Clinical Study Report

Effect of Brain Pill™ on working memory capacity and mood behavior in healthy adults with subjective memory complaints and mild mood disturbances.

CSR ID: LM/161103/BP/MCI

VERSION: 1.0

DATE: Apr 16, 2018

CRO's Signature			
Written by	**Reviewed by**	**Approved by**	**Authorized by**
Dr. Surekha Pimple (Medical Writer)	Dr. Shalini Srivastava (Associate Director – CD)	Anil Yadav (Manager-QA)	Jayesh Chaudhary (CEO)
for May 17, 2018	May 17, 2018	May 17, 2018	May 20, 2018
Sponsor's Signature			
Sponsor's Representative	Mr. Doug MacKay President Leading Edge Marketing Ltd	Signature with Date May 11, 2018	

TABLE OF CONTENTS

TITLE PAGE

Study Title	"Effect of Brain Pill™ on working memory capacity and mood behavior in healthy adults with subjective memory complaints and mild mood disturbances."
Name of Investigational product	Brain Pill™
Dose	296. 4 mg / capsule 2 capsules twice a day amounting to 1185.6 mg/ Day
Indication studied	Working Memory
A brief description of design	A randomized, double-blind, placebo-controlled, parallel group study
Protocol identification	LM / 161103 / BP / MCI
Comparator	Placebo
Duration	12 Weeks
Patient population	- Males & females aged ≥18 and ≤ 60 years. - Subjects randomized – 79 - Subjects completed – 74
Sponsor	Leading Edge MarketingLtd
Study initiation date	Apr-11-2017 (First Subject First Visit)

Study completion date	Nov-13-2017 (Last Subject Last Visit)
Clinical Research Organization (CRO)	Vedic Lifesciences
Sponsor's signatory	Mr. Doug MacKay President, Leading Edge Marketing Ltd 100-645 Tyee Road, Victoria, BC V9A 6X5, USA.
Contact details - Sponsor	Phone: 1-(250) 383-8267 extension 447; 1-(250) 383-0896 e-mail : doug@dmcontact.com
CRO signatory	Mr. Jayesh Chaudhary CEO; Vedic Lifesciences 118, Morya House, Andheri (West), Mumbai: 400 053. India.
Contact details – CRO	Phone : (+91)-22- 42172300 extension 319 e-mail : jayesh.chaudhary@vediclifesciences.com
Principal investigator	Dr. Sonal Raote
ICH-GCP Statement	The study was performed in compliance with Good Clinical Practices (GCP) ICH-E6 guidelines.
Date of the report	**Apr-28-2018**

STATEMENT OF COMPLIANCE

As a CRO, Vedic Lifesciences assures that the right, safety, confidentiality and wellbeing of all trial subjects involved in this study has been safeguarded by trained key personnel. The trial has been conducted in accordance with the ICH-GCP Guidelines for Biomedical Research on Human Participants). The study data has been collected using an efficient data management matrix. Study quality has been assured by double-layered check of clinical data by monitors as well as auditor. The statistical evaluation and analysis has been performed by trained biostatician. The study documents as well as the data has been archived at secured electronic location. The organization is committed to abide to the sponsor to maintain the privacy and confidentiality. Vedic stands well-versed in preparing and maintaining the study report applying the quality standards specified by the E3 guidelines.

STUDY SYNOPSIS

Name of Sponsor	Leading Edge Marketing Ltd.
Name of Product	Brain Pill™
Title of Study	Effect of Brain Pill™ on working memory capacity and mood behavior in healthy adults with subjective memory complaints and mild mood disturbances.
Study Center	Vedic Life Sciences Pvt. Ltd. (Site specific details are provided in section)
Number of Participants	Randomized : 80; Completed: PP = 73, ITT =79
Dose & Mode of Administration	2 capsules twice a day; to be taken orally with meals with a glassful of water.
Reference Therapy	Placebo
Main Inclusion Criteria	• Age between **18 and 60** years. • A score of **40-70 %** on AMQ, indicating mild to moderate subjective memory lapse. • Minimum **12 years** of education. • **MMSE score > 23 (Mentally healthy).** • T-score on 8-item PROMIS Depression Short Form: **50.0 - 59.9**.
Main Exclusion Criteria	• Participants with MMSE score **≤ 23.** • Participants with AMQ score of **< 40%** (Negligible memory complaints) **or > 70%** (severe memory loss) • T score on 8-item PROMIS Depression Short Form **< 50 (normal) and ≥ 60** (moderate and severe). • Confirmed diagnosis of dementia/ Alzheimer's disease.

	• Current evidence of any medical or psychiatric disorder that could significantly influence cognition. • Current evidence of hearing impairment or other information processing impairment. • Pregnant women or women not using medically accepted means of birth control.
• **Efficacy Evaluation**	
Primary Objective	• To evaluate the effect of Brain Pill™ on working memory capacity using Operation Span Task (Digit Recall).
Secondary Objectives	• To evaluate the effect of Brain Pill™ on the attention and concentration using mean response time using Picture Recognition Task. • To evaluate the effect of Brain Pill™ on the improvement of problem solving capability using Mathematical operations of Operation Span Task. • To evaluate the effect of Brain Pill™ on the improvement of visuospatial memory using Matrix Span Task. • To evaluate the effect of Brain Pill™ on Mood disturbances using BRUMS – TMD Questionnaire.
Safety Evaluation	• Vital signs (Pulse Rate, Blood pressure). • Adverse and Serious adverse event.
• **Result Summary**	
Efficacy	• As age is considered as the most influencing confounding factor in memory related studies, and has also been reported in the clinical studies of ingredients of Brain Pill™, to the population was cohorted into two groups: 18 to 39 years (N=45) and ≥ 40 years (N=28).

- **Operation Span Task (Digit Recall):**

The result obtained for primary efficacy variable exhibited statistically significant increase in accuracy factor of the digit recall phase of the operation span. This beneficial effect became visible as early as Day 56 and maintained its statistical significance until Day 84. The cumulative analysis of accuracy and mean response time in terms of composite Z score, exhibited a significant improvement (p= 0.044) in Brain Pill™ group, thus substantiating the claim of improvement in working memory capacity.

Secondary Efficacy Variables:

- **Mean Response Time (MRT) using Picture Recognition Test:**

There was statistically significant reduction in mean reaction time in Brain Pill™ group at the end of day 28 (p=0.019) and day 56 (p=0.031). This finding proves that this memory boosting supplement is able to improve a person's ability to learn and experience clearer focus and improved ability to absorb and retain the information with a decreased forgetfulness. The efficacy variable experienced an insignificant change at the end of day 84 (p=0.476), which can be attributed to the higher placebo effect. Also, it is noteworthy that there is no accuracy tradeoff as the accuracy in terms of % correct hits increased over the span of 84 days.

- **Operation Span Task (Mathematical operations):**

Within group statistical significance was observed in mean response time in Brain Pill™ group.

- **BRUMS Score:**

The BRUMS score insignificantly decreased in both the groups however Brainpill group had higher decrease as compared to the placebo group.

- **Matrix span:**

	The matrix span task exhibited beneficial results in terms of accuracy factor with a significant p = 0.001. This finding further ascertains that the investigational product is indeed bears an efficacy to enhance visuospatial memory.
Safety	• The safety of Brain Pill™ was comparable to placebo. Pulse rate and blood pressure were reported to be in clinically safe range throughout the study period in both the groups. Also, no serious adverse event was reported throughout the study.
Conclusion	The result of the study proves that **Brain Pill™** is capable of improving working memory capacity in healthy individuals. Supplementation had a significant positive effect on various measures of cognition
Date of Report Compilation	**10th Apr 2018**

INDEX OF TABLES

LIST OF ABBREVIATIONS

5-HTP	5-hydroxytrytophan
Ach	Acetylcholine
AChE	Acetylcholine esterase
AD	Alzheimer Disease
ADHD	Attention Deficit/Hyperactivity Disorder
ADHD-RS	Attention Deficit/Hyperactivity Disorder-Rating Scale
AE	Adverse Event
AMQ	Adult Memory Questionnaire
BP	Brain Pill™
BRUMS	Brunel Universal Mood Scale
CRF	Case Report Form
CRO	Contract Research Organization
DHA	Docosahexanoic Acid
EEG	Electroencephalogram
EPA	Eicosapentaenoic Acid
holoTC	Holotranscobalamin
HT	Head Trauma
Hup A	Huperzine A
ITT	Intent to treat
L-DOPA	L-3,4-dihydroxyphenylalanine
LTP	Long Term Potentiation
MMC	Mild Memory Complaints
MMD	Mild Mood Disturbances
MMSE	Minimental State Examination
MRT	Mean Response/Reaction Time
NMDA	N-methyl-d-aspartate
PLP	Pyridoxine-5'-phosphate
PP	Per protocol
PROMIS-DSM-5	PROMIS-Diagnostic and Statistical Manual of Mental Disorders, 5th Ed.

