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 to moderate Alzheimer's Disease (US202)

Protocol & SAP Synopsis

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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 to moderate Alzheimer's Disease (US202)
STUDY SPONSOR	Toyama Chemical Co., Ltd.
COORDINATING CENTER	Alzheimer's Disease Cooperative Study (ADCS)
STUDY PHASE	2
INDICATION	For the treatment of mild to moderate Alzheimer's disease.
OBJECTIVES	The primary objective is to evaluate the efficacy of T-817MA as measured by ADAS-cog and ADCS-CGIC. The secondary objectives are: • To evaluate the safety and tolerability of T-817MA measured by clinical safety laboratories, physical examinations, ECGs and solicitation of adverse events. • To evaluate the efficacy of T-817MA as measured by ADCS-ADL, FAQ, Neuropsychiatric Inventory (NPI) and Mini-mental State Examination (MMSE).
ADDITIONAL OBJECTIVES	Population pharmacokinetics of T-817 will be analyzed. Volumetric MRI (vMRI) scans will be evaluated. CSF biomarkers will be evaluated in a subset of the study population.
PRIMARY ENDPOINTS	The change in the ADAS-cog and ADCS-CGIC from Baseline to Week 52 between each T-817MA treatment group (high or low dose) and the placebo group.
SECONDARY ENDPOINTS	• The change in the ADAS-cog from Baseline to Weeks 12, 24, 36, 44 and 56. • The change in the ADCS-CGIC from Baseline to Weeks 12, 24, 36 and 44. • The change in the MMSE from Baseline to Weeks 12, 24,

	36, 44, 52 and 56. • The change in the ADCS-ADL, FAQ and NPI from Baseline to Weeks 12, 24, 36 and 52. • Safety as measured by occurrence of adverse events, clinical laboratory tests, vital signs, physical examinations, ECGs, use of concomitant medications, and the C-SSRS Pediatric.
STUDY DESIGN	This is a Phase 2 multi-center, randomized, double blind, placebo-controlled, parallel group study. Patients will be screened at the investigative site in order to determine their 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 will be randomized to one of three treatment groups: placebo, 224 mg T-817MA, or 448 mg T-817MA in a 1:1:1 allocation. Donepezil or rivastigmine transdermal system, concomitant treatment for Alzheimer's disease, will be required to be taken as prescribed by the PI or other prescribing physician, and will be encouraged to be maintained throughout the study. Memantine will be allowed only when prescribed in combination with donepezil or rivastigmine transdermal system. Patients will be seen every four weeks for the first 12 weeks of the study, and then will be seen every 6 weeks thereafter until Week 36, then at Week 44 and Week 52. A final follow-up visit will be conducted at Week 56. Safety evaluations will be carried out at each visit. Efficacy will be assessed every 12 weeks beginning at Baseline through Week 36 then at Week 44 and 52 and finally during the follow up visit at Week 56. Volumetric MRI scans of the brain will be done at Screening and Week 52. Blood collection for population pharmacokinetic (PPK) assessments will be done at Baseline and Weeks 12, 24, 36, 44 and 52. A subset of patients will undergo lumbar puncture at Weeks 0 and 52 to evaluate

	CSF biomarkers.
SAMPLE SIZE	In order to arrive at 110 evaluable patients in each study group, it is necessary to randomize at least 450 patients (at least 150 per group), assuming a 26% dropout rate during the treatment period.
KEY ELIGIBILITY CRITERIA	• Ages 55 to 85 years (inclusive), with probable AD • MMSE 12-22 (inclusive) at screening • Receiving donepezil or rivastigmine transdermal system treatment for at least 4 months prior to Baseline and on a stable dose for 3 months prior to Baseline • Brain MRI or CT consistent with Alzheimer's disease • Residing in the community with a designated study partner who will accompany the patient to all clinic visits and participate in the evaluations (see protocol details) • Informed consent or Legally Authorized Representative (LAR) proxy informed consent with patient's assent
DRUG DOSAGE AND FORMULATION	Two dosing levels of T-817MA (224 and 448 mg/day) or placebo. The 448 mg dose arm will be started at 224 mg for 4 weeks, and then increased to 448 mg. Film-coated tablets are 112 mg T-817MA or placebo and dispensed in blister packs. The study medication will be taken once daily after breakfast.
ROUTE OF ADMINISTRATION	Oral
TREATMENT DURATION	Duration of treatment is 52 weeks. There is also a screening period of up to 6 weeks; and a 4-week post-treatment observation period. Each patient may participate in the study for up to 62 weeks.
PROCEDURES	Physical examinations, cognitive and functional test batteries, clinical and research venipunctures, volumetric MRIs, and lumbar puncture in a subset of patients. Visits: Screening (within 42 days prior to randomization),

	Baseline (Week 0), Weeks 4, 8, 12, 18, 24, 30, 36, 44, 52, and 56 (follow-up)

STATISTICAL METHODS

1.1 Sample Size Determination

The change in the ADAS-cog score in the placebo group is expected to be 3.5 points in one year. Assuming that the difference in the ADAS-cog scale between each T-817MA treatment group and the placebo group is 2.5 points after one year, with a Standard Deviation of 6.5, the required number of cases to show a significant difference in the ADAS-cog is estimated at 110 per group. This calculation has 80% statistical power at the 5% significance level.

