STATISTICAL ANALYSIS PLAN

Protocol Name

A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Donepezil Hydrochloride (E2020) in Patients with Dementia Associated with Cerebrovascular Disease

Protocol No.

E2020-K082-418

Investigational Product

E2020/Aricept (Donepezil Hydrochloride)

Effective Date

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1.0	Approval date	PPD	First Version
2.0	Approval date		2.0 Version

Abbreviation

Term	Definition
ADAS-cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
ADR	Adverse Drug Reaction
AE	Adverse Events
ANCOVA	Analysis of Covariance
ATC code	Anatomical Therapeutic Chemical code
CIBIC-plus	Clinicians Interview-Based Impression of Change-plus
CIBIS-plus	Clinician's Interview-Based Impression of Severity-plus
CI	Confidence Interval
CVD	Cerebrovascular Disease
DB	Double-Blind
FAS	Full Analysis Set
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
KGCP	Korea Good Clinical Practice
LNH	Low/Normal/High
LOCF	Last Observation Carried Forward
LS mean	Least Squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental Status Examination
OC	Observed Cases
OLE	Open-label Extension
PPS	Per-Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SOC	System Organ Class
SOP	Standard Operating Procedure
VaD	Vascular Dementia

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1. Study Design

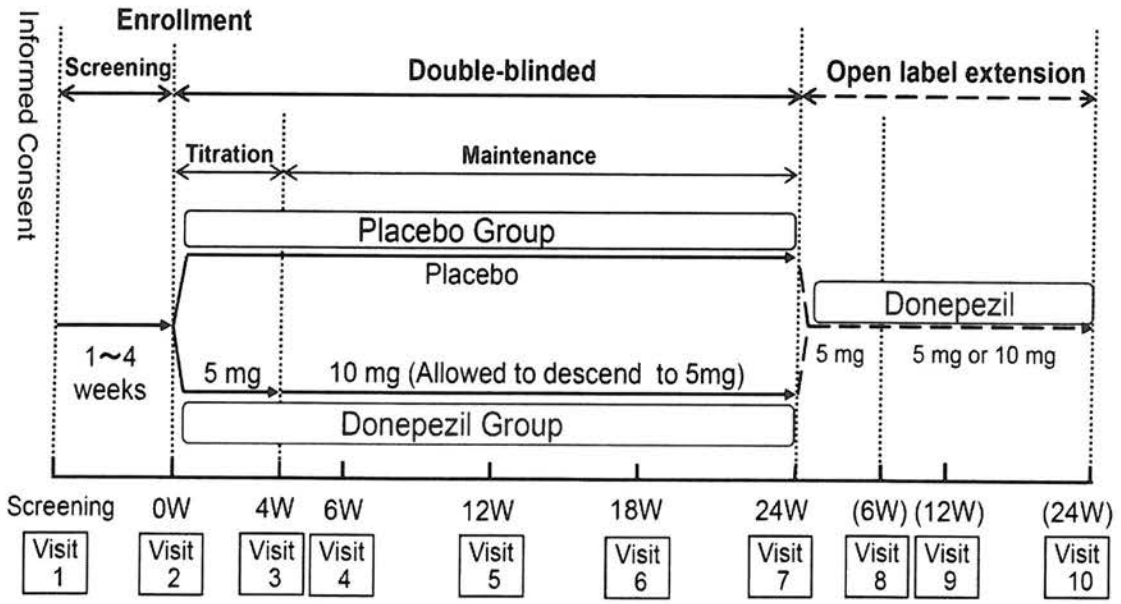
This is a multi-center, randomized, double-blind, placebo-controlled, parallel-group study with an open-label extension.

Main Study

The main part of the study consists of 2 phases; screening phase (SCR; 1 to 4 weeks), and double-blind phase (DB; 24weeks, placebo-controlled). DB phase includes 2 periods; titration and maintenance. The duration of titration period is 4 weeks.

After written informed consent is obtained and evaluated for suitability for study entry, eligible subjects will be randomly assigned to receive either donepezil or placebo. Donepezil or placebo will be taken once daily in the evening. A total of 324 subjects will be randomized (162 subjects/group).