PRT	Picture Recognition Test
PS	Phosphatidylserine
SAE	Serious Adverse Event
WM	Working Memory
WMB	Working Memory Battery
WMC	Working Memory Capacity

1. STUDY ETHICS

The current study was registered at clinicaltrial.gov with a registration no. **NCT03198936**.

1.1 INDEPENDENT ETHICS COMMITTEE (IEC)

The study protocol and any amendments were reviewed and approved by an Independent Ethics Committee (IEC) before the conduct of the study. Approving ethics committee was IEC – Aditya, 001, Aradhya Apartments, Under Shreyas Crossing Flyover, Ambawadi, Ahmedabad - 380015, Gujarat, INDIA.(Date of approval: 18th March 2017).

1.2 ETHICAL CONDUCT OF THE STUDY

This study was designed, conducted, analyzed, and reported in accordance with regulatory and ethical guidelines (Declaration of Helsinki, ICH GCP, Indian GCP and Schedule-Y). It was approved and monitored by ethics committee to safeguard the rights, safety and well-being of all trial participants. Authenticity and credibility of the data were well maintained by means of regular site monitoring and audits.

1.3 SUBJECT INFORMATION AND CONSENT

IRB approved signed and dated informed consent was obtained from each subject prior to commencement of the clinical study. The subject was well informed with adequate information regarding proposed clinical trial including risks and benefits involved. All queries from subject and / or relatives were resolved before signing informed consent. Signed and dated informed consents and all other related documents of all participants were archived and the same would be maintained for three years after study completion in the dossiers of study documents. The sample subject consent form has been provided in appendix section.

2 INTRODUCTION

Working memory plays an essential role in complex cognition. Everyday cognitive tasks such as, reading a newspaper article, calculating the appropriate amount to tip in a restaurant, mentally rearranging furniture in one's living room to create space for a new sofa, and comparing and contrasting various attributes of different apartments to decide which to rent, often involve multiple steps with intermediate results that need to be kept in mind temporarily to accomplish the task at hand successfully.[1]

Working memory capacity (WMC) is one of the most frequently measured individual difference constructs in cognitive psychology and related fields which refers to the system or mechanism underlying the maintenance of task-relevant information during the performance of a cognitive task.[2,3] WMC is related to, and highly correlated with, general factors of intelligence, in particular the fluid intelligence (Gf), which involves storing and transforming information to solve novel and abstract problems.[4]

Emerging research continues to focus on how we may be able to provide nutritional support to enhance the brain functioning via enriching the efficiency of different working memory components. Also, the changing and demanding life styles are increasing the mental stress of human race, especially the younger population. This in turn is affecting the working memory and performance at tasks in hand. Thus, the increasing demand for functional food to improve the cognitive ability in humans is relevant. The food components which augment the cognitive performance by supplementing the central nervous system with a constant supply of almost all of the essential nutrients and glucose, as well as oxygen via the blood supply are absolutely required to be taken on the regular basis to cope up with brain demands and avoid the exhaustion. Brain Pill™ is a one of such mental health enhancing and successfully marketed dietary supplement with a balanced composition of scientifically proven nutrients for accelerating and restoring brain function and thereby enhancing the cognitive performance and creating positive impact on behavioral outcomes.[5]

Hence, in this double blind, placebo controlled, parallel clinical study was conducted to assess the effects of Brain Pill™ supplementation on memory performance of healthy adults with subjective memory complaints. The study duration was 84 days (12 weeks) and the efficacy of

the investigational product was captured by assessment of several aspects of working memory capacity as well as on mood behavior.

3 STUDY OBJECTIVES, RATIONALE AND HYPOTHESIS

3.1 PRIMARY OBJECTIVE: To evaluate the effect of Brain Pill™ on the working memory as assessed by the change in the composite score of the change in Z score of MRT and change in Z score of correct hits of digit recall of Operation Span Task at the end of day 84 as compared to baseline and placebo.

3.2 SECONDARY OBJECTIVES

- To evaluate the effect of Brain Pill™ on the attention and concentration as measured by a change in Mean reaction time and accuracy (% of correct hits) at the end of the study, using a picture recognition reaction time test.
- To evaluate the effect of Brain Pill™ on the problem solving capacity as assessed by the change in the composite score of the mathematical problem solving of Operation Span Task at the end of day 84 as compared to baseline and placebo.
- To evaluate the effect of Brain Pill™ on the visuospatial memory as assessed by the change in the mean response time using Matrix span task, at the end of the treatment .
- To evaluate effect of Brain Pill™ on mood disturbances as measured by a change in the Brunel Universal Mood States (BRUMS) score at the end of the study, as compared to baseline.

Null hypothesis and rejection:

H0: (Null hypothesis): The effect of Brainpill on the working memory capacity is same as that of placebo at the end of Day 84.

H1: (Rejection to null hypothesis): Brainpill significantly improves the working memory capacity as compared to placebo after 84 days of intake.

4 INVESTIGATIONAL PLAN

4.1 OVERALL STUDY DESIGN AND PLAN

This was a double blinded, randomized, and placebo-controlled trial conducted at and managed by the team of Vedic Lifesciences. This study was conducted in accordance with Good Clinical Practice and ICH guidelines. The protocol was reviewed and approved by an Independent Ethics Committee.

A total of 116 participants were screened for this study based on protocol-defined inclusion-exclusion criteria. 80 participants with subjective memory lapse and mild mood disturbances were enrolled in this study with 36 screen failures. The eligible participants were randomized in 1:1 ratio to receive either active or placebo. Treatment duration was 84 days for all participants in the study. Out of these, one subject withdrew from the study immediately after randomization, three participants were lost to follow up, three were withdrawn during the treatment phase, giving a number of 79 participants belonging to ITT population, and 73 completed participants (PP).

All participants were closely monitored for protocol compliance during entire study duration. A total of 4 efficacy time points (Baseline, Day 28, 56 and 84) and 6 efficacy data points (four data points from Working Memory Battery, 1 from Picture recognition test and 1 from BRUMS) per visit were included for this study. Thus, in this study **1896** (79 X 4 X 6) data point were captured.

Efficacy evaluations were done at each visit, whereas safety laboratory assessments were done at baseline and end of the study. The adverse events were monitored throughout the study period. General study participant's flow diagram is depicted in **Figure 1** and the particulars about various evaluations done at specific visits have been mentioned in visit specific schedule in **Table 1**.

