STATISTICAL ANALYSIS PLAN

Protocol Code: MEIF/17/BAC-COG/001
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"Effect of an antioxidants mix on cognitive performance and well being: The Bacopa, Licopene, Astaxantina, Vitamin B12" (Acronym BLAtwelve study)"

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AVLT	Rey Auditory Verbal Learning Test
CPMP	Committee For Proprietary Medicinal Products
CRF	Case Report Forms
CRO	Contract Research Organisation
DNA	DeoxyriboNucleic Acid
DSMB	Data Safety Monitoring Board
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
GHQ-12	General Health Questionnaire 12
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
GCP	Good Clinical Practice
ITT	Intent to Treat
LDL	Low-density-lipoprotein
HDL	High-density-lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
NSSS	New Sexual Satisfaction Scale
POMS	Profile Of Mood Stated
PP	Per Protocol
PT	Preferred Term
SAP	Statistical Analysis Plan
SOC	System/Organ Class
TEAE	Treatment Emergent Adverse Event
TMT	Trail Making Test
VFT	Verbal Fluency Test

1. VERSION HISTORY

1.1 Version history of the SAP

Version Number	Summary/Reason for changes	Date issued
1.0	First version	07-Feb-2019

1.2 Version history of the Protocol

Version Number	Date	Description
0.0	09-Oct-2017	Current protocol version

1.3 Version history of the CRF

Version Number	Date	Description
1.0	21-Dec-2017	Current CRF version (paper CRF)

2. INTRODUCTION

Long-term oxidative stress is believed one of the most important factors contributing to the decline of cognitive function often observable with aging. Oxidative stress, due to the generation of free radicals resulting from normal metabolism, is usually maintained at low level by antioxidant system. However, in some conditions oxidant/antioxidant balance can be perturbed by increased generation of reactive oxygen species and/or decreased endogenous ability to counteract them [Praticò et al., 2008].

Brain tissue is highly sensitive to oxidative stress because it has a high request for oxygen and has a relative weakness of antioxidant systems. Furthermore, brain also contains high levels of polyunsaturated fatty acid, making it more vulnerable to oxidative injuries [Praticò et al., 2008]. Altered mitochondrial function, the amyloid β peptides and the presence of unbound trace metal ions represent the most investigated potential sources of oxidative stress in the brain [Reddhy et al., 2005; Mattson MP, 2004]. Depending on the biomolecules attacked by reactive oxygen species, oxidative stress can promote peroxidation of protein, lipid and nucleic acids thus favoring the onset and progression of cognitive dysfunction during aging [Praticò D et al., 2008].

During the last few years an increasing interest has been focused on antioxidants such as carotenoids, flavonoids and vitamins as potentially useful agents in the prevention of the onset and progression of cognitive dysfunction [Rao et al., 2013; de Rijk et al., 1997; Deschamps et al., 2001; Engelhart et al., 2002].

In this regard, lycopene, a lipid-soluble carotenoid compound, well represented in tomatoes and red fruits, including watermelon, pink grapefruit and guava, has been proposed as a brain protective agent. In vitro studies indicated that lycopene protects against neuronal death induced by different neurotoxic compounds, including 1-methyl-4-phenylpyridinium (MPP+), methylmercury, amyloid β, trimethyltin and 6-hydroxydopamine [Di Matteo et al., 2009; Yi et al.;2013]. Furthermore, animal experiments using rat models demonstrated that lycopene prevents brain injury caused by focal or global ischemia and reperfusion [Fujita et al., 2013] and alleviates cognition dysfunction induced by colchicine and rotenone [Kaur et al., 2011]. A population-based follow-up study demonstrated that males in the highest quartile of serum lycopene concentrations exhibited 59 and 55% lower risks of ischemic stroke when compared with males in the lowest quartile [Karppi et al., 2012].

Astaxanthin is a xanthophyll carotenoid nutrient known for having potent antioxidant and anti-inflammatory actions thanks to molecular properties that precisely position it within cell membranes and circulating lipoproteins [Kidd, 2011; Lim SY et al. 2016]. Astaxanthin has shown a variety of brain benefits under experimental conditions [Kidd, 2011; Lim SY et al. 2016].

Bacopa monniera is a creeping herb extensively investigated for its pharmacological and therapeutic effects. Its ethanol extract contains a mixture of triterpenoid saponins designated as bacosides A and B [Chatterjee et al., 1963; Chatterjee et al., 1965]. In vitro studies using Bacopa Monnieri have shown that it inhibits free radical formation and DNA damage in a dose dependent manner [Russo et al.;2003]. Promising indications for use in humans include improving cognition in the elderly and in subjects with neurodegenerative disorders [Stough C et al., 2013].

Vitamin B12, also called cobalamin, is a water-soluble vitamin that has a key role in the normal functioning of the brain and nervous system, and for the formation of red blood cells [Aisen et al.; 2008]. Serum levels in the subclinical low-normal range (<250 pmol/L) are associated with Alzheimer's disease, vascular dementia and Parkinson's disease [Moore et al.; 2012] while some evidences suggest that vitamin B12 administration might be useful in preserving brain health.

Starting from these evidences it is conceivable that a food supplement containing bacopa, lycopene, astaxantina, vitamin B12 could be effective in improving brain health.

The purpose of this study is to evaluate if the mix of these four bioactive compounds, orally administered for 8 consecutive weeks, can be of help on cognitive performance, mood state and well-being in a target population with no evidence of cognitive dysfunctions.

The study is conducted in compliance with this protocol, GCP and the applicable regulatory requirements.

3. STUDY OBJECTIVES

The aim of this study is to evaluate the influence of a mix of four bioactive compounds – bacopa, lycopene, astaxanthin and vitamin B12 – on cognitive performance, mood state and well-being in subjects aged ≥ 60 years with no evidence of cognitive dysfunction.