Donepezil 5mg will be administered in the titration period and then the dose will be increased to 10mg at Week 4 according to investigator's clinical judgment. During the maintenance period, dose reduction to 5mg/day will be permitted only when 10mg/day is intolerable due to adverse events. In this case, the dose cannot be escalated up to 10mg/day again.



Open-label Extension

Subjects, who have completed the DB phase and have consented to continue participation of the study, can be enrolled in the 24-week Open-Label Extension (OLE) phase. In this phase, treatment will be initiated at

5mg/day, and the dose is maintained until Week 6. After assessing clinical response by examination, the dose can be increased to 10mg/day. Dose reduction (from 10mg/day to 5mg/day) will be permitted when the investigator judges it difficult to continue the 10mg/day administration. It is possible to increase the dose to 10mg/day again. In the OLE phase, subjects will visit the study institution at Week 6, 12, and 24.

Determination of Sample Size

The primary endpoints are the change from baseline to Week 24 (Last Observation Carried Forward (LOCF)) in Alzheimer's Disease Assessment Scale-Coginitive Subscale (ADAS-cog) and the measurement at Week 24 (LOCF) of the Clinicians Interview-Based Impression of Change-plus Caregiver Input (CIBIC-plus).

The estimates of these endpoints were referred from the result of subgroup (Mini-Mental Status Examination (MMSE) less than 24) in pooled data of previous double blind studies (E2020-A001-307 and E2020-A001-308).

The mean difference and standard deviation of the change from baseline to final visit in ADAS-cog were estimated as -2.404±5.955, using pooled data of E2020 groups (5mg+10mg). When the significance level was set as 5.0% (two-tailed) and statistical power as 80.0%, the subject number needed to detect statistically significant difference by 2 sample t-test was calculated to be 196 (98/arm).

On the other hand, the mean difference and the standard deviation of CIBIC-plus score at the final visit were estimated as -0.261±1.162, when CIBIC-plus was regarded as continuous measurement [scored from 1 (marked improvement) to 7 (marked worsening) point]. The subject number needed to reduce the probability that donepezil is inferior to placebo in point estimate to 2.5% or less, was calculated to be 308 (154/arm).

Therefore, the subject number required to achieve primary objectives simultaneously became 308 (154/arm). In consideration of exclusion from the analysis set (approximately 5%), the sample size was defined as 324 (162/arm).

2. Study Objectives

2.1 Co-Primary Objectives

1) To confirm that donepezil hydrochloride (E2020) has superior efficacy compared with placebo in improving cognitive function, as measured by ADAS-cog, in patients with dementia associated with cerebrovascular disease (VaD).

2) To demonstrate that donepezil hydrochloride (E2020) has superior efficacy compared with placebo in improving global function, as measured by CIBIC-plus, in patients with VaD.

2.2 Secondary Objectives

To evaluate the efficacy (as measured by MMSE and executive function test) and safety of E2020 compared with placebo, in patients with VaD.

3. Efficacy and Safety Variables

3.1 Efficacy Variables

3.1.1 Primary efficacy variables

1) Cognitive function: ADAS-cog Subscale

   ADAS-cog will be assessed at Visit 2, 3, 5, 6, and 7 (Week 0, 4, 12, 18, and 24).

2) Global function: CIBIC-plus

   CIBIC-plus will be assessed at Visit 2, 3, 5, and 7 (Week 0, 4, 12, and 24).

3.1.2 Secondary efficacy variables

1) MMSE will be assessed at Visit 2, 3, 5, 6, and 7 (Week 0, 4, 12, 18, and 24).
2) Executive function test (Trail making test) will be assessed at Visit 2, 5, and 7 (Week 0, 12, and 24).

3.2 Safety Variables

1) Adverse events
2) Clinical laboratory evaluation (Hematology, Chemistry, Urinalysis)
3) Vital signs
4) Electrocardiograms

4. Analysis Sets

For the DB phase, the analysis will be performed on Full Analysis Set (FAS), Modified Full Analysis Set (mFAS), Per Protocol Set (PPS), and Safety Analysis Set (SAS), and for the OLE phase, the analysis will be performed on FAS and SAS only. Each analysis set will summarize the number of subjects and its percent from randomized subjects by each treatment group and by total.