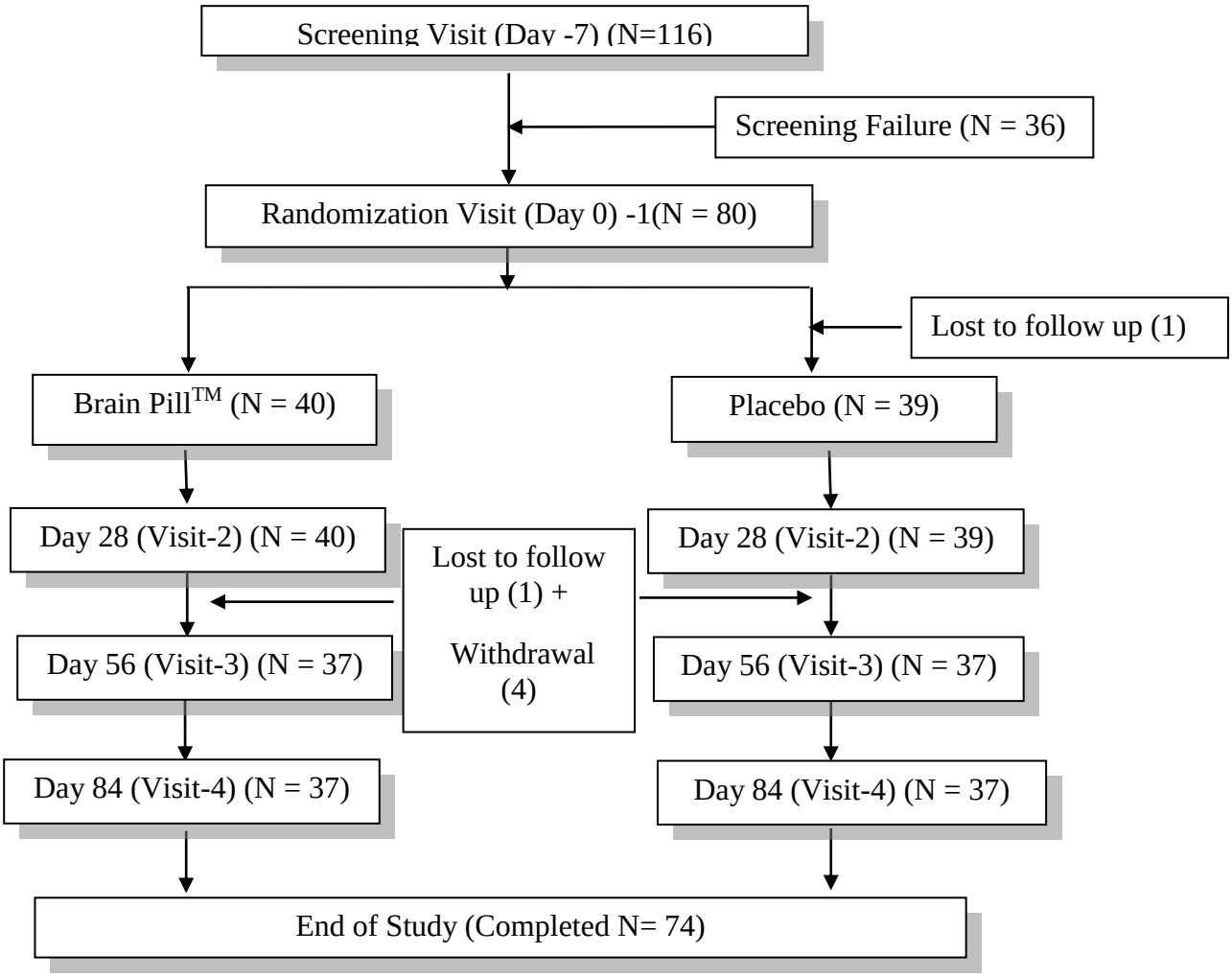

Figure 1. Participant's Flow Diagram

Table 1. Visit Specific Schedule for Efficacy and Safety Assessment					
Visit	**Day (-7) (Screening)**	**Day 0 (Baseline)**	**Day 28 ± 2 (Week 4)**	**Day 56 ± 2 (Week 8)**	**Day 84 ± 2 (Week 12)**
Informed consent	X				
Clinical examination	X	X	X	X	X
Demographics	X				
Vitals	X	X	X	X	X
Screening assessments (MMSE, AMQ, DSM-5)	X				
Working Memory Battery (WMB)		X	X	X	X
Picture Recognition Test (PRT)		X	X	X	X
Brunel Universal Mood States (BRUMS) Questionnaire		X	X	X	X
Monitoring of AE/SAE			X	X	X
IP Dispensing		X	X	X	
IP compliance			X	X	X

4.2 SELECTION OF STUDY POPULATION

4.2.1 Screening Criteria

The participants were assessed and screened on the following criteria in order to be included in the study:

- Mini Mental State Examination (MMSE) is a tool which provides systematic and thorough detail of the mental status. It is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30**. A score of > 23 was indicative of normal cognitive state.**

- Adult Memory Questionnaire (AMQ) is a validated questionnaire which was conducted to analyze individual level of subjective memory complaints. **A range of 40-70% was selected to cover a wide range of subject memory complaints.**

- 8-item PROMIS Depression Short form (DSM-5) is a scoring tool to evaluate the severity in depression in individual in the course of past 7 days. **A range of 50.0-59.9 was pre-determined for the T-score which corresponds to mild mood disturbances.**

4.2.2 Inclusion Criteria

Participants who met ALL of the following criteria were included in the study.

- Participants with MMSE score > 23 indicating a healthy cognitive state.
- Participants with AMQ score of 40-70% indicating subjective memory lapse.
- Participants with T-score on 8-item PROMIS Depression short form: 50.0-59.9.
- Male or female participants with age of 18 to 60 years, both inclusive.
- Participant willing to maintain his or her habitual diet and usual physical activity patterns throughout the study.
- Participant with no health conditions that would prevent him or her from fulfilling the study requirements as judged by the investigator based on medical history and routine laboratory test results.

4.2.3 Exclusion Criteria

Participants who met ANY of the following criteria were excluded from the study.

- Participants with MMSE score ≤ 23 indicative of clinical dementia.
- Participants with AMQ score < 40 and >70 %.
- T score on 8-item PROMIS Depression Short Form <55 (normal) and ≥60 (moderate and severe).
- Confirmed diagnosis of dementia/ Alzheimer's disease.
- Current evidence of hearing impairment or other information processing impairment.
- Participants who are using amphetamines, barbiturates, benzodiazepines, cannabis, cocaine, methamphetamines, methadone, 3,4-methylenedioxymethamphetamine, opiates or tricyclic antidepressants, as disclosed at the screening visit.
- Participants with uncontrolled hypertension (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg) as defined by the average blood pressure measured at the screening.
- Participants with a history or presence of clinically important cardiac, renal, hepatic, endocrine (including diabetes mellitus), pulmonary, biliary, gastrointestinal, pancreatic, or neurologic disorders that, in the judgment of the Investigator, would interfere with the subject's ability to provide informed consent, comply with the study protocol (which might confound the interpretation of the study results), or put the subject at undue risk.
- Subject with a history, in the judgment of the Investigator, of a psychological illness or condition such as to interfere with the subject's ability to understand the requirements of the study or which could significantly influence cognitive abilities.
- Use of any sleep aid medication.
- Pregnant female participants or planning to be pregnant during the study period, lactating, or women of childbearing potential who are unwilling to commit to the use of a medically approved

form of contraception throughout the study period. The method of contraception must be recorded in the source documentation.

- Excessive habitual caffeine consumption (>300 mg caffeine/d or ≥3 cups of caffeinated coffee/d), following screening and throughout the study period.

- Use of any psychotropic medication within four weeks of screening and throughout the study.

- Use of antibiotics or signs of active systemic infection. Treatment visits will be rescheduled to allow the subject to wash off of the antibiotic for at least five days prior to any test visit.

- Participant had exposure to any non-registered drug product within 30 days prior to the screening visit.

- Use of dietary supplements containing any of the ingredients of the investigational product.

- Recent history of (within 12 months of screening visit 1) or strong potential for alcohol or substance abuse. (Alcohol abuse is defined as >14 drinks per week.)

- Participant who has a known allergy or sensitivity to the study product or any ingredients of the study product or meals provided.

- Participant is unable to perform the tests on the computer for participation in this type of study.

4.2.4 Withdrawal Criteria

Participants meeting ANY of the following criteria were withdrawn from the study.

- Participants were given complete liberty to withdraw from the study at any point in time and the investigator should have discuss the reasons for withdrawal with the subject.

- In case during the study, the subject develops any systemic condition that in the opinion of the investigator, renders the participant ineligible for further participation in the study.

- Participants with major protocol deviations.

- Any other condition or circumstance as per the discretion of the investigator.

4.3 TREATMENTS

4.3.1 Treatment Exposure

The participant was asked to consume 2 capsules twice a day and to be taken with meals with a glassful of water orally. The same treatment regimen was followed for a period of 84 days.

4.3.2 Investigational Product

4.3.2.1 Brain Pill™:

The composition of the investigational product has been described in **Table 2**. The COA of the same is displayed in **Figure 2**.