3.1 Primary Objectives

The primary objective of the study is to evaluate the changes in TMT scores from baseline (V2) to 8 weeks of treatment (V4), analyzed in the following hierarchical order: TMT-B, TMT-A and TMT B-A

3.2 Secondary Objectives

Secondary objectives of this study are to evaluate changes from baseline (V2) to 8 weeks of treatment (V4) in Verbal Fluency Test (VFT) score, Montreal Cognitive Assessment (MoCA) score, Mini Mental State Examination (MMSE) score, Rey Auditory Verbal Learning Test (AVLT), psychological well-being as assessed by General Health Questionnaire (GHQ-12), mood states as assessed by the Profile of Mood Stated (POMS), sexual satisfaction as evaluated by the New Sexual Satisfaction Scale (NSSS).
Changes of metabolic parameters from baseline (V2) to 4 weeks of treatment (V3) and from baseline (V2) to 8 weeks of treatment (V4) will be also evaluated as secondary objectives (glucose, insulin, HOMA-IR, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, uric acid).
Changes of plasma markers of oxidative stress from baseline (V2) to 4 weeks of treatment (V3) and from baseline (V2) to 8 weeks of treatment (V4) will be evaluated as secondary objectives (8-iso-Prostaglandin F2alpha, Plasma malondialdehyde).
Finally, the safety and tolerability of the study product will be assessed.

4. STUDY METHODS

4.1 Study Design

This study has been designed as 9 weeks double-blind, randomized, placebo-controlled, parallel-arm, superiority study.
The study is conducted in 1 Italian clinical site and will involve about 80 subjects.

4.2 Treatment Administration

Subjects are randomly allocated to one of the following groups:

- Group I. mix of the four bioactive compounds (bacopa, lycopene, astaxanthin and vitamin B12), once a day for 8 weeks *per os*;
- Group II: placebo, once a day for 8 weeks *per os*.

The study is double blind. Neither the study staff at clinical sites (Investigators, nurses, pharmacist) nor the subject are aware of the treatment assigned.

4.3 Randomization and Blinding

Each subject for whom written consent is obtained is assigned a five-digit screening code, consisting of the site number (i.e. 01) and a progressive number within the site: for example, the first subject screened is assigned the code 01-001, the second one 01-002 etc.
All screened subjects receive the code irrespective of whether they are randomized or not. If a subject discontinues from the study at any time, the code is not re-used.
All subjects who sign the informed consent and receive the screening code are entered into a Subject's Register, containing the name and surname of the subjects and the date they have signed the consent form.
The randomization list was generated by Latis S.r.l., using the PROC PLAN of SAS 9.4 for Windows (SAS Institute Inc., Cary, NC, USA). Once eligibility of a subject is established, according to Inclusion/Exclusion Criteria, the study treatment is assigned through envelopes randomization system: the site has been provided with sealed envelopes, numbered in progressive number starting from R-001, containing the treatment kit to be assigned to the subject. The Investigator opens the first available envelope in progressive order. Inside the envelope there is the kit number of the treatment to be assigned to that subject. Opened envelopes are signed and dated by the Investigator and stored in the Investigator's File.
The Investigator keeps record of all enrolled subjects in the Subject's Enrolment Log: the subject screening number, the date of consent, the treatment assigned to the subject, if applicable, or the reason for not being randomized is recorded.
The study is designed as a double-blind study and neither the subject nor the clinical site personnel (Investigator, sub-Investigator, study nurse, psychologists, pharmacist) know which treatment is being administered. The identity of the treatments can't be revealed except in an emergency under the discretion of the Investigator.
The Principal Investigator receives study treatment identification keys as sealed envelopes containing the kit number and the corresponding treatment.
The envelope can be opened only in case of an emergency presenting the need to disclose the identification of the *study treatment assigned to the subject, to establish the appropriate therapy. Once the code is broken for a subject,* this subject shall be withdrawn from the study, with the completion of the final study evaluation, indicating the specific reason of the subject withdrawal.
The Study Monitor must be notified immediately by the Investigator of any emergency unblinding; the date and time, along with the reason for the unblinding, is noted. Treatment codes are not freely available to the Investigator or personnel monitoring the study until after the study completion and database lock.

5. STUDY ENDPOINTS

5.1 Primary Endpoints

The primary efficacy endpoints are the changes of TMT scores from baseline (V2) to 8 weeks of treatment (V4), analyzed in the following hierarchical order: TMT-B, TMT-A and TMT B-A.

Trail Making Test (TMT) is a frequently used neuropsychological test because of its sensitivity to brain damage. It explores visual-conceptual and visual-motor tracking. TMT is administered in two parts. Part A is a visual-scanning, timed task where participants are asked to connect with lines 25 circles numbered from 1 to 25 as quickly as possible. The test is terminated after 5 minutes even if not completed In Part B participants are asked to connect circles containing numbers (from 1 to 13) or letters (from A to L) in an alternate numeric/alphabetical order. The test is terminated in every case after 10 minutes even if not completed. The TMT B-A score calculated as the difference between TMT-B and TMT-A times is considered a measure of cognitive flexibility relatively independent of manual

dexterity. Should the difference *TMT-B - TMT-A* be negative (i.e. *TMT-B < TMT-A)*, TMT B-A will be conventionally set to 0 (zero).