4.1 Efficacy Sets

The analysis of FAS is primary, and those of mFAS and PPS are sensitivity analysis of FAS.

- FAS (Full Analysis Set): is the group of randomized subjects who received at least one dose of study drug and had at least one post-dose primary efficacy assessment. FAS will be analyzed according to the "planned treatment group (as randomized)".
- mFAS (modified Full Analysis Set): is the group of subjects from FAS. mFAS will be analyzed according

to the "actual treatment group (as treated)".

- PPS (Per Protocol Set): is the subset of subjects in FAS who sufficiently complied with the protocol without any major violations. The reasons for exclusion from PPS are defined in blind data review report.

4.2 Safety Sets

The evaluation of safety parameters will be conducted on the SAS.

- SAS (Safety Analysis Set): is the group of subjects who received at least one dose of study drug and had at least one post-dose safety assessment.

SAS will be analyzed according to the "actual treatment group".

4.3 Analysis Sets in Open Label Extension Phase

- FAS-OLE (the Efficacy Analysis Set of OLE-phase): the group of subjects who received at least one dose of study drug and had at least one post-dose MMSE measurement after starting OLE phase.
- SAS-OLE (the Safety Analysis Set of OLE-phase): the group of subjects who received at least one dose of study drug and had at least one post dose safety assessment after starting OLE phase.

5. Statistical Analysis

5.1 General Analysis Considerations and Conventions

All statistical tests will be conducted at the significance level of 5.0% (two-tailed) unless otherwise specified. Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. Categorical variables will be summarized by counts and by percentages of subjects in corresponding categories, and the percentages will be based on available data and denominators will generally exclude missing values. All *p*-values will be rounded down to four decimal places, and for a rounded down *p*-value <0.05 of any analysis will be considered statistically significant. Other than *p*-values, means, standard deviations, medians, percentages, and other values that carry decimal places will be rounded to two decimal places.

Statistical analyses for DB phase will be performed after database lock and released for unblinding. Statistical analyses for OLE phase will be performed after the study is completed and the database is locked.

All analyses will be conducted using SAS® Version 9.2 or higher (SAS Institute, Cary, NC).

5.2 Handling Missing Data

The efficacy analysis will be conducted on the FAS, mFAS and PPS. For FAS analysis, the observed cases (OC) for each visit will be used and the LOCF method will be applied for Week24 only, to impute missing data, unless otherwise specified. For mFAS and PPS analysis, the same method will be applied as of FAS. No imputation is planned for safety set analysis.

If only a partial date of onset for dementia is available and is required for a calculation, the following standards will be applied:

- If day is missing, it will be imputed as 15
- If month is missing, it will be imputed as 6 (June)
- If year is missing, date will be considered as missing

5.3 Adjustments of Covariates

The co-primary efficacy variables and secondary efficacy variables will be analyzed using ANCOVA model adjusted for the covariates, which is specified in detail in section 5.10 Efficacy Analyses.

5.4 Multiplicity

No multiple testing for primary hypothesis is planned in this study.

5.5 Pooling Sites

All analyses will be conducted by pooling all subjects of all sites, unless otherwise specified.

5.6 Subject Enrollment Status

5.6.1 Subject Disposition

The disposition of all subjects will be summarized. Subject disposition tables will include the number (percent) of subjects who are:

- Screened subjects and ineligible subjects;
- Randomized into each treatment group;
- Included in each analysis populations (SAS, FAS, mFAS, PPS);
- Discontinued from the study early, summarized by reasons for discontinuation.

5.6.2 Subject Disposition by Study Site

Subject disposition by study site will be summarized by number of screened subjects, number of randomized subjects, number (percent) of subjects who completed the study and who discontinued from the study early by treatment group and total.

5.6.3 Protocol Violations

Major protocol violations that led to the exclusion from PPS will be listed.

5.7 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics for each analysis set will be summarized for each treatment group and total of treatment groups using descriptive statistics (eg., mean, SD, median, minimum, maximum and frequency, proportion).

