them by the investigator and will be given a copy of the written Informed Consent Form (ICF). When they have had sufficient time to study this information and the opportunity to ask any questions they wish, they will be invited to give their consent to participation by

signing the ICF. The study partner must also sign the study partner ICF.

Once the patient and study partner have given consent, the following procedures will be undertaken to confirm eligibility for the study:

- Verification of Inclusion/Exclusion criteria
- Documentation of AEs (after informed consent)
- Confirmation of clinical syndrome of cognitive impairment consistent with either MCI due to AD or mild AD per NIA-AA diagnostic criteria
- MMSE (score must be between 24-30, inclusive)
- CDR-sb
- CFC (ADAS-cog, A-IADL-Q, CFT, LFT, WAIS-IV-DS and WAIS-IV-DSST)
- Documentation of demographics, medical history, smoking habits and education
- Documentation of concurrent pathologies and concomitant treatment, including AChE inhibitors used within 3 months of Screening visit
- Physical examination (including neurological examination)
- Vital signs (heart rate, blood pressure, weight and height)
- Resting 12-lead ECG
- Blood sampling for safety laboratory tests (hematology and serum biochemistry, as listed in Section 11.2). NOTE: Retesting for a specific lab parameter during the screening period is allowed once if it is suspected that the abnormal lab result is transient and likely to be normal on repeat.
- Urine sample for urinalysis (parameters listed in Section 11.2)
- vMRI

  NOTE: vMRI scans must either be completed before or more than 3 days after the CSF collection (in order to avoid any MRI artifacts due to low CSF pressure).

  Additionally, in case the MRI is sub-optimal, a repeat MRI must be done prior to randomization of the patient.

- Lumbar puncture for CSF sample

  NOTE: CSF sample must be taken between 11AM and 2PM.

- Eligibility check by the CRMM.

The CDR-sb and CFC must be performed at least 14 days prior to the CDR-sb and CFC performed at the Baseline visit to minimize learning effects. Preferably, all other screening assessments should be performed at least 14 days prior to randomization to allow for sufficient time for the eligibility review by the CRMM and the Baseline visit procedures.

Following completion of all screening assessments, results for patients who meet all inclusion and none of the exclusion criteria will be recorded in the eCRF for review by the Central Review Medical Monitor (CRMM) for confirmation of eligibility. The eligibility check by the CRMM that is scheduled before the Baseline visit, may take up to 5 business days. If confirmed to be eligible, permission to perform the Baseline visit and randomization will be issued and the patient may be randomized at Baseline. Patients will be given an appointment to return for the Baseline visit.

Randomization must be done within 56 days of the first screening assessment (excluding consent administration). If randomization does not occur up to 56 days, the patient will be

considered a screen failure.

9.1.2 Baseline Visit (Week 0, from -7 days to randomization)

Baseline is defined as the day that patients are randomized after all baseline assessments have been performed.

Before randomization the following baseline assessments will be performed in eligible patients, who are given permission from the CRMM:

- Verification of Inclusion/Exclusion criteria
- Documentation of concomitant treatment
- Documentation of AEs
- Vital signs (heart rate , blood pressure and weight)
- Blood samples for:
  - ApoE genotyping
  - Biomarkers
- CDR-sb

  NOTE: Must be performed at least 14 days after the Screening CDR-sb
- CFC (ADAS-cog, A-IADL-Q, CFT, LFT, WAIS-IV-DS and WAIS-IV-DSST)

  NOTE: Must be performed at least 14 days after the Screening CFC
- EEG

  NOTE: Every effort must be taken to ensure the Baseline EEG is approved prior to the first administration of study drug. The quality check for the Baseline EEG may take up to 2 business days after submission of the EEG file.

When all assessments listed above have been completed, the patient can be randomized in EDC. The first dose of study drug will be administered to the patient in the clinic, after all Baseline visit assessments have been completed.

Patients will receive a supply of study drug with instructions on how to take it. Patients will be given an appointment to return at Week 4 (± 7 days).

9.1.3 Week 4 (± 7 days)

All patients returning for Week 4 will undergo the following procedures:

- Documentation of concomitant treatment
- Documentation of AEs
- Tablet count to verify compliance with study treatment
- Vital signs (heart rate, blood pressure and weight)
- Physical examination (including neurological examination), if clinically indicated
- Resting 12-lead ECG, if clinically indicated
- Blood samples for:
  - Safety laboratory tests (hematology and serum chemistry, as listed in Section 11.2)
- Urinalysis (see Section 11.2)

Patients will receive a supply of study drug with instructions on how to take it. Patients will

be given an appointment to return at Week 16 (± 7 days).

9.1.4 Week 16 (± 7 days)

All patients returning for Week 16 will undergo the following procedures:

- Documentation of concomitant treatment
- Documentation of AEs
- Tablet count to verify compliance with study treatment
- Vital signs (heart rate, blood pressure and weight)
- Physical examination (including neurological examination), if clinically indicated
- Resting 12-lead ECG, if clinically indicated
- Blood samples for:
  - Safety laboratory tests (hematology and serum chemistry, as listed in Section 11.2)
  - PPK analysis (to be taken 1 to 6 hours *after* intake of the last dose)
- Urinalysis (see Section 11.2)

Patients will receive a supply of study drug with instructions on how to take it. Patients will be given an appointment to return at Week 28 (± 7 days). With respect to the Week 28 appointment, patients will be reminded not to take their study medication before their visit, as they will take it in the clinic *after* their PPK blood draw.