5.2 Secondary Endpoints

Secondary efficacy endpoints of the study are:

a) changes of VFT score from baseline (V2) to 8 weeks of treatment (V4);
b) changes of MoCA score from baseline (V2) to 8 weeks of treatment (V4);
c) changes of MMSE score from baseline (V2) to 8 weeks of treatment (V4);
d) changes of AVLT score baseline from baseline (V2) to 8 weeks of treatment (V4);
e) changes of GHQ-12 score baseline from baseline (V2) to 8 weeks of treatment (V4);
f) changes of POMS score from baseline (V2) to 8 weeks of treatment (V4);
g) changes of NSSS score from baseline (V2) to 8 weeks of treatment (V4);
h) changes of metabolic parameters (glucose, insulin, HOMA-IR, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides and uric acid from baseline (V2) to 4 weeks of treatment (V3) and from baseline (V2) to 8 weeks of treatment (V4);
i) changes of circulating levels of 8-iso-Prostaglandin F2alpha and malondialdehyde from baseline (V2) to 4 weeks of treatment (V3) and from baseline (V2) to 8 weeks of treatment (V4).

5.3 Exploratory Endpoints

Exploratory endpoints of this study are:

a) correlation between changes of cognitive scores (TMT, VFT, MoCA, MMSE, AVLT) and changes of blood pressure and metabolic parameters including indices of oxidative stress;
b) quantify the effect of time in the change for the primary endpoint.

5.4 Safety Endpoints

Safety endpoints are assessed though the description and analysis of adverse events.

6. PLANNED ANALYSIS

6.1 Interim Analysis

No interim analysis is planned.

6.2 Final Analysis

Efficacy analysis

The primary variables (changes of TMT-B, TMT-A and TMTB-A scores) will be analyzed using an ANCOVA model with the treatment group (main effect) and baseline as covariates A fixed sequence multiple test will be performed,

with the following hierarchical order: 1) changes of TMT B, 2) changes of TMT A and 3) changes of TMT B-A scores.
All the other continuous variables (changes of test scores, changes of metabolic parameters, changes of circulating levels of 8-iso-Prostaglandin F2alpha and malondialdehyde) will be analyzed using an ANCOVA model with the treatment group (main effect) and baseline as covariates. As additional covariate for testing the homogeneity of the regression coefficients the interaction term of treatment*baseline will be included in the model and removed if not significant.
Categorical variables (gender, eventually present cardiovascular risk factors or pharmacological treatment) will be tested by using a Chi-Square test or the Fisher exact test if necessary.

Explorative analysis

- Pearson correlation will be used to evaluate correlations between changes of cognitive scores (TMT scores, VFT, MoCA, MMSE, AVLT) and changes of blood pressure and metabolic parameters including indices of oxidative stress. Spearman nonparametric correlation will be also applied when one or both of the variables are not assumed to be normally distributed and interval (but are assumed to be ordinal).
- in order to evaluate and quantify the effect of time itself (i.e. 8 weeks after the treatment intake) in the change for the primary endpoint a two-way analysis of variance (treatment*time) with time as a repeated measure will be also implemented.

Safety analysis

All adverse events will be duly assessed for identifying any emergent safety finding.
Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, Version 21.1, to give a preferred term (PT) and a system/organ class term (SOC) for each event.
The number of AEs, study product-related AE, serious AE, severe AE will be summarized by treatment arm. The number of subjects who experienced at least one AE and the number of subjects withdrawn due to AE will also be summarized.
AEs occurred after the first treatment intake will be considered Treatment Emergent Adverse Events (TEAEs), selected and analyzed separately.
For each SOC and preferred term, summaries will be made with respect to the proportion of subjects having at least one occurrence of that event during the trial and the total number of events. The incidence of AEs in each treatment arm will be presented overall, by SOC and preferred term, and additional grouping by severity and relationship to the trial treatment. The comparisons will be analyzed using chi-square test.

7. SAMPLE SIZE AND STATISTICAL POWER CONSIDERATION

The primary objective of this study will be assessed using three primary variables (changes in TMT-B, TMT-A and TMT B-A) in a hierarchical order. According to the "Points to consider on multiplicity issues in clinical trials", issued by the Committee for Proprietary Medicinal Products (CPMP - 2002), no sample size adjustment for multiplicity is needed. The study will be based on an estimated sample size of 68 subjects, with a ratio of 1:1 for the 2 treatment groups, which has been calculated to be adequate to achieve 90% power to detect a large effect size (f=0.40) using an ANCOVA model with a baseline covariate and an α of 0.05 between treatment and control (G*power version 3.1.9.2). To consider a possible 15% dropout rate, 80 subjects will be enrolled.

8. ANALYSIS POPULATIONS

8.1 Intent-to-Treat Population (ITT)

The study will be analyzed using an Intent-to-Treat (ITT) approach. All randomized subjects receiving at least a treatment dose and having the post-randomization efficacy evaluation will be included in the ITT population for efficacy analysis.

8.2 Per-Protocol (PP) Population

All subjects without protocol deviations affecting the primary endpoint will be included in the Per-Protocol (PP) analysis. Protocol deviations affecting the protocol can include deviations to the treatment dose or assessment schedule, violations of some inclusion/exclusion criteria, etc.

8.3 Safety Population

All randomized subjects receiving at least a treatment dose will be included in the safety analysis.

9. GENERAL ISSUES FOR STATISTICAL ANALYSIS

9.1 Definitions, Derived Variables and Datasets

Definitions of indicators and methods to derive variables are described in the relevant sections of this document.
Datasets will be derived from the database used to record the information gathered through the paper CRF.

9.1.1 Baseline Values

The baseline values are assessed at V2 (7 days after V1).

9.1.2 Duration of Exposure

Each participant will attend 4 visits over a total period of about 9 weeks: an initial screening phase of 7 to 1 days and then a treatment phase of 8 weeks.
Duration of the treatment: 8 weeks in a double blind scheme (food supplement versus placebo).

Unless premature interruption occurs, the end of the study will be the closure visit at clinical site.

