3. CLINICAL PROTOCOL SYNOPSIS

Compound No.	E2020
Name of Active Ingredient	Donepezil hydrochloride
Title of Study	A 24-weeks, Multi-center, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Donepezil Hydrochloride in Chinese Subjects with Severe Alzheimer's Disease
Investigators	To be determined
Study Centers	Approximately 18 centers in China
Study Period and Phase of Development	Total Treatment Duration: Approximately 24 weeks Phase 3
Objectives	**Primary Objective** • To demonstrate that donepezil hydrochloride 10 mg/day has superior efficacy compared with placebo for changes from Baseline to Week 24 in cognitive function in Chinese subjects with severe Alzheimer's disease (AD), as measured by the Severe Impairment Battery (SIB) **Secondary Objectives** • To evaluate the safety of donepezil 10-mg/day over 24 weeks in Chinese subjects with severe AD • To assess secondary efficacy parameters in support of the primary efficacy parameter
Study Design	This will be a 24-weeks, multi-center, randomized, double-blind, placebo-controlled, parallel-group study. Subjects with severe AD who meet all inclusion and none of the exclusion criteria will be randomized in a 1:1 ratio to receive double-blind treatment of either donepezil 10-mg or matching placebo. The study will consist of two phases: the Prerandomization Phase and the Randomization Phase. The Prerandomization Phase will include two periods, Screening and Baseline. The Randomization Phase will comprise two periods, Titration and Maintenance.
Number/Type of Subjects	Approximately 290 randomized subjects are needed to achieve over 200 completer
Key Inclusion Criteria	**Key Inclusion Criteria for Subjects:** Separate inclusion and exclusion criteria will be required for subjects enrolled in the study and for their caregivers. Subjects and caregivers must meet all specified inclusion and none of the exclusion criteria in order to be eligible to participate in the study. Written informed consent (IC) will be obtained from the subject or from the subject's legal guardian or other representative prior to beginning screening activities. The caregiver must provide informed consent separately for his/her own participation in the study. SI-1. Subject age range: male and female subjects, 50 to 90 years of age, inclusive

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Key Inclusion Criteria (cont'd)	SI-2. Diagnosis: diagnostic evidence of probable AD consistent with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) 294.10 and 294.11 and National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria SI-3. Mini-Mental State Examination (MMSE) 1 to 12, inclusive, at both Screening and Baseline SI-4. Severe Impairment Battery (SIB) ≤ 90 and ≥ 10 at both Screening and Baseline SI-5. Comorbid medical conditions must be clinically stable prior to Baseline unless otherwise specified. **Key Inclusion Criteria for Caregivers:** CI-1. Sufficiently familiar with subject to provide accurate data
Key Exclusion Criteria	**Key Exclusion Criteria for Subjects:** SE-1. Subjects with a known history of disorders that affect cognition or the ability to assess cognition, but are distinguishable from AD such as: schizophrenia, bipolar or unipolar depression, Parkinson's disease, multi-infarct dementia, dementia due to cerebrovascular disease, Huntington's disease, Pick's disease, Creutzfeld-Jacob disease, Lewy Body disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, or multiple sclerosis, as well as subjects with known human immunodeficiency virus disease, neurosyphilis, or a history of significant head trauma followed by persistent neurological deficits or known structural brain abnormalities SE-2. Evidence of focal disease to account for dementia on any cranial image (magnetic resonance imaging [MRI] or computed tomography [CT]). MRI or CT obtained within 24 months prior to Screening is acceptable. If subjects have not had a cranial image in the past 24 months, then an image (preferably with contrast) must be obtained between Screening and Baseline that shows no evidence of focal disease. SE-3. Subjects with dementia complicated by other organic disease or AD with delirium according to DSM-IV criteria SE-4. Subjects who cannot swallow or who have difficulty swallowing whole tablets, as tablets should not be broken or crushed SE-5. Illiteracy prior to AD SE-6. Subjects or Legal Representatives who are unwilling or unable to fulfill the requirements of the study SE-7. Treatment with another cholinesterase inhibitor and/or memantine in