9.1.5 Week 28 (± 7 days)

All patients returning for Week 28 will undergo the following procedures:

- Documentation of concomitant treatment
- Documentation of AEs
- Tablet count to verify compliance with study treatment
- Vital signs (heart rate, blood pressure and weight)
- Physical examination (including neurological examination)
- Resting 12-lead ECG
- Blood samples for:
  - Safety laboratory tests (hematology and serum chemistry, as listed in Section 11.2)
  - PPK analysis (sample to be taken *before* dosing)
- Urinalysis (see Section 11.2)
- CDR-sb
- CFC (ADAS-cog, A-IADL-Q, CFT, LFT, WAIS-IV-DS and WAIS-IV-DSST)

Patients will receive a supply of study drug with instructions on how to take it. Patients will be given an appointment to return at Week 40 (± 7 days).

9.1.6 Week 40 (± 7 days)

All patients returning for Week 40 will undergo the following procedures:

- Documentation of concomitant treatment

- Documentation of AEs
- Tablet count to verify compliance with study treatment
- Vital signs (heart rate, blood pressure and weight)
- Physical examination (including neurological examination), if clinically indicated
- Resting 12-lead ECG, if clinically indicated
- Blood samples for:
  - Safety laboratory tests (hematology and serum chemistry, as listed in Section 11.2)
  - PPK analysis (sample to be taken 1 to 6 hours *after* intake of the last dose)
- Urinalysis (see Section 11.2)

Patients will receive a supply of study drug with instructions on how to take it. Patients will be given an appointment to return at Week 52 (± 7 days).

9.1.7 Week 52 (± 7 days)

All patients returning for Week 52 will undergo the following procedures:

- Documentation of concomitant treatment
- Documentation of AEs
- Tablet count to verify compliance with study treatment
- Vital signs (heart rate, blood pressure and weight)
- Physical examination (including neurological examination)
- Resting 12-lead ECG
- Blood samples for:
  - Safety laboratory tests (hematology and serum chemistry, as listed in Section 11.2)
  - Biomarkers
- Urinalysis (see Section 11.2)
- CDR-sb
- CFC (ADAS-cog, A-IADL-Q, CFT, LFT, WAIS-IV-DS and WAIS-IV-DSST)
- EEG
- vMRI

  NOTE: vMRI scans must either be completed before or more than 3 days after the CSF collection (in order to avoid any MRI artifacts due to low CSF pressure).
- Lumbar puncture for CSF sample

  NOTE: CSF sample must be taken between 11AM and 2PM.

Patients will receive a supply of study drug with instructions on how to take it. Patients will be given an appointment to return at Week 65 (± 7 days). With respect to the Week 65 appointment, patients will be reminded not to take their study medication before their visit, as they will take it in the clinic *after* their PPK blood draw.

9.1.8 Week 65 (± 7 days)

All patients returning for Week 65 will undergo the following procedures:

- Documentation of concomitant treatment
- Documentation of AEs
- Tablet count to verify compliance with study treatment
- Vital signs (heart rate, blood pressure and weight)
- Physical examination (including neurological examination), if clinically indicated
- Resting 12-lead ECG, if clinically indicated
- Blood samples for:
  - Safety laboratory tests (hematology and serum chemistry, as listed in Section 11.2)
  - PPK analysis (sample to be taken *before* dosing)
- Urinalysis (see Section 11.2)

Patients will receive a supply of study drug with instructions on how to take it. Patients will be given an appointment to return at Week 78 (± 7 days).

9.1.9 Week 78 (± 7 days)/End of Treatment or Premature Discontinuation

All patients returning for Week 78 or premature discontinuation will undergo the following procedures:

<u>If a patient discontinues earlier than the Week 28 visit or after the Week 52 visit, EEG, vMRI and Lumbar puncture are not necessary.</u>

- Documentation of concomitant treatment
- Documentation of AEs
- Documentation of the reason of premature discontinuation (if this is a visit for premature discontinuation)
- Tablet count to verify compliance with study treatment
- Vital signs (heart rate, blood pressure and weight)
- Physical examination (including neurological examination)
- Resting 12-lead ECG
- Blood samples for:
  - Safety laboratory tests (hematology and serum chemistry, as listed in Section 11.2)
  - Biomarkers
- Urinalysis (see Section 11.2)
- CDR-sb
- CFC (ADAS-cog, A-IADL-Q, CFT, LFT, WAIS-IV-DS and WAIS-IV-DSST)
- EEG
- vMRI

  NOTE: vMRI scans must be completed before or more than 3 days after the CSF collection (in order to avoid any MRI artifacts due to low CSF pressure).
- Lumbar puncture for CSF sample

  NOTE: CSF sample must be taken between 11AM and 2PM.

Patients will be given an appointment to return at Week 82 (± 7 days), the post-treatment follow-up visit, except those who came for premature discontinuation.

9.1.10 Week 82 (± 7 days)/Follow-up

All patients returning for Week 82 or post-treatment follow-up will undergo the following procedures:

- Documentation of concomitant treatment
- Documentation of AEs
- Vital signs (heart rate, blood pressure and weight)
- Physical examination (including neurological examination), if clinically indicated
- Resting 12-lead ECG, if clinically indicated
- Blood samples for:
  - Safety laboratory tests (hematology and serum chemistry, as listed in Section 11.2)
- Urinalysis (see Section 11.2)

9.1.11 Rescreening

Rescreening of a patient who previously screen failed is allowed if there is a substantial change in a patient's condition as compared to the initial screening visit.

In order to rescreen a patient, the following conditions apply:

- If a patient screen failed on inclusion criterion #3 (the Aβ1-42-value, p-tau value or the p-tau/ Aβ1-42 ratio):
  - Rescreening may be performed **after** 3 months of the last assessment of the initial screening period;
  - All screening assessments must be repeated, except for the vMRI if performed within the previous 6 months of the date of rescreening and if the results were within eligible ranges.