9.1.3 Methods for Withdrawals and Missing Data

The subject may withdraw from the study at any time without explanation, without losing the right to future medical care. The participation of the subject may, at any moment, be terminated by the Investigator, if considered appropriate.
Subjects who discontinue from the study early will complete an early termination visit (Visit 4).
Study treatment must be terminated during the study for any of the following reasons:

- Request of the subject (consent withdrawal);

- An AE occurs that, in the opinion of the Investigator, makes unsafe for the subject to continue in the study;
- Investigator deems it to be in the best interest of the subject to discontinue;
- Failure to comply adequately with the dosing, evaluations, or other requirements of the study

The Investigator must immediately notify the CRO (see CRO officer contacts on page 37) by telephone or fax when a subject has been discontinued/withdrawn due to an AE.
The reason for the withdrawal must be well documented in the CRF.
Withdrawn subjects will not be replaced as already foreseen in the sample size estimation.
Any deviation from the protocol (to be classified as major or minor) will be accepted only in case of emergency and/or after a written agreement with the Sponsor.

9.2 Multicenter Studies Considerations

Not applicable: the study is monocenter.

9.3 Multiple Comparisons and Multiplicity

The primary objective of the study is to evaluate the changes in TMT scores from baseline (V2) to 8 weeks of treatment (V4). The three scores (TMT-B, TMT-A and TMT B-A) will be analyzed in a hierarchical order, and then no adjustment for multiplicity is needed.

9.4 Data Safety Monitoring Board (DSMB)

Not applicable.

10. STUDY SUBJECTS

10.1 Disposition of Subjects

The disposition of subject at each visit will be assessed through information reported on the CRF. The number and percentage of dropouts at each visits will be reported, together with the reason for dropout.

10.2 Protocol Deviations

Protocol deviations are registered during the course of the study. Protocol deviations can be identified in various ways: during onsite monitoring, during remote data checking, during or after data entry, thanks to data checks on CRFs or automated data checks during or after data entry. The impact of each deviation and the opportunity to drop subjects following a deviation will be discussed. Blind data review will be performed prior to database lock, to assess data completeness and protocol deviations
Number and type of deviation per each treatment arm will be assessed and reported.

The following deviations will be assessed and reported:

- Informed consent not obtained
- Inclusion/exclusion criteria not matched
- Visits performed out of window

- Uncorrect assignment of study treatment
- Compliance lower than 80% or higher than 120%
- Primary endpoints not assessed.

11. EFFICACY ANALYSIS

11.1 Analysis datasets

The study will be analyzed using an Intent-to-Treat (ITT) approach. All randomized subjects receiving at least a treatment dose and having the post-randomization efficacy evaluation will be included in the ITT population for efficacy analysis.

All subjects without protocol deviations affecting the primary endpoint will be included in the Per-Protocol (PP) analysis. Protocol deviations affecting the protocol can include deviations to the treatment dose or assessment schedule, violations of some inclusion/exclusion criteria, etc.

All randomized subjects receiving at least a treatment dose will be included in the safety analysis.

11.2 Demographics and Baseline Characteristics

Demographic variables include age, sex and race. Age will be estimated as difference between birth date and informed consent date.

Other characteristics at screening (Visit 1) will be summarized: Mini Mental State Examination (MMSE) and Geriatric Depression Scale (GDS), Medical and surgical history, physical examination, height, weight, bmi (kg/m^2), waist circumference and blood pressure.

In the same way, characteristics assessed or re-assessed at baseline will be summarized: physical examination, height, weight, BMI (kg/m^2), waist circumference, blood pressure, Trail Making Test (TMT), Verbal Fluency Test (VFT); Montreal Cognitive Assessment (MoCA), MMSE, Rey Auditory Verbal Learning Test (AVLT), Profile of Mood States Assessment (POMS), General HEALTH Questionnaire (GHQ-12), New Sexual Satisfaction Score (NSSS), Metabolic parameter (Glucose, Insulin, HOMA-IR, Total Cholesterol, LDL Cholesterol; HDL Cholesterol, Tryglicerides, Uric Acid), Biomarkers (8-iso-Prostaglandin F2alpha, Plasma malondialdehyde).

Demographic, screening and baseline characteristics will be compared between treatment groups in order to assess any major displacement between treatment groups. T-test will be used for continuous variables (SAS TTEST procedure), chi-square (SAS FREQ procedure) for categorical ones.

Demographic and baseline characteristics will be used as covariates in efficacy analyses.

11.3 Measurements of Treatment Compliance

The subject compliance for study treatment period is calculated by the following formula:

$$\%\ \text{compliance} = \frac{\text{number of tablets actually taken}}{\text{expected number of tablets to be taken}} \times 100$$

The number of tablets actually taken will be calculated as the difference between the number of tablets handled out to the subject and the number of unused tablets returned or declared lost by the subject.

The expected number of tablets to be taken will be calculated using the difference (in days) between Visit 3 and Visit 2 and between Visit 4 and Visit 3.

A subject that has taken at least 80% and no more than 120% of the required product intake since the last visit will be considered compliant.

11.4 Efficacy Analysis

All efficacy analyses are aimed to assess changes between baseline and one or two subsequent timepoints [4 weeks of treatment (V3) and 8 weeks of treatment (V4)]. ANCOVA models will be used to adjust for baseline values.

11.4.1 Primary Efficacy Endpoints

The primary variables (changes of TMT-B, TMT-A and TMT B-A scores), will be analyzed in a hierarchical order. An ANCOVA model with the treatment group (main effect) and baseline value of each score as a covariates will be used. ANCOVA will be performed using SAS GLM procedure with treatment and baseline values as factors.

ANCOVA assumptions will be checked. Normality assumption will be tested using Shapiro-Wilks' test, and homogeneity of variances across treatment groups will be tested using Levene's test. As additional covariate for testing the homogeneity of the regression coefficients, the interaction term of *treatment*baseline* will be included in the model and removed if not significant. If ANCOVA assumptions are violated, Kruskal-Wallis test will be used.