Continuous variables will be summarized using descriptive statistics by treatment group and total of treatment groups. Categorical variables will be summarized using frequencies and percentages by treatment group and total of treatment groups.

Subject's baseline characteristics include:

- Age (continuous), age group 1 (40-49/ 50-59/ 60-69/ 70-79/ 80-), age group 2 (<65/ ≥65), sex (male/ female), race (Korean/ other), weight, smoking status (never/ former/ current), duration of dementia (continuous), score of Hachinski Ischemia scale (continuous and categorical: ≤4/ 5-6/ ≥7), Clinical Dementia Rating (CDR) (continuous and categorical: 0/ 0.5/ 1/ 2/ 3), total score of MMSE (continuous and categorical: ≤19/ ≥20), CIBIS-plus, NIND-AIREN Checklist* (Yes/ No), CT Scan Findings/ MRI (Number of cortical infarct(s) (size ≥2cm) at any location, Number of cortical infarct(s) (size <2cm) at any location, Number of subcortical infarct(s) as continuous, and Yes/ No for other categories **), stroke type*** (Yes/ No), clinical diagnosis of vascular dementia (Probable/ Possible)

  Duration of dementia will be calculated as: ((Date of informed consent (include verbal consent)– Date of onset for dementia +1 day)/365.25days) x 12 months.

*: NIND-AIREN checklist consists:

Cognitive Decline from Previous Higher Level	Yes	No
Memory	o	o
Orientation	o	o
Attention	o	o
Language	o	o
Visuospatial Function	o	o
Executive Function	o	o
Motor Control	o	o
Praxis	o	o
Other Features		

Onset of Dementia within 3 Months of a Recognized Clinical Stroke	o	o
Abrupt Onset	o	o
Fluctuating Course / Step-wise Progression	o	o
Early Onset of Gait Disturbance	o	o
Unsteadiness and Frequent Falls	o	o
Personality and Mood Changes	o	o
Early Onset of Urinary Tract Problems	o	o
Pseudobulbar Palsy	o	o

**: CT / MRI Scan Findings categories (Yes/ No categories):

CT / MRI Scan Findings	Yes	No
Normal	o	o
Diffuse Cerebral Atrophy Disproportionate for Age	o	o
White Matter Lesions Periventricular only	o	o
White Matter Lesions Periventricular (≥ 25%)	o	o

***: Stroke Type categories:

Stroke Type	Yes	No
Cerebral Infarct	o	o
Intracerebral Hemorrhage	o	o
Subarachnoid Hemorrhage	o	o
Unknown	o	o

Caregiver's characteristics include:

- Caregiver's age (continuous), relationship to the subject (spouse/ child/ other relatives/ other), caregiver lives with the subject? (Yes/ No), average days to spend together with the subject per one week (continuous), average hours to spend together with the subject per one day (continuous)

5.8 Medical History and Comorbidity

Medical history and comorbidity will be summarized in number and percentages of subjects by SOC and PT and by treatment group. If the disease/surgery is checked "No" for the question 'Ongoing at Screening' on CRF page 6. Medical History (including Surgery), then it is considered as medical history. If the disease/surgery is checked "Yes" for the same question, then it is considered as comorbidity.

5.9 Prior and Concomitant Medications

Prior medication is defined as any medication taken prior to the first dose of study drug (End date of medications < Start date of study drug). Concomitant medication is defined as any medication taken during the treatment period between the date of the first dose of study drug and the date of the last dose of study drug, inclusive (End Date of medications ≥ Start Date of study drug and/or "Ongoing" is checked on CRF page 12. Prior/Concomitant Medications). Prior medications and concomitant medications will be summarized in number and percentages of subjects by Anatomical Therapeutic Chemical (ATC) code by treatment group.

Subjects who have taken prohibited medication and restricted medication which will be confirmed during the data review meeting will be listed.

5.10 Efficacy Analyses

Efficacy values that are within the visit window as described below are included in the efficacy analysis.