- If a patient screen-failed for **any other reason** than inclusion criterion #3 (Aβ1-42-value, p-tau value or the p-tau/ Aβ1-42 ratio):
  - Rescreening is allowed. If the date of rescreening is within 3 months of the last assessment of the initial screening period, the CSF results and vMRI results may be reused;
  - If the date of rescreening is after 3 months of the last assessment of the screening period, the lumbar puncture must be repeated to obtain new CSF results. The vMRI results of the initial screening may be reused if performed within 6 months of the last assessment of the screening period and if the results were within eligible ranges.

Rescreening for MMSE is never allowed.

Rescreening may only be done once. If a patient who previously screen failed due to inadequate vMRI and/or CSF results, written approval for rescreening must be obtained from the CRMM prior to rescreening. The patient and study partner must reconsent and a new subject ID will be assigned to the patient. Finally, it must be clearly documented in the patients' source that the patient is rescreened.

9.2 CSF and Plasma Biomarker Assessments

CSF will be taken at Screening and at Weeks 52 and 78 to measure the CSF biomarkers p-

tau181 (primary endpoint), p-tau217, total tau, Aß1-42, Aß1-40, NFL, neurogranin and YKL-40. CSF must be collected at the same time of day between 11AM and 2PM. Note that vMRI (see Section 9.6) should be conducted before or more than 3 days after the lumbar puncture. Anti-platelet medications may be discontinued at the investigator's discretion for lumbar puncture. Details of the CSF sampling are contained in a separated manual.

Blood will be taken at Baseline, Weeks 52 and 78 for plasma biomarkers Aß1-42, Aß1-40, NFL, GFAP, p-tau181 and p-tau217.

The unused portion of CSF and/or plasma may be banked for possible further investigations of biomarkers and levels of T-817 and its metabolites. Patients will be given the choice to allow retention and further investigation of their samples (see Section 4.3).

The Central Laboratory will provide the investigational sites with all appropriate materials for collection, processing, packaging and shipping of the samples. Full details of sampling, sample preparation and storage methods will be given in a separated manual.

9.3 Laboratory Safety Assessments

The safety laboratory parameters to be measured in blood and urine samples are outlined in Section 11.2. Blood will be collected for serum chemistry and hematology analyses. Urine will be collected at each visit for urinalysis. The Central Laboratory will provide the investigational sites with all appropriate materials for specimen collection, sample processing, packaging and shipping. Full details of sampling (blood and urine), sample preparation and storage methods will be given in a separated manual.

9.4 Pharmacokinetic Assessments

Blood samples for PPK assessments will be collected for all patients at Weeks 16, 28, 40 and 65. These blood collections consist of a single blood draw at each of these visits. The site will record in the eCRF the time and date that the last dose of study drug was consumed, the number of the tablets taken and the time and date the blood sample was collected. The PPK blood draw shall be done *prior to* dosing on the day of the Weeks 28 and 65 clinic visit, and 1-6 hours *after* the time that the last study drug is taken on the scheduled visit day at Week 16 and 40. Full details of sampling, sample preparation and storage methods will be given in a separated manual.

The unused portion of plasma may be banked for possible further investigations of biomarkers and plasma levels of T-817 and its metabolites. Patients will be given the choice to allow retention and further exploratory investigation of their plasma (see Section 4.3).

CSF samples for PK assessment will be collected for all patients at Weeks 52 and 78.

The CSF sample collection must be performed as per Section 9.2.

9.5 Genotyping

Blood sample for genotyping will be collected for all patients at Baseline to measure ApoE. Full details of sampling, sample preparation and storage methods will be given in a separated manual.

The unused portion of plasma and DNA may be banked for possible further investigations. Patients will be given the choice to allow retention and further exploratory investigation of their plasma and DNA (see Section 4.3).

9.6 vMRI Assessments

MR imaging of the brain will be performed at Screening, Weeks 52 and 78 in order to assess changes in brain volume and cortical thickness over time. vMRI scans will also be centrally reviewed, to assess the presence of brain abnormalities which may exclude the patient from participating in the study (Screening scan), and to monitor patient's safety over time. All vMRI

scans will use the same imaging protocol. Protocol will include a 3D T1-weighted sequence which will be used for the volumetric analysis. FLAIR, T2* Gradient Echo and Diffusion Weighted sequences will also be included for eligibility/safety purposes.

Images will be centrally checked for image quality and adherence to imaging protocol. If at Screening a vMRI scan is found to be sub-optimal and a repeat scan is requested, this repeat scan must be performed prior to randomization of the patient.

3D T1-weighted datasets passing quality checks will be analyzed using automated image processing algorithms in order to assess Baseline measures and change over time in the following brain structures: whole-brain, lateral ventricles and hippocampus. Cortical thickness will also be assessed.

vMRI should be conducted before, or more than 3 days after the lumbar puncture. Scanners that have passed the study's qualification procedures will be used. Patients must be scanned using the same scanner throughout the study. Further details of MRI assessments will be provided in a separate MRI manual.

9.7 EEG Assessments

EEGs will be derived at Baseline and at Weeks 52 and 78.

Task-free, eyes-closed EEG recordings will be performed at sites in a pre-specified and standardized manner to minimize inter-center variability. 15-minute EEG data will be recorded at 21 electrode positions of the standard 10-20 system: Fp2 / Fp1, F8 / F7, F4/ F3, A2 / A1, T4 / T3, C4 / C3, T6 / T5, P4 / P3, O2 / O1, Fz, Cz, Pz, using a montage with a common reference. Sample frequency will be at least 200 Hz and analog to digital (A-D) precision will be 12 bit or higher. The EEG technicians will be trained to monitor the EEG and minimize artefacts and drowsiness during the recording. Data will be converted into ASCII format which will be collected and analyzed centrally by the EEG analysis center of the Amsterdam UMC. Central analysis will not include visual inspection nor a diagnostic report. EEG recordings will be checked for quality within 3 working days to request repeat recordings in the case of insufficient quality. Further information on technical and recording requirements and data collection is given in a separate EEG manual. Every effort must be taken to ensure the Baseline EEG is approved prior to the first administration of study drug.