The analysis in a hierarchical order implies that the statistical significance of changes in TMT-B will be first assessed, followed by the assessment of the statistical significance of changes in TMT-A and the statistical significance of changes in TMT B-A will be assessed as the last one.

11.4.2 Secondary Efficacy Endpoints

All continuous variables (changes of test scores, changes of metabolic parameters, changes of circulating levels of 8-iso-Prostaglandin F2alpha and malondialdehyde) will be analyzed by using an ANCOVA model with the treatment group (main effect) and baseline as covariates. ANCOVA will be performed using SAS GLM procedure with treatment and baseline values as factors.

a) changes of VFT score from baseline (V2) to 8 weeks of treatment (V4);
Verbal Fluency Test (VFT) is a short test of verbal functioning. Participants are given 1 min to produce as many unique words as possible within a semantic category (category fluency) or starting with a given letter (letter fluency). The participant's score in each task is the number of unique correct words.

b) changes of MoCA score from baseline (V2) to 8 weeks of treatment (V4);
Montreal Cognitive Assessment (MoCA) evaluates a broader array of cognitive domains (e.g., attention/executive functioning, visuospatial abilities and language) and it has been demonstrated to be able to detect cognitive impairment with scores ranging from 0 to 30.

c) changes of MMSE score from baseline (V2) to 8 weeks of treatment (V4);

Mini Mental State Examination (MMSE) is a widely used screening tool for cognitive impairment and covers five areas of cognitive function including orientation, attention, calculus, recall and language with scores ranging from 0 to 30.

d) changes of AVLT score baseline from baseline (V2) to 8 weeks of treatment (V4);
Rey Auditory Verbal Learning Test (AVLT) is a neuropsychological assessment designed to evaluate the nature and severity of memory dysfunction and to track changes in memory function. The examiner reads aloud a list of 15 words at the rate of one per second. The participant is then asked to repeat all words from the list that she/he can remember. This procedure is carried out a total of five times. After a 15-minute delay, the participant is again asked to recall as many words as possible from the first list. The participant is then requested to read a list of words and asked to indicate whether each word was from the first list. The score for each trial is the number of words correctly recollected.

e) changes of GHQ-12 score baseline from baseline (V2) to 8 weeks of treatment (V4);
General Health Questionnaire (GHQ-12) is a relevant instrument for measuring psychological well-being. It has been extensively evaluated in terms of validity and reliability as a one dimensional indicator of the severity of psychological morbidity, and it has already been validated for Italy.

f) changes of POMS score from baseline (V2) to 8 weeks of treatment (V4);
Profile of Mood Stated (POMS) is a widely used tool in assessing mood states that has already been validated for Italy. Higher scores reflect mood decrements, except for the vigor subscale, where higher scores reflect improved mood. Taking into consideration the two components characteristic of the POMS that measure negative affect and positive affect, respectively, the data collected with the questionnaire will be analyzed both as global score and by separately considering a Positive Affect Scale (PAS-POMS, 48 items, score ranging from 0 to 192) and a Negative Affect Scale (NAS-POMS, 10 items, score ranging from 0 to 40).

g) changes of NSSS score from baseline (V2) to 8 weeks of treatment (V4);
New Sexual Satisfaction Scale (NSSS) is a 20 item, multidimensional, composite measure of sexual satisfaction based on a five-dimension, conceptual model that emphasized the importance of multiple domains of sexual behavior including sexual sensations, sexual awareness and focus, sexual exchange, emotional closeness, and sexual activity.

h) changes of metabolic parameters from baseline (V2) to 4 weeks of treatment (V3) and from baseline (V2) to 8 weeks of treatment (V4);
Metabolic profile will be evaluated by the following variables:
1. glucose (normal range 60-100 mg/dL)
2. insulin (normal range 2.7-10.4 mcUI/mL)
3. HOMA-IR (derived from glucose and insulin, normal ranges not applicable)
4. total cholesterol (normal range 150-200 mg/dL)
5. LDL cholesterol (normal range 40-130 mg/dL)
6. HDL cholesterol (normal range 35-90 mg/dL)
7. triglycerides (normal range 60-170 mg/dL)
8. uric acid (normal range 3.5-7.0 mg/dL).

i) changes of circulating levels of oxidative stress biomarkers from baseline (V2) to 4 weeks of treatment (V3) and from baseline (V2) to 8 weeks of treatment (V4).
Oxidative stress will be evaluated by measuring circulating levels of 2 soluble biomarkers:

A. 8-iso-Prostaglandin F2alpha (no predefined normal range)
B. Plasma malondialdehyde (no predefined normal range)

j) changes of circulating levels of systolic and diastolic blood pressure from baseline (V2) to 4 weeks of treatment (V3) and from baseline (V2) to 8 weeks of treatment (V4).
Clinic systolic and diastolic blood pressure levels will be recorded in the morning, using a validated oscillometric device with appropriately sized cuffs on the non-dominant upper arm after 5 min resting in a seated position; the first blood pressure measurement will be discarded and the subsequent three consecutive blood pressure readings, taken at 3-min intervals, will be recorded. The average of these latter measures will be considered for statistical analysis. [O'Brien et al., 2005].

11.4.3 Explorative analysis

- Pearson correlation will be used to evaluate correlations between changes of cognitive scores (TMT scores, VFT, MoCA, MMSE, AVLT) and changes of blood pressure and metabolic parameters including indices of oxidative stress. Spearman nonparametric correlation will be also applied when one or both of the variables are not assumed to be normally distributed and interval (but are assumed to be ordinal). Pearson correlation coefficients, Spearman nonparametric correlation and related plots will be obtained using SAS CORR procedure.
- in order to evaluate and quantify the effect of time itself (i.e. 8 weeks after the treatment intake) in the change for the primary endpoint a two-way analysis of variance (treatment*time) with time as a repeated measure will be also implemented. Two-way ANOVA will be performed using SAS GLM procedure and SAS MIXED procedure.

