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Study Protocol

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

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SYNOPSIS

Title	A Multicenter, Non-comparative, Phase IV Clinical Trial for Evaluation of the Effect of Cogmax® in the Treatment of Memory Loss in Postmenopausal Women
Study Identification	EF152 – COGMAX Trial
Sponsor	Eurofarma Laboratórios S.A.
Experimental Product	Cogmax® (soybean oil, magnesium bisglycinate, di-magnesium malate, choline bitartrate, fish oil, purified water, zinc bisglycinate, selenomethionine, DL-alpha-Tocopherol acetate, calcium pantothenate, cyanocobalamin, pyridoxine hydrochloride, thiamine mononitrate, folic acid, colecalciferol)
Study Phase	Phase IV
Study Rationale	Complaints regarding memory loss are very frequent in women in the menopausal transitional period. The effectiveness of estrogen replacement therapy in cognitive improvement is controversial. Partial positive results were obtained in some studies regarding memory improvement; currently, there is no standard of care that is considered effective for these cases. Effective pharmacological approaches for treatment of memory loss associated with menopause comprise an unmet medical need. Cogmax® is a polyvitamin and mineral supplement containing several essential elements for cognitive function, which may be a safe therapeutic option for these cases.
Objectives	***Primary Objective*** To assess the effect of Cogmax® on subjective memory loss observed after menopause. ***Secondary Objectives*** - To assess the effect of Cogmax® on attention of postmenopausal women. - To assess the safety of Cogmax® on postmenopausal women.
Study Outline	A Multicenter, non-comparative, phase IV clinical trial (single arm).
Study Population	80 participants aged between 45 and 60 years old and with complaints of memory loss associated with menopause.
Eligibility Criteria	***Inclusion Criteria*** Female subjects who meet *all* the criteria below will be included:

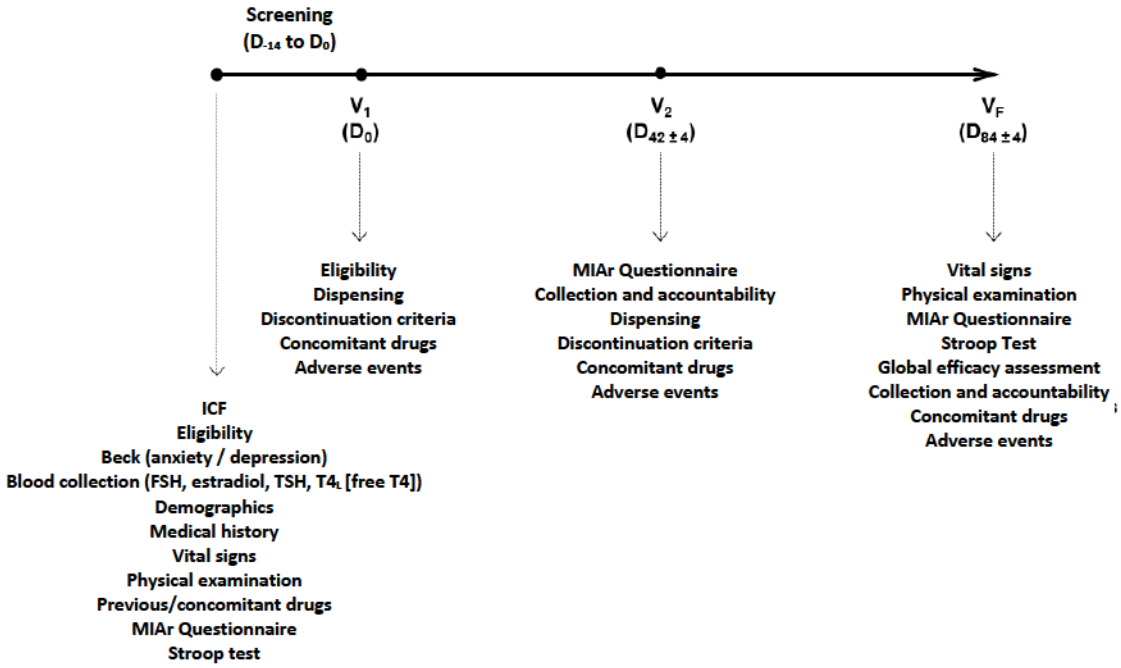
	1. Age ≥ 45 years and ≤ 60 years. 2. Complaint of memory loss associated with menopause. 3. Score ≤ 3.0 (mean value found in elderly subjects[1]) related to the self-efficacy factor, consisting of the sum of the scores for the Capability, Control and Change domains obtained through the Metamemory in Adulthood Questionnaire - reduced version (MIAr)[2]. 4. Amenorrhea for at least 1 year and no more than 6 years. 5. Dosage of Serum FSH > 30 mIU/mL. 6. Dosage of serum estradiol < 20 pg/mL. 7. Knowledge of the Portuguese language sufficient to answer the questionnaires. 8. Signature of the Informed Consent Form (ICF) prior to the conduction of any study procedure. ***Exclusion criteria*** Subjects who meet *at least one* of the criteria below will be excluded: 1. Complaints of hot flashes, insomnia and/or very intense sleep disorders, at the discretion of the investigator. 2. Presence of moderate to serious depression, with score ≥ 18 at assessment through the Beck depression inventory.[3,4] 3. Presence of moderate to serious anxiety, with score ≥ 30 on the Beck anxiety inventory.[5,6] 4. Initiation of hormone replacement therapy within 6 months prior to study inclusion. Patients receiving hormone replacement therapy starting more than 6 months before inclusion in the study may be included in the study provided that the treatment is regular with the same drug and the same dose during the last 6 months before inclusion and provided that this treatment is maintained throughout the study. 5. Use of psychotropic medications (anticonvulsants, benzodiazepines, antipsychotics), selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and noradrenaline reuptake inhibitors (SNRIs) 6. Alcoholism and/or use of other illicit drugs. 7. History of allergy or intolerance to any component of the experimental product formulation. 8. Diagnosis of neurological diseases associated with cognitive deficit (including dementia and mental retardation) or psychiatric diseases.