As mentioned in Section 7.9.3, hypnotics are permitted, but not during a period of 72 hours prior to EEG recording.

9.8 Disease Scales

At Screening, the MMSE will be performed to verify that patients fulfil Inclusion Criterion 2 (Section 8.1). To qualify for the study, scores should be between 24 and 30 (inclusive) at Screening.

The CDR-sb and CFC (ADAS-cog, A-IADL-Q, CFT, LFT, WAIS-IV-DS and WAIS-IV-DSST) will be performed at Screening and at Baseline, as well as during the treatment phase at Weeks 28, 52 and 78 to assess cognitive and functional impairment.

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. PREMATURE DISCONTINUATION/WITHDRAWAL PROCEDURES

The entire study may be discontinued at the discretion of the sponsor. In these circumstances the investigator will arrange for all ongoing patients to be seen and for their study medication to be discontinued as soon as is safely possible.

Patients are free to withdraw from study participation at any time, for any reason, and without penalty or loss of benefits to which the patient is otherwise entitled.

The participation of an individual patient in the study will be terminated in the following circumstances:

1. Withdrawal of informed consent by the patient. If the study partner withdraws his/her consent to participate then attempts will be made to find a replacement. In any event the patient will be continued in the study as far as possible. Patients who withdraw consent will be advised by the investigator regarding subsequent treatment and investigation.
2. The patient loses the ability to consent, in the opinion of the investigator.
3. Treatment of a patient with a non-permitted concomitant medication may necessitate discontinuation from study medications, to be determined by the investigator in conjunction with the Medical Monitor.
4. Adverse event or other significant medical condition which, in the opinion of the investigator, renders it necessary to discontinue study medication.
5. The patient experiences a medical emergency that necessitates unblinding treatment assignment. (See Section 7.3)
6. Any other occurrence that, in the investigator's opinion, makes continued participation contrary to the patient's best interests.
7. Movement of the patient into a nursing home. Movement into an assisted living facility is not a valid cause for discontinuation from the study.
8. If the patient cannot return to full dose within a month of a dose holiday, the patient must be discontinued (see Section 7.6).

The investigators at each site will make every reasonable effort to maximize patient retention. However, if an investigator removes a patient from treatment or study, or if a patient declines further treatment or study participation, a Premature Discontinuation Visit as indicated in Section 1.1 and 9.1.9 under Week 78/Premature Discontinuation will be completed as soon as possible following discontinuation of the study medication and/or at time of study discontinuation.

It will be the responsibility of the investigator to ensure that all withdrawn patients receive appropriate follow-up and medical care.

11. EFFICACY, SAFETY, AND OTHER EVALUATIONS

11.1 Assessment of Efficacy

11.1.1 Assessments Used for the Primary Endpoint

The primary efficacy endpoint is the change in the CSF biomarker p-tau181 from Baseline to Week 78.

11.1.2 Assessments related to Secondary Endpoints

The secondary efficacy endpoints are:

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 biomarker p-tau181 from Baseline to Week 52.
3. The change in the CSF biomarkers p-tau217, total tau, Aβ1-42, Aβ1-40, NFL, neurogranin, YKL-40 and Aβ1-42/Aβ1-40 ratio from Baseline to Weeks 52 and 78.
4. The change in plasma biomarkers Aβ1-42, Aβ1-40, NFL, GFAP, p-tau181, p-tau217 and Aβ1-42/Aβ1-40 ratio from Baseline to Weeks 52 and 78.

5. The change in brain volume (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

11.2 Assessment of Safety

Safety will be assessed by:

1. Recording of AEs
2. Physical examination
3. Measurement of vital signs (heart rate, blood pressure and weight)
4. 12-lead ECG
5. Safety laboratory parameters
   - Hematology:
     Red blood cell count (RBC), hemoglobin, hematocrit, total leukocyte count, differential leukocyte count (neutrophil, lymphocyte, monocyte, eosinophil, basophil), platelet count
   - Chemistry:
     AST, ALT, γ-GT, ALP, total bilirubin, LDH, BUN, creatinine, serum electrolytes (Na, K, Cl, Ca, P, CO_2), total protein, albumin, albumin/globulin ratio, total cholesterol (TC), HDL cholesterol, LDL cholesterol, triglyceride (TG), uric acid, free triiodothyronine (FT3), free thyroxin (FT4), Thyroid Stimulating Hormone (TSH)
   - Urinalysis:
     pH, specific gravity, protein, glucose, ketones, urobilinogen, bilirubin, blood

11.3 Assessment of Pharmacokinetics

The PPK analysis of T-817MA will be performed using plasma T-817 concentration data. The PPK analysis involves assessment of the following PK parameters: maximum plasma concentration at steady-state ($C_{ss,max}$), minimum plasma concentration at steady-state ($C_{ss,min}$), and area under the plasma concentration-time curve during a dosage interval at steady-state ($AUC_{ss,tau}$). The penetration of T-817 from plasma into CSF will be assessed with the ratio of T-817 levels in CSF to plasma (CSF/plasma).

For this analysis blood samples and CSF samples will be collected as described in Section 9.4, while details of collection and preparation methods of samples will be given in the Laboratory manual. The determination of concentrations of T-817 will be performed by means of validated LC/MS/MS assays by LSI Medience Corporation.

Details on the methods will be provided in the final PPK report.

