Statistical Analysis Plan (SAP)

Official Title of the study: A Multicenter, Non-comparative, Phase IV Clinical Trial for Evaluation of the Effect of Cogmax® in the Treatment of Memory Loss in Postmenopausal Women

NCT number: NCT03835325

Date of the document: Draft version 1.0 dated June 06, 2018

1. STATISTICAL CONSIDERATIONS

1.1. SAMPLE SIZE DETERMINATION

The sample size was calculated according to study primary endpoint, i.e., change (between $\mathbf{V_S}$ and $\mathbf{V_F}$) obtained by **SELF-EFFICACY** factor, defined as the sum of the CAPABILITY, CONTROL and CHANGE domains in MIAr Questionnaire.

For each of the questions, a score from 1 to 5 will be assigned as indicated in Table 1.

Table 1 - Scores assigned to MIAr questionnaire.

Response	***Score***
a. totally agree	1
b. agree	2
c. I do not know	3
d. disagree	4
e. totally disagree	5

Therefore, the sample size required to identify an improvement of at least 0.2 point (between $\mathbf{V_S}$ and $\mathbf{V_F}$), with a standard deviation of 0.6 points**Erro! Indicador não definido.**, in the mean score of MIAr questionnaire SELF-EFFICACY factor is 56 patients.

Considering the characteristic of assessment through scores varying from 1 to 5, an addition of 15% of patients is recommended for the correct use of the nonparametric test**Erro! Indicador não definido.**, and considering a loss of approximately 20% of patients, the inclusion of at least **80 patients** is recommended, so that an improvement in memory capacity may be identified (measured by MIAr questionnaire SELF-EFFICACY factor), with 80% power and 5% statistical significance (one-sided test).

1.2. ANALYSIS POPULATIONS

1.2.1. Efficacy population - primary objective

The main population used for analysis of the study's primary objective will be the modified Intent-to-Treat (mITT) population. This population encompasses all participants who perform baseline visit (V_1), take at least one dose of the study treatment and have at least one post-baseline assessment (**V_2** and/or **V_F**).

The per-protocol (PP) population will also be used, only for primary objective analysis. This population encompasses all included patients who complete the study without major protocol breaches.

1.2.2. Efficacy population – secondary objectives

All the secondary objectives will be assessed in the mITT population. Secondary objectives will not be assessed in the PP population.

1.2.3. Safety Population

The safety population encompasses all the participants who take at least one dose of the study treatment. In this population, participants lost to follow-up and/or participants for whom there is uncertainty if they used or not at least one dose of the study treatment will be included.

1.3. STATISTICAL ANALYSIS PLAN

1.3.1. Disposition of participants

A table with the disposition of participants should be presented, as follows:

- Screened patients: total patients screened at visit **V_S** and who signed the ICF;

- Included patients: total patients screened at visit **V_S**, re-assessed at visit **V_1**, and who met all the eligibility criteria. The reason(s) for not including patient(s) in the study should be presented. The same patient may present more than one reason for not being included;

- mITT Population: total participants assessed in the modified intent-to-treat population. The reason(s) for not including participant(s) in the mITT population should be presented;

- PP Population: total participants assessed in the per-protocol population. The reason(s) for not including participant(s) in the PP population should be presented;

- Safety Population: total participants assessed for safety. The reason(s) for not including participant(s) in the safety population should be presented;

1.3.2. Baseline characteristics

All the participants will be described for their baseline characteristics, i.e., demographics, medical history, previous and concomitant treatments, vital signs and physical examination assessed at visit V_S.

Variables with continuous distribution will be summarized by mean, standard deviation, median, minimum and maximum values. Categorical variables, or with discrete numerical distribution, will be summarized by absolute (n) and relative (%) frequencies of cases compared to total of mITT population.

1.3.3. Efficacy analysis

Primary efficacy analysis (assessment of Cogmax® effect on subjective memory loss observed after menopause) will be performed in mITT and PP populations. The difference between $\mathbf{V_S}$ and $\mathbf{V_F}$, of the sum of CAPABILITY, CONTROL and CHANGE scores in MIAr Questionnaire (SELF-EFFICACY factor) will be assessed by nonparametric Wilcoxon test. Obtaining statistical significance will indicate that the treatment was effective in reducing subjective memory loss observed after menopause.

Secondary efficacy analysis (assessment of total score by MIAr QUESTIONNAIRE, score obtained by Stroop color-word test and global efficacy assessment by the participant) will only be assessed in the mITT population.

Assessment of total score of MIAr Questionnaire: the change in the total sum obtained by MIAr questionnaire will be compared between all the visits in

which the questionnaire was used, i.e., screening visit (**V_S**), visit 2 (**V_2**) and final visit (**V_F**), by nonparametric Friedman test.

Assessment of the score obtained by the Stroop color-word test: the change in the score obtained by the Stroop color-word test between screening visit (**V_S**) and final visit (**V_F**) will be assessed by the nonparametric Wilcoxon test.

Global efficacy assessment: global efficacy assessment (measured by assigning a score from 1 to 5, according to attachment 5), will only be assessed at final visit (**V_F**). Therefore, the analysis will only have a descriptive character, and it will include the 95% confidence interval for the mean, in addition to summary measurements: mean, standard deviation, median, minimum and maximum values, as well as absolute and relative frequencies for each response.

1.3.4. Safety analysis

The safety assessment will be based on the incidence of adverse events and the change in vital signs between the study screening visit (**V_S**) and final visit (**V_F**).

The AEs will be summarized by occurrence frequency (number and percentage of patients with at least 1 event) according to the MedDRA code, using the classifications: PT (preferred term), HLT (high-level group term) and SOC (system organ class).

The AEs occurred must also be summarized according to seriousness (serious, non-serious), severity (mild, moderate, severe), causal relationship with the study treatment (defined, likely, potential, unlikely, conditional, unrelated, inaccessible/unclassifiable), outcome (ongoing, resolved, resolved with sequelae, fatal, unknown) and actions taken to control or treat the event (drug administration, hospitalization, extended hospitalization, study treatment interruption, study treatment discontinuation, therapy without drug use).

All the events occurred during the study must be recorded in the eCRF and followed up until their resolution and stabilization. Non-serious adverse events that initiated or worsened after 5 days of the last dose of the study drug must

not be recorded in the eCRF, as they will not be included in the analysis. As for serious adverse events that initiated or worsened within a period of 30 days after the last dose of the study treatment must be recorded in the eCRF and followed up until their complete resolution.

1.3.5. Procedures for missing data

Overall, there will be no imputed values for missing data. For categorical variables, patients with missing data will not be included in percentage calculations, unless otherwise indicated. When relevant, the number of patients with missing data for a given variable will be presented.

The date of last administration of study treatment will be useful to calculate the “experimental product extension” (calculated in days, such as: final date - initial date + 1), regardless of temporary interruptions in the use of the experimental product. For patients lost to follow-up, where there is no certainty about the date of last administration of the experimental product, the calculation will not be performed.

Only for assessment of the study’s primary objective (MIAr questionnaire SELF-EFFICACY effect), the procedure known as LOCF (Last Observation Carried Forward), where the missing value is replaced by the last known value, will be adopted.