Table 2. Composition of Brain Pill™

Ingredients	Quantity/Day	Quantity/Capsule
Cognizin®	250 mg	62.5 mg
Synapsa™	320 mg	80 mg
Huperzine A	5 mg	1.25 mg
Gingko Biloba Leaf Extract	100 mg	25 mg
Phosphatidylserine	100 mg	25 mg
DHA Complex	100 mg	25 mg
Vitamin B_{12}	50 mcg	12.5 mcg
L-Tyrosine	175 mg	43.8 mg
L-Theanine	100 mg	25 mg
Vitamin B_6	5 mg	1.25 mg
Pantothenic Acid	30 mg	7.5 mg
Folic Acid	400 mcg	100 mcg
Total	**1185.45 mg**	**296. 4 mg**

CERTIFICATE OF ANALYSIS

Product:	LEM Brain Pill Capsules
VC Code #	VC4264
Batch #	16B007
Date of Manufacture:	02/2016

	SPECIFICATIONS	RESULTS	ANALYSIS
Physical Testing:			
Description:	Beige powder in white gelatin capsule	Conforms	Visual
Size & Shape:	#00 Gelatin White Capsule	Conforms	Visual
Target Weight:	729 - 891 mg	799 mg	USP/NF <2091>
Disintegration:	< 30 min. in water w/out disks	Conforms	USP/NF <2040>

	SPECIFICATIONS	LIMIT (% LABEL CLAIM)	RESULTS	METHOD OF ANALYSIS
Ingredients per Capsule:				
Vitamin B6 (as Pyridoxine HCl)	2.500 mg	90 - 135%	112.00%	HPLC
Folic Acid	0.200 mg	90 - 150%	100.00%	By Input
Vitamin B12 (Cyanocobalamin)	0.025 mg	90 - 150%	100.00%	By Input
Pantothenic Acid (as Calcium D-Pantothenate)	15.000 mg	90 - 135%	118.00%	HPLC
L-Tyrosine	87.500 mg	90 - 125%	100.46%	HPLC
Ginkgo Biloba Leaf Ext. 24/6% SE	50.000 mg	100%	100.00%	By Input
PhosphatidylSerine	50.000 mg	100%	100.00%	By Input
Cognizin™	125.000 mg	100%	108.56%	HPLC
DHA Complex (Omega 3-Fish Oil Powder)	50.000 mg	100%	100.00%	By Input
Vinpocetine	2.500 mg	90 - 125%	100.00%	By Input
L-Theanine	50.000 mg	90 - 125%	100.00%	By Input
Bacopa Monniera Ext. SE 55% - Bacosides (Synapsa™)	160.000 mg	100%	100.00%	By Input
Huperzia Serrata Ext. SE 1% - Huperzine A	2.500 mg	100%	100.00%	By Input

Other ingredients: Silicon Dioxide, Magnesium Stearate, Gelatin, Titanium Dioxide (Capsule)

Allergens: Contains Fish & Soyabeans

MICROBIOLOGICAL PROFILES: (USP/NF <2023>)

	Specifications	Results	Method of Analysis
Total Microbial Count	< 10,000 cfu/g	Complies	USP/AOAC
Total Yeast & Mold	< 1,000 cfu/g	Complies	USP/AOAC
Coliforms	< 100 cfu/g	Complies	USP/AOAC
E.coli	Negative/10 g	Complies	USP/AOAC
Salmonella	Negative/25 g	Complies	USP/AOAC
Staphylococcus aureus	Negative/10 g	Complies	USP/AOAC

Product:	LEM Brain Pill Capsules
VC Code #	VC4264
Batch #	16B007
Date of Manufacture:	02/2016

HEAVY METALS: (USP/NF <2232>)

	Specifications	Results	Method of Analysis
Lead	<1.0 ppm	Complies	ICP/MS
Arsenic	<1.5 ppm	Complies	ICP/MS
Mercury	<1.5 ppm	Complies	ICP/MS
Cadmium	<0.5 ppm	Complies	ICP/MS

Issued By/Date: (Anjana Patel/QC Lab)	AP, 02/29/16	**Approved By/Date: (Narendra Bhavsar/QA)**	02/29/16

Figure 2. Certificate of Analysis of Brain Pill™

4.3.2.2 Placebo

Each placebo capsule contained equivalent amount of Microcrystalline cellulose (MCC).

4.3.3 Subject Assignment to Treatment Groups

Simple randomization was performed using the Graph Pad PRISM Version 7. At day 0, participants were randomized as per the provided randomization chart to receive active or placebo in the ratio of 1:1. The blinding codes were secured in tamper-evident sealed envelopes with limited access. The Master Randomization Chart was sealed in an envelope and maintained in the Trial Master File (TMF).

4.3.4 Randomization & Blinding

As this was a double-blind study, the participants as well as the study team which include investigator, site coordinators, and study monitors were blinded. Sixty capsules exactly similar in size (size 0) and color (blood red) were packed in white HDPE bottle (with a silica gel inside and sealed with a foil) and labelled in a similar way for both active and placebo to preserve the blinding. The subject IDs were arranged in a chronological order as per the randomization chart. The blinding codes were secured in tamper-evident sealed envelopes with limited access at the study site. Each envelope was mentioned with the subject ID and the investigational product allocation (active or placebo). The Master Randomization Chart was sealed in an envelope and maintained in the Trial Master File (TMF). The secured soft-copy back up of the same was stored in the respective folder under the sponsor's TMF.

As no Serious Adverse Event (SAE) occurred throughout the study, the investigator never opened the blinding code. The groups were blinded only after the finalization of the statistical results.

4.3.5 Prior and Concomitant Therapy

No concomitant medication was permitted during this study. The list of prohibited concomitant medications was provided to each investigator before the screening visit. The medical history of prior medication was taken and documented at the screening visit for each subject. The same

practice for the concomitant medication was followed at each subsequent visit. The compliance to this list by an investigator and/ or a subject was monitored during each monitoring visit.

Following medicines were prohibited during the study period: Amphetamines and methamphetamines, Barbiturates, Benzodiazepines, Cannabis alkaloids, Methadone, 3,4-methylenedioxymethamphetamine, Cocaine opiates, Tricyclic antidepressants.

Apart from above listed prohibited medications, any other drugs or supplements which as per the investigator's opinion impact the memory components or neurocognitive functions were prohibited during the study.

4.3.6 Treatment Compliance

All participants were given a calculated quantity of IP (60 capsules) at each visit. The investigator instructed the participants regarding the use of the IP. At each visit, the participants' compliance to treatment was confirmed and any instances of non-compliance were recorded in the CRF. The clinical research coordinator (CRC) at the site regularly contacted the participants through telephone to ensure that they adhere to the treatment completely. Accountability of consumed versus remaining IP for an earlier visit was done at subsequent visit. The percentage treatment compliance was calculated at each visit. The protocol-defined criteria for treatment compliance was considered as ≥ 80% compliance.

4.4 EFFICACY AND SAFETY VARIABLES

4.4.1 Efficacy and Safety Measurements Assessed

The efficacy variables were assessed at baseline and at day 28, 56, and 84. The safety parameters were assessed at the baseline and day 84, whereas the adverse events were monitored and recorded throughout the study period. The efficacy and safety variables and the respective tools used have been discussed in detail in this section.

Working memory (WM) is a key construct within cognitive science. It is an important theory in its own right, but the influence of WM is enriched due to the widespread evidence that measures of its capacity are linked to a variety of functions in wider cognition. To analyze the effect of IP on WM, we used a computer-based working memory battery that provides the estimates of short-term and working memory. It incorporated both visuospatial and verbal memory assessment

tasks. The tasks administered were: digit span, matrix span, operation span, and symmetry span. These tasks were built to be simple to use and flexible to adapt to the specific needs of the research design.[vi]

4.4.2 Primary Efficacy Variable: MRT and Accuracy of Digit Recall of Operation Span Task

The primary efficacy variable was the mean response time (MRT) and the accuracy while performing digit recall of **operation span task.** The study assessed the change in composite score of the change in Z-score* of MRT and change in Z- score of correct hits of at day 84 from baseline to end of treatment in each group and between groups.

*Individual Z-score for MRT and correct hits was calculated using the formula: (Individual score-Mean score/SD) which was averaged for the group and used to calculate day-wise change in respective parameters. This information was finally used to decide the composite score.

Method of Assessment:

The task was installed on the laptops and administered to the subject via a "Tatool" interface. All the program-costumed instruction were given to the subject. The operation span task involved a complex span coupled with the digit span task (**Table 3**). The participant was shown a digit that was to be remembered in the correct serial position. After each digit, a mathematical operation such as "10 + 14 = 24" was shown which was to be solved on the veracity of the given answer. The task was approximately 10 minutes at the end of which results were exported in the respective folder. After a break of 10 minutes, another task was followed.

Table 3. Operation Span Task

Task	Task details	Assessed WM aspect	Results
Operation Span (Digit Recall and mathematical problem solving)	• Complex span/paired associate task). • Dynamic verbal WM (selective attention and execution, processing speed, recall and memory storage)	• Arithmetic skills with delayed memory recall • Measure of WM to perform complex cognitive activities. • Episodic secondary verbal recall	Mean response time and accuracy (number of correct hits) for digit recall (out of 81) and operation processing (mathematical problem) (out of 81).

4.4.3 Secondary Efficacy Variables:

4.4.3.1 Picture Recognition Test

Assessment of effect of IP on attention and concentration being the secondary objective was assessed by picture recognition test (PRT) whereas the accuracy and MRT were captured through a simple reaction time task. The details have been mentioned in **Table 5**.