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Key Exclusion Criteria (cont'd)	the 3 months prior to Screening SE-8. Subjects with a poor response (tolerability) to prior exposure to donepezil **Key Exclusion Criteria for Caregivers:** CE-1. Caregivers who are unwilling or unable to give IC or fulfill the requirements of the study CE-2. MMSE below 27 (below 25 if the caregiver is illiterate). A caregiver may be rescreened once if the initial MMSE is 26 (24 if illiterate)
Study Treatments	**Test drug:** Donepezil Titration Period: Donepezil 5-mg tablet taken orally once daily for 6 weeks. Maintenance Period: Donepezil 10-mg tablet taken orally once daily for 18 weeks
	Active Control/Placebo: Titration Period: Placebo matched to donepezil 5-mg tablets taken orally once daily for 6 weeks Maintenance Period: Placebo matched to donepezil 10-mg tablets taken orally once daily for 18 weeks
Duration of Treatment	The duration of the study phases and treatment for each subject is as follows: Prerandomization Screening and Baseline: 4 weeks (or up to 6 weeks given certain circumstances described in the protocol) Randomization Titration Period: 6 weeks Maintenance Period: 18 weeks
Criteria for Evaluation	**Efficacy Assessments:** • Cognitive function, as assessed by the total SIB score and total MMSE score • Disease status (i.e., cognition, behavior, and function), as assessed by the Clinician Interview-Based Impression of Change, Plus Caregiver Input Version (CIBIC+) overall score
	Pharmacokinetic: Not applicable (N/A)
	Pharmacodynamic: N/A
	Pharmacokinetic-Pharmacodynamic: N/A
	Safety: Safety will be assessed by monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), regular monitoring of hematology, blood chemistry and urine values, measurement of vital signs, weight, and electrocardiograms (ECGs). Concomitant medications will also be reported.

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Other Criteria for Evaluation	N/A
Bioanalytical Methods	N/A
Statistical Methods	**Analysis Sets:** **Safety Set:** Randomized subjects who took at least one dose of study medication and had at least one post-Baseline safety assessment **Full Analysis Set (FAS):** Safety Set subjects for whom a total SIB score is available at Baseline and at least one post-Baseline visit **Per Protocol Set (PP):** Subjects who complied with the study protocol up to the end of the 24-week treatment period. Whether or not the subjects can be included in this population will be determined before code break/database lock, and will be described in the statistical analysis plan (SAP). **Efficacy Analyses:** **Primary and secondary efficacy endpoints** The primary efficacy endpoint for this study is the change from Baseline to Week 24 in the total SIB score. The secondary endpoints in the study are the overall score at Week 24 in the CIBIC+ and the change from Baseline to Week 24 in the total MMSE score. The analysis of efficacy according to primary and secondary parameters will be conducted on the FAS. All statistical tests will be conducted at the 0.05 level of significance (two-tailed). A positive outcome will be declared if for the primary efficacy endpoint as measured by the SIB, the change from Baseline to Week 24 in the total SIB score (last observation carried forward [LOCF] demonstrates superiority for donepezil 10 mg, compared with placebo. For the continuous efficacy endpoint analysis of SIB change from Baseline to Week 24, an analysis of covariance (ANCOVA) model with terms for baseline, center, and treatment will be used as the primary model for estimating and testing treatment effects. For the secondary efficacy endpoint analysis of the CIBIC+ score at Week 24, an ANCOVA with embedded Cochran-Mantel-Haenszel (CMH) test will be used with the Clinician Interview-Based Impression of Severity (CIBIS+) plus and center in the model. For MMSE, overall change from Baseline in scores at Week 24 (LOCF) will be analyzed with the same model as the SIB.
Interim Analyses	Interim analyses will not be performed. There will be no data safety monitoring board or data monitoring committee.
Pharmacokinetic and/or Pharmacodynamic Analyses	**Pharmacokinetic:** N/A **Pharmacodynamic:** N/A **Pharmacokinetic-Pharmacodynamic:** N/A

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Safety Analyses	The evaluation of safety parameters will be conducted on the Safety Set. For the safety analysis, individual vital signs will be descriptively summarized by treatment group and clinic visit. Changes from Baseline to each individual post-Baseline visit and to the last study visit will be calculated. Incidence rates for AEs by body system, preferred term, severity, and relationship to study medication will be calculated. Changes from Baseline for each clinic visit, with number of subjects, mean, median, standard error (SE), and range of change from Baseline, will be summarized for clinical laboratory parameters. Shift tables depicting shifts in or out of the laboratory normal range, from Baseline to the last study visit, will also be constructed. ECG data will be categorized at Baseline, and results for each subject at the end of treatment will be compared to those at Baseline. Data on other medications used by subjects during the study will be collected and summarized by therapeutic class and generic components.
Sample Size Rationale	A total of 290 subjects in the FAS will be randomized to 1 of 2 treatment groups (donepezil or placebo) in a 1:1 ratio, i.e., 145 subjects in each treatment group on FAS will be needed to provide over 80% power at the significance level of 0.05. The planned sample size in this study was generated based on the total SIB score (the primary efficacy endpoint of this study) observed in a previous donepezil study. In that study, the observed mean difference in change from Baseline in the total SIB score between placebo and donepezil 10-mg groups at Week 24 was 5.6, the pooled standard deviation (SD) at Week 24 was 12.53. The total sample size of 160 was calculated based on the mean difference of 5.6, the SD of 12.53 as observed in the above mentioned study. The POWER procedure in SAS® Version 9.2 was used to calculate the sample size through a two-tailed t test with a significance level of 5% and statistical power of 80%. However, it is necessary to entry over 100 subjects per treatment group as completer. Therefore, the planned sample size in this study is approximately 145 per treatment group to take into account discontinuation rate of 30% for this completer, for a total of 290 subjects.