The power calculation of 80% as shown above corresponds to achieving significance on the ADAS-cog alone, which would be considered a successful outcome for a proof of concept study. Achieving significance on both co-primary endpoints is not fully powered, but would be considered a successful outcome for a pivotal study.

In order to have 110 evaluable patients in each group, it is necessary to randomize at least 450 patients (at least 150 per group) to double-blind treatment, assuming a 26% dropout rate during the treatment period.

1.2 Randomization and Stratification

Each patient will be randomly allocated in a 1:1:1 ratio into one of the 3 groups: treatment with 448 mg or 224 mg of T-817 or placebo. A randomization schedule will be generated and incorporated into the Electronic Data Capture system (EDC) and the treatment group will be assigned as 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. Site and baseline MMSE will be stratification factors.

1.3 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 (Data Blind Review). After database lock, the responsible statistician will request the treatment codes, the study will be unblinded, and the statistical analysis will be conducted.

1.4 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:
  - took the assigned medication during the 52 weeks of treatment, and
  - did not have any major protocol 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.

1.5 Efficacy Endpoints

1.5.1 Primary Efficacy Endpoints

The co-primary efficacy endpoints are the change in the ADAS-cog and ADCS-CGIC from Baseline to Week 52 between each T-817MA treatment group (high dose or low dose) and the placebo group in the mITT population. A Mixed-effects Model Repeated Measure will be used to calculate the differences in change of ADAS-cog at 52 weeks, with baseline ADAS-cog score as covariate. A Mixed-effects Model Repeated Measure will be used to calculate the differences in change of ADCS-CGIC at 52 weeks.

1.5.2 Secondary Efficacy Endpoints

1. The change in the following assessments from Baseline to Week 52 between each T-817MA treatment group (high dose and low dose) and the placebo treatment group in the mITT population:
   a. ADCS-ADL
   b. FAQ
   c. NPI

d. MMSE

A Mixed-effects Model Repeated Measure will be used to calculate differences at 52 weeks, using baseline assessment as a covariate.

2. The following will also be analyzed in the mITT population:
    a. The change in ADAS-cog, ADCS-CGIC, ADCS-ADL, FAQ, NPI and MMSE from Baseline to Weeks 12, 24 and 36
    b. The change in ADAS-cog, ADCS-CGIC and MMSE from Baseline to Week 44
    c. The change in ADAS-cog and MMSE from Baseline to Week 56
3. Primary and secondary endpoints will similarly be assessed in the per-protocol population.

1.6 vMRI

Observed Case analysis for differences in change of vMRI over 52 weeks with mITT and PP.

1.7 CSF Substudy

Observed Case analysis for differences in change of CSF biomarkers over 52 weeks with mITT and PP.

1.8 Safety Endpoints

- Occurrence of adverse events (AEs)
- Clinical laboratory tests
- Vital signs
- Physical examinations
- ECGs
- Use of concomitant medications
- C-SSRS Pediatric

1.9 Statistical Methods

Complete details of efficacy and safety analyses will be provided in a separate Statistical Analysis Plan (SAP).

1.9.1 Efficacy Analysis

Analysis of primary and secondary efficacy endpoints will be performed on the mITT, and PP populations.

The primary efficacy hypothesis is that treatment with one or both of the T-817MA doses will result in a statistically significant reduction in total ADAS-cog score relative to the placebo group at Week 52 in the mITT population. The first stage in the hierarchical analysis will test the statistical hypothesis of no difference between the three treatment groups.

A hierarchical strategy will be used to preserve alpha: the primary analysis will first compare the high dose arm to placebo at an alpha level of 0.05, and if this is positive the low dose group will be compared to placebo again at an alpha level of 0.05.

The first stage in the hierarchical analysis will test the statistical hypothesis of no difference between the three 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).

OC and Imputation analysis of primary and secondary efficacy endpoints (the change in ADAS-cog and MMSE from Baseline to Weeks 12, 24, 36, 44, 52 and 56, the change in ADCS-ADL, FAQ and NPI from Baseline to Weeks 12, 24, 36 and 52 and the change in ADCS-CGIC from Baseline to Weeks 12, 24, 36, 44 and 52) will be performed in the mITT and PP populations.

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

1.9.2 Safety Analysis

The Safety population will be used for analyses of each of the safety endpoints. All concomitant medications will be tabulated according to drug class and preferred term using the WHO dictionary. Clinical laboratory tests, vital signs, physical examinations and 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. C-SSRS results will be summarized by mean values and changes from baseline at each visit.

1.9.2.1 Adverse Events

Adverse events (AE) 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 withdrawal
- Severe events

1.9.2.2 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, 8, 12, 18, 24, 30, 36, 44, 52 and 56) and Baseline visit by time point and treatment group. Urinalysis values will be cross-summarized at pre-dose and post-dose.

1.9.2.3 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. Concomitant medications will be summarized by treatment group, drug class and preferred term. Vital signs will be summarized by visit using descriptive statistics.

The change in the C-SSRS Ped score from Baseline to Weeks 12, 24, 36 and 52 will be summarized between each T-817MA treatment group (high dose and low dose) and the placebo treatment group.

1.10 Population Pharmacokinetic Analysis

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

1.11 Interim Analyses

An interim analysis is not currently planned, but may be added at a later time if it is deemed necessary. If so, an amendment to the protocol will be filed at that time.