- Week 4: 14 ~ 42 days from visit 2 (baseline)
- Week 12: 70 ~ 98 days from visit 2 (baseline)
- Week 18: 112 ~ 140 days from visit 2 (baseline)
- Week 24: 154 ~ Minimum (182, visit 7 date (start date of OLE phase) – visit 2 (baseline) date +1) days from visit 2 (baseline)

If any efficacy values are measured 7 days after the final date of DB phase (either the completion or the discontinuation date of DB phase), then those efficacy values are not included in the efficacy analysis.

5.10.1 Co-Primary Efficacy Analyses

The co-primary efficacy variables are used as follows to determine whether donepezil has superior efficacy compared to placebo. Primary analysis is defined as follows:

- For ADAS-cog change from baseline to Week 24 (LOCF), an analysis of covariance (ANCOVA) model with baseline as covariates and treatment as main effect will be used for testing main effect. When the *p*-values of the difference of Least Squares (LS) mean scores of main effect are less than 0.05 then they will be considered as statistically significant and confirmed hypothesis.
- For CIBIC-plus scores, LS mean scores at Week 24 (LOCF) will be compared between groups to demonstrate numerical superiority of donepezil to placebo (the difference is less than 0), using ANCOVA model with CIBIS-plus (covariate) and treatment group (main effect). When the difference of LS mean scores are less than 0 then they will be considered as demonstrated hypothesis.

When the primary analysis results meet both the above criteria, this study objectives will be considered confirmed and demonstrated.

For the measurements of each visit of both endpoints (ADAS-cog: Baseline, Week 4, Week 12, Week 18, Week 24, CIBIC-plus: Week 4, Week 12, Week 24) and change from baseline to each visit of ADAS-cog, descriptive statistics (mean, SD, median, minimum, maximum and number of patients with non-missing data for both variables; number and percentages of each score for CIBIC-plus) will be presented. Where appropriate, LS mean, between-treatment difference in LS means, 95% confidence intervals (CIs) for the difference and *p*-value in each visit will also be presented. The statistical test will be conducted for CIBIC-plus as continuous variable using ANCOVA and as categorical variable using Cochran-Mantel-Haenszel test (CIBIS-plus as covariate). Group difference wil be calculated LS mean of Donepezil group minus LS mean Placebo group in ANCOVA for both endpoints. CIBIC-plus and CIBIS will be scoreed as next tables.

Table CIBIC-plus Scoring as conitunous

Variables	Category	Score
CIBIC-plus	Marked improvement	1
	Moderate improvement	2
	Minimal improvement	3
	No change	4
	Minimal worsening	5
	Moderate worsening	6
	Marked worsening	7
CIBIS	Normal	1
	Borderline mentally ill	2
	Mildly mentally ill	3
	Moderately mentally ill	4
	Markedly mentally ill	5
	Severely mentally ill	6
	Among most extremely ill	7

The LS means of change from baseline to each visit of ADAS-cog over time by each group will be presented in graphs with standard error. The frequency distributions of CIBIC-plus at Week 24 (LOCF) will be presented with bar charts. For these figures, FAS and mFAS will be used.

The following additional analyses will be conducted using FAS and mFAS:

1. Subgroup analysis (ANCOVA with baseline as covariate and treatment group as main effect) of the primary endpoints described above will be conducted for the following subgroups:
   A. Baseline MMSE total score (≤19/ ≥20)
   B. VaD (Probable/ Possible)

C. Baseline ADAS-cog measurement (<15 / ≥15)

D. Hachinski Ischemia scale (≤4/ 5~6/ ≥7)

E. Stroke type (Cerebral Infarct/ Intracerebral Hemorrhage/ Subarachnoid Hemorrhage)

2. The frequencies and percentages of the responders and non-responders will be presented in contingency tables and will be analyzed using Fisher's exact test. Odds ratios and 95% confidence intervals will be presented as well.

   Responders are defined as below:

   - Subjects who experienced an improvement in the CIBIC-Plus ("Marked improvement", "Moderate improvement" or "Minimal improvement") at Week24 (LOCF)

5.10.2 Secondary Efficacy Analyses

For MMSE and executive function test score (Part A, Part B), change from Baseline to Week 24 will be analyzed using the same ANCOVA model as described for the ADAS-cog. Other statistical inference (estimating and testing) will also be analyzed in the same way with the primary analysis for each visit. For executive function test score the following analysis will be performed additionally. The data excluded subjects whose score reached to '300' or above at least one test will be used for analysis.