12. DEFINITION OF ADVERSE EVENT

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation patient who is administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. If there is an adverse event that leads to a medical or surgical procedure, the condition that leads to the procedure is the AE. Pre-existing conditions, which increase in frequency or severity or worsen in nature during or as a consequence of use of a drug in human clinical trials, will also be considered as adverse experiences. Adverse events may also include pre- or post-treatment complications that occur

as a result of protocol-mandated procedures (e.g. invasive procedures such as biopsies).

An AE **does not** include:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) that were planned before informed consent is signed.
- Worsening of symptoms associated with expected decline in AD is not considered an adverse event in this study.
- Overdose of either study drug or concomitant medication without any signs or symptoms unless the patient is hospitalized for observation. Overdoses should be reported as outlined in Sections 7.8 and 12.5.

12.1 Evaluation and Reporting of Adverse Events

All events (i.e. a new event or an exacerbation of a pre-existing condition) that occur after informed consent has been signed and up to 28 days after the study drug has been discontinued must be recorded as an AE or serious adverse event (SAE) (if applicable), in the Adverse Event eCRF and SAE form, as applicable. The investigator must follow all AEs until the AE resolves, or until the investigator and/or the Medical Monitor determine the event is chronic or clinically stable. If an AE remains unresolved at the conclusion of the study, the investigator will make a clinical assessment to determine whether continued follow-up of the AE is warranted. All patients who have received at least one exposure to study drug will be evaluated for safety of study treatment.

The investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms. To avoid vague, ambiguous, or colloquial expressions, all AEs should be recorded in standard medical terminology in the eCRF and on the medical record rather than in the patient's own words.

12.2 Assessment of Adverse Events

All AEs must be promptly documented in the Adverse Event eCRF and assessed by the investigator. Details of the event must include the dates of onset and resolution, severity, relationship to study drug, seriousness, whether the event caused the patient to withdraw from the study or to change the dosage of study medication, outcome and timing with regard to administration of the study drug.

Severity: Severity should be graded and recorded according to the table below and in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Severity	Definition
Mild	Awareness of event but easily tolerated
Moderate	Discomfort enough to cause interference with usual activity
Severe	Inability to carry out usual activity, incapacitating, requires medical intervention

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is determined by the criteria in Section 12.3.

Relationship: The relationship of the Adverse Event to the study drug will be determined by

the investigator, and assessed using the following definitions:

- **Definite:** There is a distinct temporal relationship between the event onset and administration of the study drug. There is a known reaction to agent or chemical group, or predicted by known pharmacology. The event cannot be explained by patient's clinical state or other factors.
- **Probable:** A reasonable temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the patient's clinical state, intercurrent illness or concomitant therapies. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. The AE is likely to be a known reaction to the agent or chemical group or is predicted by known pharmacology. It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.
- **Possible:** A reasonable temporal relationship exists between the event onset and administration of the study drug. The event could be explained by the patient's clinical state, intercurrent illness or concomitant therapies. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge.
- **Unlikely:** A poor temporal relationship exists between the event onset and administration of the study drug. The event could easily be explained by the patient's clinical state, intercurrent illness or concomitant therapies.
- **Unrelated:** Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment. Reasonable explanations should be provided for each causal assessment.

For reporting and statistical purposes, "Definite", "Probable", and "Possible" will be considered as positive causal relationship with the study drug and the event (i.e. Related to study drug), while "Unlikely" and "Unrelated" will be considered unrelated to study drug.

12.3 Serious Adverse Events

All events (serious and non-serious) that occur after informed consent is signed and up to 28 days after the study drug has been discontinued will be reported in the eCRF. All SAEs occurring more than 28 days after last study drug administration and considered at least possibly drug-related must also be reported.

An SAE is an AE from this study that:

- Results in death
- Is life-threatening situation (patient is at immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in the offspring of a patient who received study drug
- Is considered significant by the investigator for any other reason

Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Within 24 hours of identifying a SAE, the responsible investigator or qualified study personnel must record the SAE in the AE eCRF as "serious" and all SAEs must be submitted

during the course of the study.

A life-threatening AE is defined as any adverse experience that places the patient in the view of the Investigator, at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity.

Hospitalizations for study therapy, disease-related procedures, palliative or hospice care, elective procedures (planned before signing the ICF) or placement of an indwelling catheter are not considered to be SAEs.

"Inpatient hospitalization" means the patient has been formally admitted to a hospital for medical reasons, for any length of time. Presentation and care within an emergency department does not necessarily constitute an SAE. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization, it is an SAE.

All deaths, regardless of cause, must be reported for patients on study (within 28 days of last study drug dose). The SAE term should reflect the event that leads to the death with "death" recorded as the outcome.

12.4 Serious Adverse Event Reporting Requirements

The procedure for reporting SAEs, regardless of causal relationship, is as follows:

- Within 24 hours of the investigator's knowledge of an SAE, the site must notify the Sponsor by completing the AE eCRF and selecting "Serious". The Medical Monitor will be automatically notified by EDC that an SAE has been entered.
- The initial SAE report should provide as much of the required information as is available at the time. The following minimum information is required for reporting an SAE: event verbatim term, seriousness criterion, Investigator causality, and an event outcome. Submission of the SAE via the EDC should not be delayed in order to collect additional information to complete the form.
- Follow-up SAE reports may be generated in cases in which additional information becomes available. The follow-up SAE report should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.
- The investigator should notify the local IRB/IEC of Serious Adverse Events occurring at the site and other adverse event reports received from Julius Clinical in accordance with local procedures, if required.
- In accordance with ICH Guidelines and/or local regulatory requirements, Julius Clinical or its designee will report SAEs as expedited and/or periodic safety reports as applicable, to CAs, IRBs/IECs, and investigators. Expectedness of SAEs will be determined on the basis of the Reference Safety Information in the Investigator's Brochure.

The investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded in the concomitant medication section of the patient's eCRF.