11.5 Summary of Efficacy Analyses

Endpoint	Analysis	Populations
Changes of TMT scores from baseline (V2) to 8 weeks of treatment (V4)	ANCOVA will be used to assess treatment effect.	*ITT* *PP*
Changes of VFT score from baseline (V2) to 8 weeks of treatment (V4)	ANCOVA will be used to assess treatment effect.	*ITT*
Changes of MoCA score from baseline (V2) to 8 weeks of treatment (V4)	ANCOVA will be used to assess treatment effect.	*ITT*
Changes of MMSE score from baseline (V2) to 8 weeks of treatment (V4)	ANCOVA will be used to assess treatment effect.	*ITT*
Changes of AVLT score baseline from baseline (V2) to 8 weeks of treatment (V4)	ANCOVA will be used to assess treatment effect.	*ITT*
Changes of GHQ-12 score baseline from baseline (V2) to 8 weeks of treatment (V4)	ANCOVA will be used to assess treatment effect.	*ITT*

Changes of POMS score from baseline (V2) to 8 weeks of treatment (V4)	ANCOVA will be used to assess treatment effect.	*ITT*
Changes of NSSS score from baseline (V2) to 8 weeks of treatment (V4)	ANCOVA will be used to assess treatment effect.	*ITT*
Changes of metabolic parameters (glucose, insulin, HOMA-IR , total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides and uric acid) from baseline (V2) to 4 weeks of treatment (V3) and from baseline (V2) to 8 weeks of treatment (V4)	ANCOVA will be used to assess treatment effect.	*ITT*
Changes of circulating levels of 8-iso-Prostaglandin F2alpha and plasma malondialdehyde from baseline (V2) to 4 weeks of treatment (V3) and from baseline (V2) to 8 weeks of treatment (V4)	ANCOVA will be used to assess treatment effect.	*ITT*
Changes of systolic and diastolic blood pressure from baseline (V2) to 4 weeks of treatment (V3) and from baseline (V2) to 8 weeks of treatment (V4)	ANCOVA will be used to assess treatment effect.	*ITT*

12. SAFETY EVALUATION

12.1 Extent of Exposure

For each subject, the extent of exposure will be assessed as the number of days on treatment:
Extent of exposure = (Last day of treatment – First day of treatment) + 1
The number of treatment doses taken will be estimated as the difference between the number of tablets handled out to the subject and the number of unused tablets returned or declared lost by the subject.
Mean number of treatment doses per day will be estimated as:

$$\frac{Number\ of\ doses\ taken}{Extent\ of\ exposure}$$

12.2 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, Version 21.1, to give a preferred term (PT) and a system/organ class term (SOC) for each event.
The number of subjects who experienced at least one AE and the number of subjects withdrawn due to AE will be summarized.
The number of AEs, study product-related AE, serious AE, severe AE will be summarized by treatment arm.
AEs occurred after the first treatment intake will be considered Treatment Emergent Adverse Events (TEAEs) and analyzed separately.
Adverse events will be summarized for each SOC and preferred term, including the number of subjects having at least one occurrence of each event.

The incidence of AEs in each treatment arm will be presented overall, by SOC and preferred term, and additional grouping by severity and relationship to the trial treatment.
The comparisons will be analyzed using chi-square test.

12.3 Other safety endpoints

Not applicable.

13. DEVIATIONS FROM THE PROTOCOL SPECIFIED ANALYSIS

None

14. LIST AND SAMPLES OF TABLES, FIGURES AND GRAPHS

Table 14.1. Subject disposition

Table 14.2. Dropout subjects

Table 14.3. Protocol Deviation

14.1 Demographic data and clinical characteristics

Table 14.1.1. Demographic and baseline characteristics

Table 14 1 2 Details about the disease at screening

Table 14 1 3. Compliance with product administration

Table 14.1.4 Medical surgical and medical history

Table 14.1.5. Physical examination

Table 14 1.6. Vital signs

Table 14 1 7. Concomitant medications

Table 14 1 3. Blood tests

14.2 Efficacy data

14.2.1 Primary endpoint

Table 14 2 1.1. Changes of TMT scores from baseline to eight weeks of treatment (ITT population)

Table 14.2.1 2 Changes of TMT scores from baseline to eight weeks of treatment (PP population)

Figure 14.2.1.1. Mean TMT B score between baseline and eight weeks of treatment (ITT population)

Figure 14.2.1.2. Mean TMT A score between baseline and eight weeks of treatment (ITT population)

Figure 14.2.1.3. Mean TMT B-A score between baseline and eight weeks of treatment (ITT population)

Figure 14.2.1.4. Mean TMT B score between baseline and eight weeks of treatment (PP population)

Figure 14.2.1.5 Mean TMT A score between baseline and eight weeks of treatment (PP population)

Figure 14.2.1.6. Mean TMT B-A score between baseline and eight weeks of treatment (PP population)

14.2.2 Secondary endpoints

Figure 14.2.2.17 Mean malondialdehyde blood level between baseline and eight weeks of treatment

Figure 14.2.2.18 Mean systolic blood pressure between baseline and eight weeks of treatment

Figure 14.2.2.19 Mean diastolic blood pressure between baseline and eight weeks of treatment

14.2.3 Exploratory analysis

Figure 14.2.3.1 to Figure 14.2.3.60 Correlation analysis plots with Pearson correlation coefficients or Spearman nonparametric correlation

14.3 Safety data

Table 14.3.1 Analysis of adverse events observed

Table 14 3.2. Display of adverse events observed

Table 14 3 3. Listing of deaths, other serious and significant adverse events

Table 14.3 4. Abnormal laboratory value listing (each subjects)

Table 14.3 5. Clinically significant abnormalities after physical examination

14.4 Sample tables

Tables reporting statistical analysis will be issued as both PDF and RTF file. Mock samples are reported in the following sections.