5.11 Safety Analyses

All of safety analyses will use safety analysis set.

5.11.1 Treatment Compliance

Treatment compliance will be summarized using descriptive statistics (mean, SD, median, minimum, maximum). The medication will be inventoried, and the percent compliance in double blind phase will be calculated by dividing the number of actual doses administered by the number of days of the treatment period in DB phase.

$$\text{Compliance (\%)} = \frac{\text{Actual number of doses administered}}{\text{The number of days of the treatment*}} \text{ X100\%}$$

* The number of days of the treatment = final visit date – visit 2 date

For subjects who completed the DB phase, final visit date will be the completion date of DB phase.
For subjects who discontinued the DB phase, final visit date will be the date of discontinuation in DB phase.

(Subjects will start taking the dose at the Baseline visit.)

The treatment compliance in open-label extension phase will be calculated by dividing the number of actual doses administered by the number of days of the treatment period in OLE phase. When 5 mg dosage was prescribed, the number of actual doses administered in OLE phase will be the number of tablets subject taken and when 10 mg dosage was prescribed, the number of actual doses administered in OLE phase will be half of the number of tablets subject taken.

$$\text{Compliance (\%)} = \frac{\text{Actual number of doses administered}}{\text{The number of days of the treatment*}} \text{ X100\%}$$

* The number of days of the treatment = final visit date – visit 7 date

For subjects who completed the OLE phase, final visit date will be the completion date of OLE phase.
For subjects who discontinued the OLE phase, final visit date will be the date of discontinuation of OLE phase.

The number of subjects whose dose ascended to 10mg in DB phase and its percentage will be presented in a table. Also, the number of subjects whose dose descended to 5mg after ascending to 10mg in DB phase and its percentage will be presented in a table.

5.11.2 Extent of Exposure

Total amount of drug administered, and the duration of treatment will be summarized using descriptive statistics (n, mean, SD, median, minimum, maximum) by treatment group in the DB phase.

5.11.3 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (latest version) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent AE (TEAE) is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that were treatment-emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings. Treatment-emergent adverse events

(TEAEs) will be summarized by treatment group and total. The overview TEAEs table will be summarized by any TEAEs, any treatment related TEAEs, any Serious TEAEs and by its category (Death, Life threatening, Requires inpatient hospitalization, Requires prolongation of existing hospitalization, Persistent or significant disability or incapacity, congenital anomaly/birth defect, Important medical events), any treatment related Serious TEAEs and by its category (Death, Life threatening, Requires inpatient hospitalization, Requires prolongation of existing hospitalization, Persistent or significant disability or incapacity, congenital anomaly/birth defect, Important medical events), TEAEs leading to study drug withdrawal/discontinuation (referred to "Permanently Discontinued" category on Adverse Events page of CRF for 'Action Taken with Investigational Product'), TEAEs leading to study drug dose reduction (referred to "Dose adjusted" category on Adverse Events page of CRF for 'Action Taken with Investigational Product').

The incidence of TEAEs and serious TEAEs will be reported as number (percentage) of subjects by SOC and PT. A subject will be counted only once within a SOC and PT, even if the subject experienced more than one TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs by SOC and PT will also be summarized by maximum severity (mild, moderate, or severe).

The number (percentage) of subjects with TEAEs by SOC and PT will also be summarized by relationship to the study drug. The relationship is categorized as "related" and "not related". The category "related" consists of "possibly related" and "probably related".

The details of the subjects with serious TEAEs will be presented in a separate table.

5.11.4 Laboratory Evaluations

Laboratory results including hematology, blood chemistry, and urinalysis parameters will be summarized using Système International (SI) units, as appropriate.

For all quantitative parameters, the actual value and the change from baseline to each post-baseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics (mean, SD, median, minimum, maximum).

All qualitative parameters will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each post-baseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both non-missing baseline and relevant post-baseline results.