Method of Assessment: Participants were asked to respond by clicking the mouse on the appearance of repeated picture on screen for the duration of 90 seconds and the results are displayed as percent correct hits (accuracy) and mean reaction time (seconds).

Table 4. Picture Recognition Test

Task	Task Details	Cognitive Processes Assessed	Results
Simple reaction time	Memtrax picture recognition test (https://memtrax.com/test/)	Focus and alertness which are primarily required for information processing	Mean reaction time and accuracy (% of correct hits)

4.4.4 MRT and Accuracy of Mathematical problem solving of Operation Span Task

Change in the MRT and number of correct hits of mathematical equations of operation span task at day 84 from baseline to end of treatment in each group and between groups to assess the effect of BrainPill on problem solving skills.

4.4.5 Matrix Span Task:

Effect of IP on visuospatial memory was assessed using change in MRT during Matrix Span task.

Method of Assessment:

Working Memory Battery was used to perform the Matrix Span Task. The task simply presents participants with grid locations to remember in sequence. The grid was 4x4 in dimension. After receiving all the grids, participants were notified to recall and click the grids in the same order.

4.4.6 BRUMS Score

Brunel Universal Mood States (BRUMS) is a standard validated psychological test to assess mood disturbances. The questionnaire contains 24 words/statements that describe subject's mood-based feelings and evaluates the mood feelings over the past week including day of visit. It can assess all major parameters of mood including tension, depression, anger, fatigue, confusion and vigor.[vii]

Method of Assessment:

A standard validated questionnaire was administered to the subject by a study coordinator the total score (BRUMS score) was calculated manually.

Total Mood Disturbance (TMD) score of BRUMS was calculated as:

TMD = (Tension + Depression + Anger + Fatigue + Confusion) – Vigor.

4.4.7 Other Working Memory-Related Tasks

Apart from these cognitive tasks, several other tasks were also administered to the study participants and have been listed in Table 4.

Table 5. Other Working Memory-Related Tasks

Task	Task details	Assessed WM aspect	Results
Digit Span	Verbal WM with (processing speed, recall and memory storage)	• Sub-vocal rehearsal of digit sequences Articulatory loop sub-system of working memory • Immediate verbal recall	Mean response time, accuracy (number of correct hits-out of 81).
Symmetry Span (complex span/paired associate task)	Dynamic Visuospatial WM complex span (selective attention and execution, processing speed, recall and memory storage)	• Spatial skills with visuomotor coordination. • Measure of WM to perform complex cognitive activities. • Episodic secondary visual recall.	Mean response time and accuracy (number of correct hits) for symmetry span (number of correct hits-out of 81) and symmetry processing (number of correct hits-out of 18).

Method of Assessment:

The same software as mentioned in the primary efficacy variable was used for the rest of the cognitive tasks and have been detailed here.

The digit span task is a simple short-term memory measure that involved the storage and recall of digits in correct serial position. For any given span size (n) the participant was shown n digits randomly selected between 10 and 99. At the end of the presentation phase, the participant was presented to a recall screen which requested the participant to input the numbers one by one in the order they were recalled.

The Symmetry span task is a complex span coupled to the matrix span task. The participant was shown a series of grid locations one-by-one form the 4x4 grid in the centre of the screen. The participant must remember the grids and the order they appeared. Followed by this grid, the participant was shown an 8x8 grid that displayed the number of grids filled black to form a pattern. The pattern was either be symmetrical or unsymmetrical along the vertical axis and the participant was supposed to make a judgement using the left/right arrow keys to indicate the exact type of the displayed pattern.

4.4.8 Safety Variables

- Vital signs (Blood pressure and Pulse rate) were monitored at all visits.
- All the Adverse Events (AE) and Serious Adverse Events (SAE) were planned to be reported.

4.5 DATA QUALITY ASSURANCE

The quality assurance and quality control systems were implemented to assure the superior quality of the data acquired in this study. A proper training was provided to the investigator prior to the commencement of the study to ensure that he was well-acquainted with the required study-pertaining information. To assure a study conduct in accordance with protocol, study monitoring was performed frequently to check the quality of the data. Internal audits were conducted to ensure credibility and authenticity of study data.

4.6 STATISTICAL METHODS

4.6.1 Determination of Sample Size

Based on the results published about the clinical trials on Brain Pill™ core ingredients (Cognizin[viii,ix,x], Gingko[xi], PS[xii] + DHA[xiii] and Huperzine[xiv]), we postulated to achieve a moderate effect size of 0.6, with 95 % confidence level and statistical significance (p) of < 0.05. Using an online "SAMPLE SIZE CALCULATORS FOR DESIGNING CLINICAL RESEARCH", we arrived at a sample size of 87 randomized participants with N = 44 in treatment group and N = 43 in placebo group to achieve 80% study power. Considering ~30% screening failures and placebo-run-in-phase responders [in this type of study as reported], at least 115 participants are required to be screened to have 85 randomized participants and minimum 66 completed participants after accounting for 20 % withdrawals and non-evaluable participants.

4.6.2 Data Handling

In case of a premature termination, no LOCF approach was employed for replacing the missing values. Those entries were taken out and the available data set were used for the statistical analysis.

4.6.3 Statistical Methods for Study Outcome Analysis

4.6.3.1 Demographic and Baseline Information

Summary statistics for all variables have been computed and presented in the Results section. For the continuous variables, the mean and standard deviations have been tabulated. These analyses were conducted for the ITT and PP populations.

4.6.3.2 Analysis of Efficacy Parameters

The primary efficacy variable was a change in working memory from the baseline to end of the treatment in each group and between the groups and the statistical significance was analyzed by using Student's paired and unpaired *t*-test, respectively. Also, the secondary variables of the study were analyzed in similar way. Cohen's d was calculated wherever the results were found significant for active group in comparison with placebo.

4.6.3.3 Analysis of Safety Parameters

Adverse events (AEs) and serious adverse events (SAEs) were summarized by counting the number of separate events and the number of Participants experiencing events occurring during the study period. The information was provided as classified according to the seriousness, severity, and relationship to the study medication. For vital signs independent Student's *t*-test was applied to observe the statistical significance. The results were considered statistically significant if $p < 0.05$ was observed.

4.7 CHANGES IN THE PLANNED CONDUCT/ ANALYSIS OF THE STUDY

No major changes eventuated in the conduct of the study, although statistical analysis plan was revised. As the validity and reliability of Digit Recall Task in Operation Span was higher among all the tasks[xv], the MRT and accuracy parameters captured by it were considered for formulating the primary efficacy variable. The results are presented based on revised SAP.

5 RESULTS

The study was conducted in accordance with regulatory guidelines set by ICH-GCP. On completion of the study, the data were sub-divided as Per Protocol (PP) and Intent to Treat (ITT) groups for further statistical analyses. The PP group represented the participants who completed the study without any major protocol violation and ITT group included the participants who met all inclusion-exclusion criteria, administered at least one dose of assigned product and returned for at least one post-baseline evaluation visit. In this CSR, we decided to present the results pertaining to the PP group for the extrapolation of the clinical relevance from this study. Data of the participants unable to attend the follow-up visits due to lost to follow up and withdrawal (N=6) and ambiguous data (N=1) were not considered for statistical analysis. This did not lead to

intergroup variation in number of participants (Group A=37, Group B = 36). Also, we were able to achieve more than the marginal level of calculated sample size (66 participants) as total 73 participants completed the study.

5.1 STUDY PARTICIPANTS

5.1.1 Disposition of Participants

Out of 116 participants screened in this study, 80 participants who had been screened on the basis of history of subjective memory lapses and mild mood disturbances were randomized into active and placebo groups in the ratio of 1:1. Six participants out of 80 discontinued from the study (BP-02, BP-20, BP-54, BP-61, BP-63, BP-73). There were 3 discontinuations reported in Brain Pill™ group (Group A: BP-02, -54, -73), while 3 were reported in the placebo group (Group B: BP-20, -61, -63). Participant BP-20 was lost to follow up after randomization, though no study related assessments were performed as the participant did not attend the day 0 visit and thereafter. All details pertaining to the participant disposition have been mentioned in the **Table 6**. Data pertaining to participant BP-77 were not considered for the statistical analyses due to data irregularity, hence the final analyzable PP population is n = 73.

