# Safety and Efficacy of Donepezil in Mild to Moderate Alzheimer's Disease: A Multi-center Single-arm Study in China

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## Statistical Analysis Plan (SAP)

Safety analysis is conducted on the safety set (SS, patients who receive at least one dose of donepezil 10mg/day and have at least one safety evaluation). Efficacy analysis is conducted on the per protocol analysis set (PPS, patients who complete the study with no major protocol violations) with last observation carried forward (LOCF) as well as the full analysis set (FAS, all enrolled patients are included) LOCF. In addition, in order to test the robustness and accuracy of our results, efficacy analysis is further conducted on the PPS and FAS wherein missing data is not filled in and not included and thus only actual data of every patient who take the efficacy test are included (FAS [actual number] and PPS [actual number], respectively).

For the safety analysis, overall incidence of AEs and SAEs, incidence of AEs and SAEs by organ systems, severity, and AEs' relationship to donepezil are calculated and/or assessed by calculating the number of patients having AEs and SAEs, the prevalence of AEs and SAEs and their 95% confidence intervals (95% CI). Laboratory abnormalities such as changes in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and changes in EKG and ECG such as HR, QT, QTc are summarized and described using means, standard deviation (SD), median, maximal, minimal, 25th and 75th percentile values, and further analyzed with paired *t*-test. Correlations of AEs and various risk factors are first assessed with univariate logistic regression analysis, and variables included patients' medical history (history of neurological, cardiovascular, mental, liver and gastrointestinal diseases), age ( grouped into ≤75 and >75 years), gender, body weight (≤55kg and >55kg), APOE genotype (ε2/ε2, ε3/ε3, ε4/ε4, ε2/ε3, ε2/ε4, and ε3/ε4), the presence or absence of APOE ε4/ε4, concomitant medications (cardiovascular and cerebrovascular, gastrointestinal, liver, neurological, mental and hypoglycemic medications), and duration of donepezil 5mg/day treatment prior to the study (days). Forward stepwise multivariate logistic regression analysis is subsequently performed to

further assess correlations between various risk factors and incidence of AEs using variables chosen from those used in the univariate analysis (SLSTAY=0.3, a significance value of 0.3 is required for a variable to stay in the multivariate model).

MMSE and ADCS-ADL are assessed at each visit. Their changes at each visit from baseline are calculated. Factors affecting MMSE and ADCS-ADL changes are assessed with a mixed model-repeated measures using an autoregressive covariance structure. Variables are the same as those used in the univariate analysis of correlations between AEs and various risk factors

All analyses are performed with SAS 9.4 (SAS Institute Inc.; Cary, NC, USA), data is analyzed with a two-tailed hypothesis, and a $p$ value $< 0.05$ is considered to indicate statistical significance.