Laboratory tests that are assigned a low/normal/high (LNH) classification according to the laboratory parameter's reference range will be presented as 3-by-3 shift tables that compare the baseline LNH classification to the LNH classification at each post-baseline visit to compare within each treatment. The

number of subjects with missing LNH classification will be indicated.

Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and the lowest value during the treatment period.

Laboratory test results that are below the reference range will be considered low; those that are within the reference range will be considered normal; and those that are above the reference range will be considered high.

5.11.5 Vital Signs and Anthropometry

Descriptive statistics for vital signs parameters (i.e., Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP), pulse rate, and weight) and changes from baseline will be presented by visit and treatment group.

5.11.6 Electrocardiograms

For electrocardiogram measurement, a 3-by-3 shift table will be presented to compare the baseline test results (normal, abnormal/not clinically significant, abnormal/clinically significant) to that of the last visit. The number of subjects with missing electrocardiogram measurement will be indicated.

The details of the subjects with clinical significant events will be presented in a separate table.

5.12 Other Analyses

5.12.1 Extension Phase Analyses

Baseline Characteristics

Tables on the total group of the FAS-OLE population will be presented for Subject Disposition, Analysis Populations, Demographics, Clinical Characteristics, Disease Baseline Characteristics, Caregiver's Characteristics, Concomitant Medications.

For concomitant medications, a medication will be summarized in the OLE phase table if the start date of the medication is on or after the start date of the OLE phase.

Efficacy Analysis

For the efficacy endpoint, MMSE by each group in DB phase and total will be summarized using descriptive statistics (mean, SD, median, minimum, maximum, and number of patients with non-missing data) and change from Baseline (Both Week 0 in DB Phase and in OLE Phase) to each visit (Visit 8, 9, 10/ Week 6, 12, 24 in OLE Phase) by each group will be presented by visit and total (no statistical testing will be performed). No LOCF method will be applied.

Safety Analysis

The same analysis methods as the double-blind phase will be presented by total. The safety analysis will include treatment compliance, extent of exposure, adverse events, laboratory evaluations, vital signs and electrocardiograms. Baseline for laboratory evaluations, vital signs and electrocardiograms will be applied Week0 in DB phase only.

If AE start date is on or after Week 24 of the DB phase (or Week 0 of OLE phase) will be summarized in the OLE AE tables.

Listings will be provided for the OLE analysis.

Figures will not be provided for the OLE analysis.

6. Changes from Protocol-Specified Analysis

Modified full analysis set has been added to take account for any randomization errors (allocation) that may have happened during the trial.

7. List of Tables, Listings, Figures

7.1 Double Blind Phase

List of Tables

Table Number	Table Description
14.1.1	Subject Disposition - Double Blind Phase - All Screened Subjects
14.1.2	Subject Disposition by Study Site - All Screened Subjects
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8. Role & Responsibilities

Role	Name	Responsibility
Biostatistician 1	PPD	Responsible for writing statistical analysis plan (SAP v1.0)
Biostatistician 2		Responsible for writing statistical analysis plan (SAP v2.0) and conducting statistical analysis and managing all the relevant tasks
QC Biostatistician		Responsible for conducting double programming and reviewing the statistical analysis results conducted by the Project Biostatistician

9. Applied SOPs &SDs

SOP No.	SOP Version_Effective Date	SOP Name
0400	2.0_23-Oct-2017	Statistical Analysis Plan
0401	3.0_01-Jun-2017	Statistical Analysis Process
0404	2.0_01-Jun-2017	Randomization Code Break Process
0406	3.0_01-Jun-2017	Definition of Analysis Population
0407	2.0_01-Jun-2017	Blind Data Review Report Writing

SD No.	SD Version_Effective Date	SD Name
0400 A	1.0_17-Aug-2015	Statistical Analysis Plan
0404 A	1.0_17-Aug-2015	Un-Blinding Request Form
0404 B	1.0_17-Aug-2015	Un-Blinding Authorization Form for Statistical Analysis
0406 A	4.0_23-Oct-2017	Definition of Analysis Population
0407 A	2.0_01-Jun-2017	Blind Data Review Report