14.4.1 Sample summary table

Sponsor: A. Menarini Industrie Farmaceutiche srl
Protocol MEIF/17/BAC-COG/01

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Table xx.x.x
....
(.................... Population)

Characteristic	Statistic	ARM A (N=xxx)	ARM B (N=xxx)
VAR 1	Class A	xx (xx.x%)	xx (xx.x%)
	Class B	xx (xx.x%)	xx (xx.x%)
	p-value		x.xxx
VAR 2	N	xx	xx
	Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Median	xx.xx	xx.xx
	Min - Max	xx.xx / xx.xx	xx.xx / xx.xx
	p-value		x.xxx
VAR 3	Class A	xx (xx.x%)	xx (xx.x%)
	Class B	xx (xx.x%)	xx (xx.x%)
	Class C	xx (xx.x%)	xx (xx.x%)
	Class D	xx (xx.x%)	xx (xx.x%)
	p-value		x.xxx
VAR 4	N	xx	xx
	Mean (SD)	xxx.xx (x.xx)	x.xx.xx (x.xx)
	Median	xxx.xx	xxx.xx
	Min - Max	xxx.xx / xxx.x	xxx.xx / xxx.x
	p-value		x.xxx
VAR 5	N	xx	xx
	Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Median	xx.xx	xx.xx
	Min - Max	xx.xx / xxx.xx	xx.xx / xxx.xx
	p-value		x.xxx
VAR 6	N	xx	xx
	Mean (SD)	xx.xx (x.xx)	xx.xx (x.xx)
	Median	xx.xx	xx.xx
	Min - Max	xx.xx / xx.xx	xx.xx / xx.xx
	p-value		x.xxx

Statistical significance: * p<0.05; ** p<0.01; *** p<0.001
Notes: [illegible]

Program: Tabxxxx xx.sas — CONFIDENTIAL — Date: xx/xx/xxxx

14.4.2 Sample table for efficacy analysis – continuous variables

Sponsor: A. Menarini Industrie Farmaceutiche Srl
Protocol MEIF/17/BAC-COG/01

Table xx.x.x.x
Summary and Analysis of ... Population)

Endpoint	Statistic	ARM A (N=xxx)	ARM B (N=xxx)
Var1	N	xxx	xxx
	Mean (SD)	-x.xx (x.xx)	-x.xx (x.xx)
	Median	-x.xx	-x.xx
	Min - Max	-x.xx / x.xx	-x.xx / x.xx
	Adjusted mean (SE)	-x.xx (x.xx)	-x.xx (x.xx)
	Treatment difference		- x.xx
	95% CI		-x.xx / -x.xx
	p-value		x.xxx
Var2	N	xxx	xxx
	Mean (SD)	-x.xx (x.xx)	-x.xx (x.xx)
	Median	-x.xx	-x.xx
	Min - Max	-x.xx / x.xx	-x.xx / x.xx
	Adjusted mean (SE)	-x.xx (x.xx)	-x.xx (x.xx)
	Treatment difference		- x.xx
	95% CI		-x.xx / -x.xx
	p-value		x.xxx

Statistical significance: * p<0.05; ** p<0.01; *** p<0.001
Note: Results on treatment difference from an ANCOVA model with factor(s) for ...

Program: Txxxxxxx xxx.sas CONFIDENTIAL Date: xxXXXxxx

14.4.3 Sample table for efficacy analysis – discrete variables

Sponsor: A. Menarini Industrie Farmaceutiche Srl
Protocol: MEIF/17/BAC-COG/01

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Table xx.x.x.x
Summary and Analysis of ____________
(________ ______ Population)

Characteristic	Statistic	ARM A (N=xx)	ARM B (N=xx)
Var1	Class A	xx (xx.x%)	xx (xx.x%)
	Class B	xx (xx.x%)	xx (xx.x%)
	p-value		x.xxx**
Var2	Class A	xx (xx.x%)	xx (xx.x%)
	Class B	xx (xx.x%)	xx (xx.x%)
	p-value		x.xxx**

Statistical significance: * p<0.05; ** p<0.01; *** p<0.001.
Note: p-values from a chi-square test.

Program: [illegible] CONFIDENTIAL Date: xxxxxxxxx

14.4.4 Sample table for adverse events analysis

Sponsor: A. Menarini Industrie Farmaceutiche Srl
Protocol MEIF/17/BAC-COG/01

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Table xx.x.x.x
Adverse Events
(Safety Population)

AE details	Statistic	ARM A (N=xxx)	ARM B (N=xxx)
Have any AE occurred?	NO	x (xx.x%)	x (xx.x%)
	YES	x (xx.x%)	x (xx.x%)
	Odds Ratio		x.xx
	95% CI		x.xx / x.xx
	p-value		x.xxx
Number of AE per subject	N	xxx	xxx
	Mean (SD)	x.xx (x.xx)	x.xx (x.xx)
	Median	x.xx	x.xx
	Min – Max	x.xx / x.xx	x.xx / x.xx
	Adjusted mean (SE)	x.xx (x.xx)	x.xx (x.xx)
	Treatment difference	.	x.xx
	95% CI		x.xx / x.xx
	p-value		x.xxx
Total number of adverse events*	N	(N=xxx)	(N=xxx)
Relatedness with study treatment	CERTAIN	x (xx.x%)	x (xx.x%)
	PROBABLE	x (xx.x%)	x (xx.x%)
	POSSIBLE	x (xx.x%)	x (xx.x%)
	UNASSESSABLE	x (xx.x%)	x (xx.x%)
	UNLIKELY	x (xx.x%)	x (xx.x%)
	NOT RELATED		
Severity	MILD	x (xx.x%)	x (xx.x%)
	MODERATE	x (xx.x%)	x (xx.x%)
	SEVERE	x (xx.x%)	x (xx.x%)
	p-value		x.xxx
Seriousness	YES	x (xx.x%)	x (xx.x%)
	NO	x (xx.x%)	x (xx.x%)
	p-value		x.xxx

* More than one adverse event per patient.