Details of the regulatory reporting of safety information of T-817MA are contained in the Medical and Safety Management Plan.

12.5 Overdose Reporting Requirements

Overdoses of study drug will be captured in the eCRF. For the purposes of this study, an overdose of T-817MA is defined as any dose greater than the highest daily dose included in the protocol. Typically, overdoses may be discovered during drug accountability or during the investigation of an AE. Any overdose of the study drug will be reported to Julius Clinical and FUJIFILM Toyama Chemical as soon as it is noted in the EDC even if there are no associated AEs or SAEs with the overdose.

12.6 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Laboratory abnormalities are usually not recorded as AEs, unless considered to be clinically significant by the investigator. An abnormal laboratory result will be considered an AE if it induces clinical signs or symptoms, if the abnormality is of a degree that requires active management (e.g. discontinuation of the study drug, dose modification), or when the event is requiring treatment or other therapeutic intervention (e.g. iron supplements, blood transfusion, etc.).

The investigator will evaluate the relationship of any significantly abnormal result to protocol treatment and clinical condition, if possible. All clinically significantly abnormal laboratory results will be followed until they return to normal or become stabilized.

12.7 Pregnancy and Breast Feeding

T-817MA should not be used during pregnancy or while breastfeeding. Women must be post-menopausal or surgically sterile to be eligible for this study. Male patients, even if he is vasectomized, must use condom to protect pregnant or non-pregnant WOCBP partner from exposure to seminal fluid. In addition, the WOCBP partner of the male patient (except a vasectomized male) must use one of the highly effective methods of contraception described in Section 8.1.

13. STATISTICAL METHODS

13.1 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 US 202 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 or before Week 78.

13.2 Randomization and Stratification

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]).

13.3 Protocol Deviations, Data Blind Review, and Unblinding

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 responsible statistician will request the treatment codes, the study will be unblinded, and the statistical analysis will be conducted.

13.4 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 deviations.

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.

13.5 Efficacy Endpoints

13.5.1 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.

13.5.2 Secondary Efficacy Endpoints

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, Aβ1-42, Aβ1-40, NFL, neurogranin, YKL-40 and Aβ1-42/Aβ1-40 ratio from Baseline to Weeks 52 and 78.
4. The change in plasma Aβ1-42, Aβ1-40, NFL, GFAP, p-tau181, p-tau217 and Aβ1-

42/Aß1-40 ratio from Baseline to Weeks 52 and 78.

5. The change in 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

13.6 Safety Endpoints

- Occurrence of AEs
- Physical examinations
- Vital signs (heart rate, blood pressure and weight)
- 12-lead ECG
- Clinical laboratory tests: hematology, serum biochemistry and urinalysis (see Section 11.2)

13.7 Statistical Methods

Complete details of efficacy and safety analyses will be provided in a separate Statistical Analysis Plan (SAP) which will be finalized before breaking the blind.

13.7.1 Efficacy Analysis

Analysis of primary and secondary efficacy endpoints (see Sections 13.5.1 and 13.5.2) will be performed on the mITT, and PP populations. For each endpoint the analyses will test the statistical hypotheses of no difference between the two treatment groups using a Mixed-effect Model for Repeated Measures.

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 statistical hypothesis of no difference between the two treatment groups.

Categorical variables will be summarized by treatment group using frequency distribution: number of non-missing observations (N) and percentages (%). Percentages will be calculated within each treatment group on the number of non-missing observations. Continuous variables will be summarized using standard quantitative statistics: number of non-missing observations (N), mean, standard deviation (SD), median and range (minimum and maximum observed values).

Subgroup analysis (e.g. gender, age, Baseline MMSE score, ApoE genotype) will be performed in the mITT and PP populations.

13.7.2 Safety Analysis

The Safety population will be used for analyses of each of the safety endpoints. Clinical laboratory tests, vital signs, physical examinations and 12-lead ECG will be summarized by number of patients, frequency rates and number of events by adverse events and by treatment group. The time point of each event will also be summarized.

13.7.2.1 Adverse Events

AEs occurring after the start of study drug dosing at Baseline (Week 0) will be summarized descriptively for the safety population. All AEs will be coded according to system organ class (SOC) and preferred term (PT) using a Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Summary tables showing the number of patients and percent within each category will be generated for each of the following types of adverse events and its relationship to study

treatment (related to study treatment):

- All events
- Serious events
- Deaths
- Events leading to drug interruption, dose change or discontinuation
- Severe events

13.7.2.2 Laboratory Parameters

Laboratory parameters will be summarized by visit. 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.

13.7.2.3 Other Safety Parameters

Vital signs and ECG parameters will be summarized across groups by visit using descriptive statistics, and at each outcome visit and at end of study.

Physical examination findings and ECG abnormalities and number of patients will be summarized as the count and percentage of patients by eCRF pre-defined categories at last visit. Change from Baseline at last visit will be summarized in a shift table crossing Baseline and last visit results. Vital signs will be summarized by visit using descriptive statistics.

13.8 Population Pharmacokinetic Analysis

Population pharmacokinetic analysis will be performed as outlined in a separate PPK statistical analysis plan.

13.9 Interim Analyses

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.

14. RECORDING AND COLLECTION OF DATA

14.1 Case Report Form

The investigator or designee will record all data collected in the eCRF provided for that purpose. The site will be suitably trained on the use of the eCRF and appropriate site personnel will be provided electronic signatures.

Completed eCRFs will be submitted according to the instructions of the CRO, and reviewed by the CRO to determine their acceptability. If necessary, data correction requests will be generated for resolution by the study site. The investigator or designee will make necessary eCRF corrections.

All site entries will be made in a secured web site and the Principal Investigator (PI) will review the record for completeness. Upon completion of the review, including review of any corrections, the PI will sign electronically in the signature page of the eCRF.