Table 6. Disposition of Participants

Subject Details	No. of Participants	
Total no. of screened participants	116	
Total no. of screening failure	36	
Total no. of randomized participants	80	
No. of participants discontinued during the treatment period (BP-02, BP-20, BP-54, BP-61, BP-63, BP-73)	6	
	Lost to Follow-up	Withdrawal
	03	03
Total no. of completed participants	74	
Total no. of participants considered for data analysis (PP)	73	
Last observation carried forward (LOCF)	5	
Total no. of participants considered for data analysis (ITT)	79	

5.1.2 Protocol Deviations

The Vedic Lifesciences study team took utmost efforts to minimize the protocol deviations (PDs), however there were total 16 PDs. 14/16 PDs were related to insufficient pause time during the tasks of working memory battery and 2/16 PDs were related to study visits, delayed beyond the allowed window period. Thus, there was no significant impact of these PDs on the study outcome. The details of protocol deviations are described in **Table 7**.

Table 7. Protocol Deviations

Sr. No.	Subject No.	Nature	Protocol Deviation
01	BP24	Minor	Day - 56: Break between digit & matrix <10 minutes.
02	BP34	Minor	Day - 56: Break between digit & matrix <10 minutes.
03	BP31	Minor	Day - 84: Break between operation & symmetry <10 minutes.
04	**BP07**	Major	**Day - 56: Not able to plan visit in window period**.
05	BP19	Minor	Day - 56: Break between digit & matrix <10 minutes.
06	**BP50**	Major	**Day - 84: Not able to plan visit in window period.**
07	BP21	Minor	Day - 0: Break between spans of WMB test <10 minutes.
08	BP21	Minor	Day- 56: Break between digit & matrix <10 minutes.
09	BP23	Minor	Day - 0: Break between spans of WMB test <10 minutes.
10	BP22	Minor	Day - 0: Break between spans of WMB test <10 minutes.
11	BP24	Minor	Day - 28: Break between operation & symmetry <10 minutes.
12	BP25	Minor	Day - 28: Break between digit & matrix <10 minutes.
13	BP32	Minor	Day - 28: Break between operation & symmetry <10 minutes.
14	BP52	Minor	Day - 0: Break between matrix & operation <10 minutes.
15	BP63	Minor	Day - 0: Break between digit & matrix <10 minutes.
16	BP35	Minor	Day - 0: Break between matrix & operation <10 minutes.

5.1.3 Baseline Demographic Characteristics of the Study Population

The demographic characteristics of the ITT population are shown in the **Table 8**. The difference in the number of dropouts across the groups did not result in significant inter-group difference in the final population for the active and placebo groups as the baseline values were almost similar for all the efficacy parameters.

All Participants were screened for the demographic parameters (age, gender, height, weight, BMI) at the screening visit to confirm the compliance with the defined protocol. The statistical evaluation of the demographic and baseline characteristics by Student's *t*-test confirmed that there was no significant standard deviation among the treatment groups (active and placebo). The mean age and mean BMI at baseline were almost similar in both the groups with no statistically significant difference. Also, the groups were similar in the screening variables cut-offs (AMQ, MMSE and PROMIS T-score) at baseline.

Table 8. Baseline Demographic Characteristics of the Study Population

Parameters		****Intent-to-Treat Population**		**Statistical Significance**
Subgroups		**Placebo (N=39)**	**Brain Pill™ (N=40)**	**p – Value (Between the groups)**
*Age (Years)		33.77 ± 11.70	34.00 ± 10.00	0.925
*BMI (Kg/m^2)		23.44 ± 4.28	24.74 ± 3.51	0.144
Sex Distribution	Male - No. (%)	14 (35.9%)	17 (42.5%)	0.548
	Female - No. (%)	25 (64.1%)	23 (57.5%)	
AMQ (%)		53.33 ± 6.74	55.03 ± 7.87	0.307
MMSE		27.10 ± 1.60	27.18 ± 1.62	0.842
PROMIS (T-score)		54.65 ± 2.22	54.76 ± 2.59	0.831
*Values are expressed as Mean ± SD;				

5.2 EFFICACY EVALUATION

In the study, we studied the population of participants who were experiencing subjective memory lapse and mild mood disturbances which was screened based on MMSE, AMQ and PROMIS scores and the eligible participants were further assessed for effect of Brain Pill™ on working

memory capacity, attention & concentration and mood disturbances. The assessment of efficacy was done by a working memory battery, picture recognition test and BRUMS.

Both PP (N = 73) and ITT (N = 79) populations were analyzed statistically. The results pertaining to the ITT population were considered for the clinical relevance for the safety variables whereas both ITT and PP population were analyzed for drawing out clinical relevance for the primary and secondary efficacy variables. However, no significance was found in any of the populations for the defined efficacy variables. Data pertaining to these have been supplemented as Annexures A and B with this CSR.

As age is the most influencing confounding factor in memory related studies[xvi,xvii] and has been also reported for few ingredients of Brain Pill™,[xviii,xix] we decided to cohort the PP population age-wise in two cohorts: 18 to 39 years (N=45) and ≥ 40 years (N=28). Also, the subject with greater than 80% of accuracy at the baseline score (BP-41) was excluded from the analysis on the basis of least probability of further improvement in their task-based performance.

The data of 44 subjects with age 18 to 39 years were statistically analyzed in similar manner. The results from the cohort of 18-39 years (**22 analyzable pairs with 22 subjects in each arm**) showed statistical significance in different efficacy variables of active group as compared to placebo and the corresponding results have been presented in the current report.

5.2.1 Primary Efficacy Variable: Working Memory Capacity

As mentioned in section **4.4.1**, the working memory capacity was assessed in terms of dynamic verbal working memory by the digit recall task of the operation span. The changes in mean response time (MRT) and number of correct hits (accuracy) between two groups were assessed and the same have been presented in **Table 9**. Further, this data was used to calculate the composite score of the changes in Z scores of MRT and correct hits of the digit recall task (**Table 10**).

As evident from **Table 9**, the change in MRT at the end of day 84 is insignificant in active group as compared to placebo, whereas change in accuracy is highly significant in active group (**p =0.039**). Similarly, if we compare the composite Z scores of the two study groups which is a

function of effect size, it is obvious that the active group bears significant p value (**p=0.044**) and thus proves the beneficial effect of Brain Pill™ on working memory capacity.

Table 9. Effect of IP on Digit Recall (Operation Span Task)

Time Points	**Mean Response Time (ms) (Mean ± SD), N=22**		**Accuracy (No. of Correct Hits) (Mean ± SD), N=22**	
	Placebo	**Brain Pill**	**Placebo**	**Brain Pill**
Day 0	2466.00 ± 425.90	2689.86 ± 949.51	32.05 ± 13.09	28.64 ± 14.52
Day 28	2238.55 ± 505.80	2537.77 ± 1009.89	34.91 ± 13.26	33.55 ± 13.72
Day 56	2168.32 ± 549.78	2386.46 ±749.43	34.50 ± 13.19	35.96 ± 14.48
Day 84	2082.18 ± 457.81	2260.68 ± 663.41	32.91 ± 15.81	37.50 ± 12.35
Day 28 - Day 0	-116.77 ± 977.49	-375.09 ± 1086.08	2.86 ± 8.08	4.91 ± 7.24
*P (Day 28)	0.114	0.610	0.475	0.256
****P (Day 0 to Day 28)**	0.649		0.381	
Day 56 - Day 0	-297.68 ± 462.85	-303.41 ± 514.90	2.46 ± 10.67	7.32 ± 7.74
*P (Day 56)	0.051	0.246	0.539	0.102
****P (Day 0 to Day 56)**	0.969		0.091	
Day 84 – Day 0	-383.82 ± 318.71	-429.18 ± 571.10	0.86 ± 13.16	8.86 ± 11.64
*P (Day 84)	**0.006**	0.090	0.844	**#0.035**
****P (Day 0 to Day 84)**	0.747		**#0.039**	

*P: Within-Group Statistical Significance, **P: Inter-Group Statistical Significance,

#: Statistically significant ($p < 0.05$).

Table 10. Effect of IP on Composite Score of Change in Z-scores of MRT and Accuracy of Digit Recall (Operation Span Task)		
Time Points	**Placebo (Mean ± SD)**	**Brain Pill ™ (Mean ± SD)**
Day 0	0.00 ± 1.31	0.00 ± 0.86
Day 28	-1.23 ± 1.35	-0.45 ± 1.39
Day 56	-1.29 ± 1.27	-1.18 ± 1.24
Day 84	-2.41 ± 1.35	-1.50 ± 1.54
****P (Day 0 to Day 28)**	0.067	
****P (Day 0 to Day 56)**	0.778	
****P (Day 0 to Day 84)**	**#0.044**	
**P: Inter-Group Statistical Significance, #: Statistically significant (p < 0.05).		