	9. Presence of serious or uncontrolled diseases (such as decompensated hypothyroidism), at the discretion of the investigator (such as stroke, Parkinson's disease, etc.). 10. Participation in clinical research protocol within the previous 12 months, unless, at the discretion of the investigator, their participation in the study may incur direct benefit to the research participant. 11. Presence of any condition that, at the discretion of the investigator, makes the patient inadequate to participate in the study.
Study Duration	Recruitment period for the study will begin after the required ethical and regulatory approvals and it will have an estimated duration of 4 months. A screening period with the maximum duration of 14 days prior to study treatment initiation is expected. Each participant will receive the treatment with Cogmax ® during 12 weeks (± 4 days).
Study Treatment	***Experimental Product*** Research participants will receive 2 capsules a day (after lunch) of Cogmax®, during 12 weeks.
Visit and assessment plan	Each participant must attend four on-site visits in the clinical trial site. During the **screening visit** (**V_S**), which should occur within no longer than 14 days prior to treatment initiation (visit 1), the following procedures will be performed after ICF signature: verification of Eligibility Criteria, collection of demographics, medical history and current use of drugs, relevant previous treatments, assessment of vital signs, physical examination, collection of blood samples for FSH, serum estradiol, TSH and free T4 tests. The MIAr questionnaire and the Stroop color-word test will be used[7,8]. During **visit 1** (**V_1**), after eligibility criteria review, experimental product dispensing will be performed. A daily contact mechanism will be implemented with participants, in order to remind them to use the study product. The study discontinuation criteria will be verified and the data regarding concomitant treatments and adverse event (AE) occurrence will be collected. During **visit 2** (**V_2**), which will occur 42 (± 4) days after visit 1, the following procedures will be performed: implementation of MIAr questionnaire, accountability and new dispensing of the experimental product. The study discontinuation criteria will also be verified and the data regarding concomitant treatments and AEs will be collected. During the **final visit** (**V_F**), which will occur 84 (± 4) days after visit 1, the following procedures will be performed: measurement of vital signs, physical examination, completion of MIAr questionnaire and performance of Stroop test and global efficacy assessment by the

	research participant. Collection and accountability of the experimental product will also be performed, collecting data regarding concomitant treatments and AE occurrence.
Endpoints	***Primary efficacy endpoint*** • Score regarding the self-efficacy factor, consisting of the sum of the scores for the Capability, Control and Change domains in MIAr questionnaire. ***Secondary efficacy endpoints*** • Total score obtained through MIAr questionnaire. • Score obtained through Stroop color-word test. • Global efficacy assessment by the participant. ***Safety endpoints*** • AE profile and incidence, expressed according to MedDRA code (The Medical Dictionary for Regulatory Activities). • Change of vital signs at the end of treatment ($\mathbf{V_F}$) compared to baseline (obtained in $\mathbf{V_S}$); • Treatment discontinuation rate due to AEs.
Sample Size	Sample size calculation was based on the following hypothesis test: **H0**: there is no improvement in memory capacity between initial ($\mathbf{V_S}$) and final assessments ($\mathbf{V_F}$), assessed by MIAr questionnaire self-efficacy factor. **Ha:** there is an improvement in memory capacity between initial ($\mathbf{V_S}$) and final assessments ($\mathbf{V_F}$), assessed by MIAr questionnaire self-efficacy factor. or **H0**: SELF-EF ($\mathbf{V_F}$) – SELF-EF ($\mathbf{V_S}$) ≤ 0 **Ha**: SELF-EF ($\mathbf{V_F}$) – SELF-EF ($\mathbf{V_S}$) > 0 where: SELF-EF ($\mathbf{V_S}$) = mean score of self-efficacy factor in pre-treatment ($\mathbf{V_s}$) SELF-EF ($\mathbf{V_F}$) = mean score of self-efficacy factor in post-treatment ($\mathbf{V_F}$) Therefore, the sample size required to identify an improvement of at least 0.2 point, with a standard deviation of 0.6 points1, 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[9]; also, 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).
Ethical aspects	The study will be conducted according to ethical standards and local/international regulations, and it will be approved by the Research Ethics Committee (REC) of each participating institution prior to its initiation.

Study Scheme



Visit and assessment schedule

	V_S	V_1	V_2	V_F
	(Day -14 to Day 0)	**(Day 0)**	**(Day 42 ± 4)**	**(Day 84 ± 4)**
Informed Consent Form (ICF) / Assent Form	X			
Inclusion and exclusion criteria	X	X		
Demographics	X			
Medical history	X			
Previous / concomitant treatments	X	X	X	X
Vital signs	X			X
Physical examination	X			X
Blood collection for FSH, serum estradiol, TSH and free T4 tests[a]	X			
MIAr questionnaire	X		X	X
Stroop color-word test	X			X
Experimental product dispensing		X	X	
Accountability and collection of the experimental product			X	X
Dispensation criteria		X	X	
Assessment of Adverse Events		X	X	X
Global efficacy assessment by the participant				X

[a] Results from dosage tests of FSH, serum estradiol, TSH and free T4 already available collected within no longer than 30 days prior to screening visit (V_S) will be accepted. In this case, visit 1 procedures (V_1) must also be performed at this visit (i.e., V_S and V_1 will be performed at the same on-site visit, and the visit day will be considered as Day 0).

References

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