14.2 Study Files and Patient Source Documents

Patient confidentiality is strictly held in trust by the participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to patients. Authorized representatives of the sponsoring institution may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the patients in this study. The clinical study site will permit access to such records. Any data, specimens, forms, reports, and other records that leave the site will be identified only by a patient identification number to maintain confidentiality.

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents include Investigators' Study Files and original patient clinical source documents generated at the study site. The term "original" means the first recording of the data.

The investigator will ensure the site master files are maintained, including the study protocol and its amendments, IRB/IEC and regulatory approvals with associated correspondence, informed consents, study drug records, staff curriculum vitae, all correspondence, and other appropriate documents.

Patient clinical source documents may include, but are not limited to, patient hospital/clinic records, physicians' and nurses' notes, appointment books, laboratory reports, ECGs, radiographs, pathology and special assessment reports, and consultant letters. The investigator must assure that all original source documents are available to support monitoring activities.

14.3 Monitoring

During the study each site will be visited at regular intervals by a clinical research monitor from Julius Clinical. The monitoring visits must be conducted according to the applicable ICH-GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements and continued adequacy of the investigational site and its facilities. The investigator will co-operate in the monitoring process by ensuring the availability of the eCRFs, source documents and other necessary documents at the time of the monitoring visits and by prompt attention to any matters brought to his/her attention by the monitor.

14.4 Audit

ICH-GCP requires independent inspection of clinical program activities. Such inspections may be performed at any time - before, during and/or after the study. The investigator and study staff are responsible for maintaining the site master file containing all study-related regulatory documentation as outlined by Julius Clinical that will be suitable for inspection at any time by FUJIFILM Toyama Chemical, its designees, and/or regulatory agencies. The investigator understands and agrees to give access to the necessary documentation and files.

14.5 Retention of Data

All records connected with this clinical study will be retained for at least 2 years following the date of an approved marketing application or at least 2 years from the formal discontinuation of T-817 development. However, these records should be retained for a longer period if required by other applicable requirements (e.g. applicable local or international regulatory requirements) or per agreement with the sponsor or its designee. The investigator should

contact the sponsor or its designee prior to any record destruction. If off-site archiving is used, all records should be retrieved and made available for review at the time of an audit or CA inspection.

14.6 Reporting of Study Results

FUJIFILM Toyama Chemical, in cooperation with Julius Clinical, will produce an integrated Clinical Study Report (CSR), which will be submitted for approval to the Project Director.

14.7 Quality Assurance/ Quality Control

The Standard Operating Procedures (SOPs) of Julius Clinical will be adhered to for all activities relevant to the quality of the study.

Documentation of all data quality control procedures will be outlined in the Data Review Plan (DRP). Some of the aspects of data quality control are edit checks and listings. These will be run and used in conjunction with the eCRF pages to support a clinical review of the data.

15. PUBLICATION POLICY

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multi-center studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

A manuscript for publication will only be written and submitted after all results are analyzed and reported at the end of the study. Any output has to be approved before submission by every author and the Sponsor. This approval should be done within a reasonable time frame. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

16. REFERENCES

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17. APPENDIX 1: STUDY-SPECIFIC INSTRUCTIONS IN CASE OF RESTRICTIONS TO REGULAR STUDY CONDUCT DUE TO COVID-19 OR OTHER INFECTIONS

17.1 Background

To prepare for possible new waves of COVID-19 or other infections in the participating countries and to minimize its effect on sites, patient safety and scientific integrity of the study data, this appendix describes how to conduct the study in case a new wave of COVID-19 or other infection occurs. Please note that the instructions in this appendix only apply in case regular conduct of the study is interrupted due to COVID-19 or other infections, for example because of traveling restrictions, an overwhelmed medical system or any other study interruption related to COVID-19 or other infections. In addition, the decision may be taken by the sponsor to (temporarily) halt recruitment at a site impacted by COVID-19 or other infection, while allowing study visits for already randomized patients to continue as much as possible. In case national or international guidelines on the conduct of clinical trials during a new wave of COVID-19 or other infections contradict the information in this appendix, these guidelines will be leading and will overrule the information provided in this appendix.

17.2 Home / Remote Study Visits

If the situation allows for an on-site visit to take place, this is strongly preferred. The decision on whether an on-site visit can take place is up to the discretion of the Principal Investigator. In case an on-site visit can take place and the study procedures can be performed as normal, despite a new wave of COVID-19 or other infections, the instructions in this appendix do not apply.

If a patient is unable to visit the site for a study visit, the visit can either be conducted by the site staff remotely, or by visiting the patient at home. Study procedures must always be performed by appropriately trained and delegated site staff.

If the visit is conducted remotely, the patient may be contacted via telephone or through a secure videocall connection. The patients' study partner must be present as well, regardless of how the visit is performed (remotely or at home).

Depending on whether the visit is performed remotely or at home, the assessments in Table 3 should be performed. Please note that in case certain study assessments have not been performed (for example because the visit was performed entirely remote), the missing assessments must be obtained as per the regular protocol as soon as the regular on-site study visits can resume again.

For study visits with efficacy assessments (lumbar puncture, CDR-sb/CFC and MRI – see 1.1 Schedule of Activities), an on-site visit (performed out of the visit window) is strongly preferred over a remote visit or home visit. Please refer to Section 17.5 for more details on the visit windows.