Thus, the statistically significant improvement in accuracy in Brain Pill™ group clinically indicates that it is able to deliver a better accuracy in the task of verbal components of WM and proves the improved efficacy to handle the constant demand with more ease.

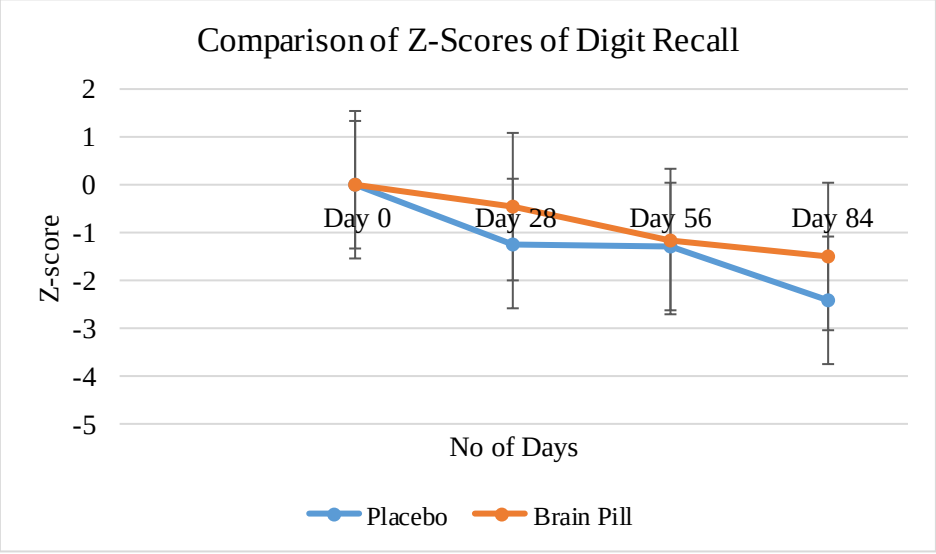

Figure 3. Effect of IP on Accuracy Factor of Dynamic Working Memory

5.2.2 Secondary Efficacy Variables

5.2.2.1 Effect of IP on Mathematic Problem Solving Component of Working Memory

Change in MRT and change in number of correct hits of mathematical problem solving of the operation span task at day 84 from baseline between the groups was set as one of the secondary efficacy variables. The results have been presented in **Table 11.**

Table 11. Effect of IP on Problem Solving (Operation Span Task – Mathematical Operations)

Time Points	**Mean Response Time (ms) (Mean ± SD), N=22**		**Accuracy (No. of Correct Hits) (Mean ± SD), N=22**	
	Placebo	**Brain Pill**	**Placebo**	**Brain Pill**
Day 0	3146.86 ± 1045.58	3667.95 ± 1385.37	72.00 ± 8.12	70.30 ± 8.00
Day 28	2746.36 ± 863.44	3233.41± 1395.28	73.36 ± 6.25	69.59 ± 11.90
Day 56	2714.86 ± 968.27	2895.95 ± 979.53	72.23 ± 7.46	71.91 ± 8.69
Day 84	2589.64 ± 1053.18	2922.41 ± 990.57	70.55 ± 10.40	71.68 ± 9.91
Day 28 - Day 0	-400.50 ± 676.29	-434.55 ± 1036.68	1.36 ± 4.56	-1.14 ± 5.92
*P (Day 28)	0.173	0.306	0.536	0.712
****P (Day 0 to Day 28)**	0.898		0.124	
Day 56 - Day 0	-432.00 ± 792.21	-772.00 ± 688.60	0.23 ± 5.48	1.18 ± 5.97
*P (Day 56)	0.162	**#0.039**	0.923	0.641
****P (Day 0 to Day 56)**	0.136		0.584	
Day 84 – Day 0	-557.23 ± 951.65	-745.55 ± 1119.53	-1.45 ± 6.97	0.95 ± 5.75
*P (Day 84)	0.085	**#0.046**	0.608	0.727
****P (Day 0 to Day 84)**	0.551		0.218	

*P: Within-Group Statistical Significance, **P: Inter-Group Statistical Significance, ($p < 0.05$).

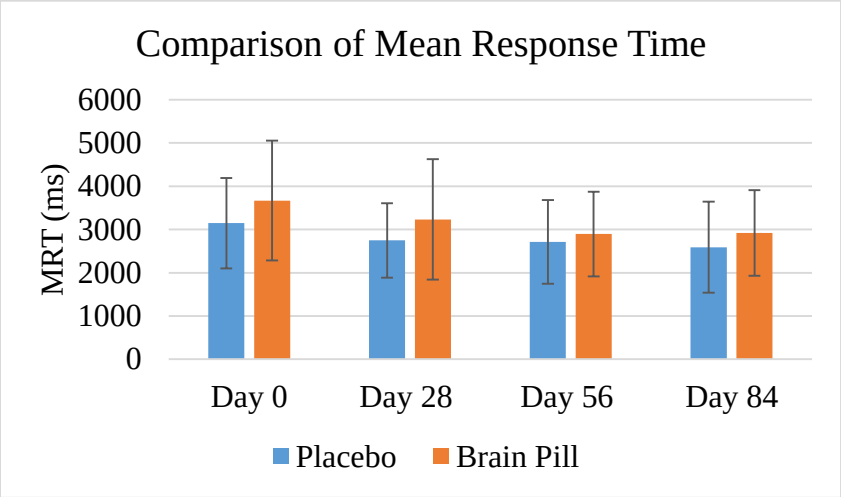

Figure 4. Effect of IP on Speed Factor of Dynamic Working Memory

The mean response time (MRT) showed statistically significant improvement within the Brain Pill group at the end of day 56 (**p=0.039**) and day 84 (**p=0.046**). As the participants were from different academic and professional backgrounds, there was certainly a distinct variation in the expertise in mathematics. Hence, the effect for number of correct hits might have got nullified as exhibited by insignificant statistical results.

5.2.2.2 Effect of IP on Attention and Concentration

Effect of IP on attention and concentration was assessed by Picture Recognition Reaction Time and changes from baseline to end of treatment were assessed using student's t test for mean reaction time (seconds) and accuracy (% correct hits) between two groups. The findings have been tabulated in **Table 12.**

Table 12. Effect of IP on Attention and Concentration assessed by Picture Recognition Test

Time Points	Mean Reaction Time (s)		Accuracy (% Correct Hits)	
	Placebo (Mean ± SD) N=22	Brain Pill (Mean ± SD) N=22	Placebo (Mean ± SD) N=22	Brain Pill (Mean ± SD) N=22
Day 0	0.89 ± 0.18	0.98 ± 0.21	84.36 ± 8.50	82.64 ± 10.84
Day 28	0.87 ± 0.14	0.85 ± 0.16	85.09 ± 8.70	83.91± 9.45

Day 56	0.83 ± 0.15	0.82 ± 0.11	85.91 ± 12.43	85.55 ± 6.56
Day 84	0.79 ± 0.12	0.83 ± 0.12	87.45 ± 8.26	87.27 ± 5.64
Day 28 - Day 0	-0.02 ± 0.14	-0.12 ± 0.13	0.73 ± 7.70	1.27 ± 8.52
***P (Day 28)**	0.643	**#0.034**	0.781	0.680
****P (Day 0 to Day 28)**	**#0.019**		0.825	
Day 56 - Day 0	-0.06 ± 0.14	-0.16 ± 0.16	1.55 ± 11.82	2.91 ± 7.11
***P (Day 56)**	0.269	**#0.003**	0.633	0.288
****P (Day 0 to Day 56)**	**#0.031**		0.645	
Day 84 - Day 0	-0.10 ± 0.13	-0.14 ± 0.23	3.09 ± 8.39	4.64 ± 9.53
***P (Day 84)**	**0.035**	**#0.009**	0.228	0.082
****P (Day 0 to Day 84)**	0.476		0.571	
*P: Within-Group Statistical Significance, **P: Inter-Group Statistical Significance, #: Statistically significant at 0.95 level ($p < 0.05$).				

Statistically significant reduction in mean reaction time in Brain Pill™ group at the end of day 28 (**p=0.019**) and day 56 (**p=0.031**) was observed, though the efficacy variable experienced an insignificant change at the end of day 84 (**p=0.476**), which may be attributed to placebo effect. Also, the observed value of % correct hits increased over the span of 84 days in Brain Pill group, indicating the absence of speed-accuracy trade-off.