Statistical significance: * p<0.05, ** p<0.01; *** p<0.001.
Note: p-values from a chi-square test for discrete variables and T-test for continuous variables.

Program: Program xxx.sas CONFIDENTIAL Date: xxXXXxxxx

14.4.5 Sample table for adverse events display

Sponsor: A. Menarini Industrie Farmaceutiche Srl — Page i of x

Protocol MEIF/17/BAC-COG/01

Table xx.x.x.x
Summary of Number (%) of Adverse Events and Patients with Adverse Events by System Organ Class and Preferred Term
(Safety Population)

System Organ Class (SOC) . Preferred Term (PT)	ARM A (N=xxx) Event	Patients	(%)	ARM B (N=xxx) Event	Patients	(%)
OVERALL	x	x	x.xx	x	x	x.xx
SOC 1	x	x	x.xx	x	x	x.xx
. PT 1	x	x	x.xx	x	x	x.xx
. PT 2	x	x	x.xx	x	x	x.xx
. PT 3	x	x	x.xx	x	x	x.xx
SOC 2	x	x	x.xx	x	x	x.xx
. PT 1	x	x	x.xx	x	x	x.xx
. PT 2	x	x	x.xx	x	x	x.xx
. PT 3	x	x	x.xx	x	x	x.xx
SOC 3	x	x	x.xx	x	x	x.xx
. PT 1	x	x	x.xx	x	x	x.xx
. PT 2	x	x	x.xx	x	x	x.xx
. PT 3	x	x	x.xx	x	x	x.xx
SOC 4	x	x	x.xx	x	x	x.xx
. PT 1	x	x	x.xx	x	x	x.xx
. PT 2	x	x	x.xx	x	x	x.xx
. PT 3	x	x	x.xx	x	x	x.xx
SOC 5	x	x	x.xx	x	x	x.xx
. PT 1	x	x	x.xx	x	x	x.xx
. PT 2	x	x	x.xx	x	x	x.xx
. PT 3	x	x	x.xx	x	x	x.xx
SOC 6	x	x	x.xx	x	x	x.xx
. PT 1	x	x	x.xx	x	x	x.xx
. PT 2	x	x	x.xx	x	x	x.xx
. PT 3	x	x	x.xx	x	x	x.xx

Program: Tnnnnnnn xxx.xxx — CONFIDENTIAL — Date: xxXXxxxx

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16. APPENDICES

16.1 Sample Listing

Sponsor: A. Menarini Industrie Farmaceutiche Srl
Protocol MEIF/17/BAC-COG/01

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Listing XX X.X.X

		Visit x				Visit x					Visit x				
ARM	SUBJECT	VAR 1	VAR 2	VAR 3	VAR 4	VAR 1	VAR 2	VAR 3	VAR 4	VAR 5	VAR 1	VAR 2	VAR 3	VAR 4	VAR 5
ARM A	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	XX.X	XX	XX	XX	XX.X	-XX.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	-XX.X	X	X	X	X.X	-XX.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	X.X	XX	XX	XX	XX.X	-XX.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	XX.X	XX	XX	XX	XX.X	-X.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	X.X	XX	XX	XX	XX.X	X.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	-X.X	XX	XX	XX	XX.X	XX.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	X.X	XX	XX	XX	XX.X	-XX.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	X.X	XX	XX	XX	XX.X	-XX.X
	XXXXX-XXX	XXX	XX	XXX	XX.X	XX	XX	XX	XX.X	-X.X	XX	XX	XX	XX.X	X.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	XX.X	XX	XX	XX	XX.X	X.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	X.X	XX	XX	XX	XX.X	-XX.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	-XX.X	XX	X	X	XX.X	-XX.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	-X.X	XX	XX	XX	XX.X	X.X
ARM B	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	-XX.X	X	X	X	X.X	-XX.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	X.X	XX	XX	XX	XX.X	-X.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	-X.X	XX	XX	XX	XX.X	X.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	-X.X					
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	-X.X	XX	XX	XX	XX.X	-XX.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	-XX.X	XX	XX	XX	XX.X	XX.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	-XX.X	XX	XX	XX	XX.X	-XX.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	-X.X	XX	XX	XX	XX.X	-XX.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	-X.X	XX	XX	XX	XX.X	-X.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	-XX.X	XX	XX	XX	XX.X	-XX.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	-XX.X	XX	XX	XX	XX.X	XX.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	-XX.X	XX	XX	XX	XX.X	-XX.X
	XXXXX-XXX	XXX	XXX	XX	XX.X	XX	XX	XX	XX.X	-XX.X	XX	XX	XX	XX.X	-XX.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	-X.X	XX	XX	XX	XX.X	-XX.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	-XX.X	XX	XX	XX	XX.X	-XX.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	-XX.X	XX	XX	XX	XX.X	-XX.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	XX.X	XX	XX	XX	XX.X	-XX.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	-XX.X	XX	X	X	X.X	-XX.X
	XXXXX-XXX	XX	XX	XX	XX.X	XX	XX	XX	XX.X	-X.X	XX	X	X	X.X	-XX.X

Program: LXXXXXXX.sas CONFIDENTIAL Date: XXXXXXXX

16.2 List and samples of Subject Data Listings

16.2.1 Discontinued subjects

16.2.2 Protocol deviations

16.2.3 Subjects excluded from the efficacy analysis

16.2.4 Demographic data

16.2.5 Compliance and/or Drug Concentration Data (if available)

16.2.6 Individual Efficacy Response data

16.2.7 Adverse event listings (each subject)

16.2.8 Listing of individual laboratory measurements by subject, when required by regulatory authorities