Table 3. Schedule of activities for Remote visits and Home visits

	Remote visit[1]	Home visit[1,2]
Physical Examination		X
Vital signs	X[3]	X
Concomitant medications	X	X
Adverse Events	X	X
12-lead ECG	X[3]	
Hematology, chemistry, urinalysis	X[3]	X[4]
Blood draw for biomarkers		X[4]
Blood draw for PPK		X[4]
CFC		X
CDR-sb		X
EEG[5]		
vMRI[5]		
Lumbar puncture for CSF[5]		
Study drug dispense	X[6]	X[7]

1. Procedures specific to the applicable study visit must be performed – please refer to 1.1 Schedule of Activities.
2. The home visit may only be conducted by site staff that is appropriately delegated.
3. Only applies in case the patient is able to visit a local lab.
4. Must be performed using central lab kits.
5. These assessments can only be done in case a visit is done on-site.
6. Shipment of study drug to the patient must be performed per Section 17.3.
7. In case of a home visit, study drug must be brought to the patient. For full instructions, please refer to Section 17.3.

Abbreviations: CDR-sb: Clinical Dementia Rating Scale Sum of Boxes; CFC: Cognitive Functional Composite; CSF: cerebrospinal fluid; ECG: electrocardiogram; EEG: electroencephalogram; PPK: population pharmacokinetics; vMRI: volumetric magnetic resonance imaging.

In case a local lab is used:

- Prior to using any other lab than the central lab, please contact your Clinical Research Associate;
- The results of the local lab, including the reference ranges, must be communicated as soon as available directly to the study site for review by the Principal Investigator and inclusion in the patients' source;
- The local laboratory results and the reference ranges should be uploaded to the eCRF within 5 business days (please see the EDC User Manual for instructions);

17.3 Dispensing of Study Medication

In case of a home visit, study drug must be provided to the patient by the visiting study staff. The study drug must be dispensed in IWRS on the same day as the home visit and must be transported to the patient using temperature-controlled transport, including a temperature logger. The temperature log must be filed in the patients' source documents. Instructions on study drug administration to the patient must be done per protocol (Section 7).

In case of a remote visit, study drug can be shipped directly from the site to the patient via a courier. Study drug may only be shipped to the patient once a check has been performed by the Investigator that the patient can continue treatment. Study drug must be shipped to the

patient immediately after the remote visit has taken place. Courier costs will be reimbursed by the sponsor.

When shipping study drug directly from a site to a patient, the following criteria must be met:

- Verbal consent must be obtained from the patient and study partner prior to shipping study drug. The date verbal consent was obtained must be documented in the patients' source;
- The study partner must be notified when study drug is shipped to ensure the study partner can assist the patient with receiving and administering study drug;
- Written instructions on the dosage regimen must be included with the study drug shipment, along with the sites' contact information for any questions that the patient may have;
- Patients and study partners must be instructed to contact the site in case there is any damage to the study drug packaging or the study drug itself;
- The shipment can be performed by a courier that is generally used by the site, but the courier must be pre-approved for use by the sponsor;
- The site must be notified by the courier upon receipt of the study drug shipment by the patient;
- The study drug shipment must be performed in a temperature-controlled environment and the temperature log of the shipment must be filed in the patients' source;
- The temperature log must be checked by the study partner before study drug is administered. In case the temperature deviates from the appropriate storage conditions (between 0ºC and 30ºC), the site must be immediately notified by the study partner. After consultation with the sponsor, the patient must be informed at the earliest opportunity whether the study drug can still be used;
- Clear records of the study drug shipment from the site to the patient must be kept by the patient or study partner, such as proof of shipment, proof of receipt and temperature log;
- The study drug must be stored between between 0ºC and 30ºC by the patient;
- The study drug shipment-to-patient tracking log must be filled out by the site in case study drug is shipped to a patient;
- Empty cartons must be kept by the patient or study partner and brought to the site during the next on-site visit;
- Drug accountability should be performed once the empty cartons are returned to the site by the patient or study partner during a next on-site visit;
- When seeking reimbursement of the shipping costs by submitting the invoice, personal data of the patient to whom the study drug was shipped must be blinded.

17.4 Timing of Obtaining Safety Information (Collection and Follow-up of [S]AE, Laboratory Assessments, Physical Examination, Vital Signs, ECG)

Obtaining safety information within the visit window is of the utmost importance for the safety of patients, especially when administering study drug. In case safety information cannot be obtained within the visit window, immediately contact the Medical Monitor to discuss this further.

17.5 Timing of Lumbar Puncture, MRI, EEG, Cognitive Tests Procedures and Collection of Biomarkers and PK Samples

Due to the importance of obtaining the CSF, MRI, EEG, biomarkers, PK samples and cognitive test results to the scientific integrity of the study, these procedures must continue as much as possible. Depending on the situation, there is a possibility that the procedures cannot be performed within the defined visit windows. If that is the case, this must be clearly documented in the patients' source. Every effort must be taken to ensure the procedures are

performed within +/- 1 week of the scheduled visit date.

If it appears that it will not be possible to perform these procedures within the defined visit window of +/- 1 week, the procedures must be performed within the visit windows as specified below:

- Lumbar puncture (Week 52, Week 78): **+/- 4 weeks**
- MRI (Week 52, Week 78): **+/- 4 weeks**
- EEG (Week 52, Week 78): **+/- 4 weeks**
- CFC and CDR-sb (Week 28, Week 52, Week 78): **+/- 4 weeks**
- Blood draw for biomarkers (Week 52, Week 78): **+/- 4 weeks**

In case the above study procedure windows cannot be met, please contact the Medical Monitor.

Note that for the blood draw for PPK samples, if due to the circumstances no samples could be collected from the patient prior to the Week 52 visit, at least 1 pre-dose and 1 post-dose sample must be collected from the patient at a subsequent visit. These samples can be collected from the patient at the subsequent on-site study visit.

17.6 Discontinuations

In addition to the discontinuation criteria as mentioned in Section 10, the below discontinuation criteria will apply:

- If safety information could not be obtained within the visit window, the Medical Monitor will assess if the patient must be discontinued;
- A study visit is skipped in its entirety by the patient