5.2.2.3 Effect of IP on Mood Disturbances

As some of the ingredients of the Brain Pill™ have been reported to correct the mood disturbances, we recruited the participants with mild mood disturbances and compared the changes in Mean BRUMS score between two study groups. The results of this assessment have been presented in **Table 13**.

Participant belonging to active group exhibited the statistically significant decrease in TMD-score as compared to placebo on day 28. However, on day 56 as well as 84, both the treatment groups exhibited $p < 0.05$. This can be attributed to the subjective nature of the self-administered BRUMS questionnaire.

Table 13. Effect of IP on Mood Disturbances Assessed by BRUMS- TMD Score			
Time Points	**Placebo (Mean ± SD), N=22**		**Brain Pill (Mean ± SD), N=22**
Day 0	232.91 ± 37.04		232.82 ± 31.50
Day 28	218.27 ± 35.20		199.91 ± 31.78
Day 56	188.95 ± 28.35		192.41 ± 36.58
Day 84	184.45 ± 31.89		184.27 ± 32.63
Change in BRUMS- TMD Score			
Time Points	**Placebo (Mean ± SD),**	**Brain Pill (Mean ± SD),**	**Intergroup p value**
Day 28 - Day 0	-14.64 ± 45.29	-32.91 ± 23.05	**0.099**
*P (Day 28)	0.186	#**0.001**	
Day 56 - Day 0	-43.95 ± 40.05	-40.41 ± 31.86	**0.747**
*P (Day 56)	#**<0.001**	#**<0.001**	
Day 84 – Day 0	-48.55 ± 40.51	-48.55 ± 35.71	**0.994**
*P (Day 84)	#**<0.001**	#**<0.001**	
***P**: Within-Group Statistical Significance	****P**: Inter-Group Statistical Significance		#: Statistically significant at 0.95 level ($p < 0.05$).

5.2.2.4 Effect of IP on Other Cognitive Tasks of Working Memory Battery

As mentioned earlier we performed other three tasks wise digit span, matrix span, and symmetry span, included in working memory battery. The results for first two tasks have been included in Annexure C and those pertaining to the matrix span which was a visuospatial memory task have been listed in **Table 14**. Although, the response time during Matrix span did not reduce in the Brainpill group, the accuracy factor had demonstrated promising in active group. The results achieved statistical significance on the day 84 (**p = 0.001**), suggesting that the visuospatial memory was significantly improved in the participants belonging to Brain Pill™ group. The insignificant results in MRT of this span can be explained on the same grounds as mentioned for digit recall-operation span in discussion section.

Table 14. Effect of IP on Matrix Span Task

Time Points	Mean Response Time (ms)		Accuracy (No. of Correct Hits)	
	Placebo (Mean ± SD) N=22	**Brain Pill (Mean ± SD) N=22**	**Placebo (Mean ± SD) N=22**	**Brain Pill (Mean ± SD) N=22**
Day 0	3586.64 ± 762.35	3206.95 ± 912.91	10.00 ± 3.12	8.82 ± 3.05
Day 28	3703.41 ± 1068.97	3582.05 ± 937.68	10.14 ± 2.71	9.36 ± 2.22
Day 56	3601.68 ± 836.85	3597.41 ± 744.04	10.55 ± 3.22	10.00 ±2.69
Day 84	3684.05 ± 1081.22	3538.95 ± 962.27	9.68 ± 3.00	10.73 ± 3.34
Day 28 - Day 0	116.77 ± 977.49	375.09 ± 1086.08	0.14 ± 1.61	0.55 ± 2.26
***P (Day 28)**	0.679	0.186	0.878	0.501
****P (Day 0 to Day 28)**	0.412		0.494	
Day 56 - Day 0	15.05 ± 844.38	390.45 ± 952.59	0.55 ± 1.92	1.18 ± 2.63
***P (Day 56)**	0.951	0.127	0.571	0.180
****P (Day 0 to Day 56)**	0.174		0.365	
Day 84 - Day 0	97.41 ± 995.15	332.00 ± 1112.54	-0.32 ± 1.99	1.91 ± 2.31

***P (Day 84)**	0.732	0.247	0.732	**0.054**
****P (Day 0 to Day 84)**	0.465		**#0.001**	

*P: Within-Group Statistical Significance, **P: Inter-Group Statistical Significance,

#: Statistically significant at 0.95 level ($p < 0.05$).

5.3 SAFETY EVALUATION

5.3.1 Vital Signs and Physical Findings Related to Safety

5.3.1.1 Mean Pulse Rate

After 84 days of treatment, mean pulse did not show any significant change from day 0 till the end of treatment in both the groups. If compared, change was comparable and difference was insignificant. Data obtained is listed in Table 15.

Table 15. Effect of Brain Pill™ Supplementation on Pulse Rate (Beats/minute)

Time Point	Placebo (N=39)	Brain Pill™ (N=40)	**P
0	75.67 ± 11.03	74.93 ± 9.72	0.752
28	74.74 ± 10.60	70.75 ± 8.60	0.069
56	75.85 ± 11.96	72.43 ± 8.47	0.146
84	73.97 ± 11.03	71.85 ± 8.67	0.344
***P (Day 0 to Day 84)**	0.389	0.111	-

***P**: Within-Group Statistical Significance, ****P**: Inter-Group Statistical Significance

5.3.1.2 Mean Systolic Blood Pressure (SBP)

After 84 days of treatment, mean SBP showed significant change from day 0 till the end of treatment in the placebo group but not in active group. If compared, change was comparable and difference was insignificant. Data obtained is listed in Table 16.

Table 16. Effect of Brain Pill™ Supplementation on Systolic BP (mm Hg)

Time Point	Placebo (N=39)	Brain Pill™ (N=40)	**P
0	115.59 ± 13.93	117.05 ± 12.39	0.624
28	114.36 ± 14.56	116.35 ± 14.56	0.545
56	114.46 ± 14.91	115.30 ± 12.50	0.787
84	114.21 ± 16.01	115.50 ± 13.38	0.697
***P (Day 0 to Day 84)**	0.449	0.323	-

***P**: Within-Group Statistical Significance, ****P**: Inter-Group Statistical Significance

5.3.1.3 Mean Diastolic Blood Pressure (DBP)

After 84 days of treatment, mean DBP did not showed any significant change from day 0 till the end of treatment in both the groups. If compared, change was comparable and difference was insignificant. Data obtained is listed in Table 17.

Table 17. Effect of Brain Pill™ Supplementation on Diastolic BP (mm Hg)

Time Point	Placebo (N=39)	Brain Pill™ (N=40)	**P
0	73.28 ± 8.76	76.15 ± 8.34	0.140
28	73.59 ± 9.60	76.25 ± 10.64	0.247
56	72.92 ± 9.23	74.95 ± 9.39	0.337
84	72.87 ± 9.53	75.00 ± 10.14	0.340
***P (Day 0 to Day 84)**	0.735	0.363	-

***P**: Within-Group Statistical Significance, ****P**: Inter-Group Statistical Significance, #: Statistically significant at 0.95 level ($p < 0.05$).

5.3.2 Adverse Events

The adverse events occurred during the course of the study have been presented in **Table 18**. There were total nine adverse events, 3 in Brain Pill™ group and 6 in placebo group. All the AEs were of mild to moderate nature and were immediately resolved. None of the events led to any serious condition. Thus, the IPs were well-tolerated in the study population.

Table 18. List of Adverse Events (Total no. of cases: A =3 and B = 6)										
Sub ID	**Treatment Group**	**Description**	**Start Date**	**End Date**	**Frequency**	**Intensity**	**Serious**	**Status**	**Relation to IP**	**Comments for AE**
BP02	A	Malaria	21-Aug-17	25-Aug-17	Single	Moderate	No	Resolved after treatment	Not related	-
BP21	B	Loose Motion	11-Jun-17	11-Jun-17	Single	Mild	No	Resolved spontaneously	Unknown	-
BP25	A	Headache	29-May-17	29-May-17	Single	Moderate	No	Resolved after treatment	Unknown	Resolved on same day after taking medication.
BP30	B	Cough since morning	09-Jun-17	11-Jun-17	Single	Mild	No	Resolved spontaneously	Unknown	Subject did warm water gargling & took steam for the same & it got resolved.
BP39	B	Loose Motion	09-Jul-17	11-Jul-17	Single	Mild	No	Resolved spontaneously	Not related	-
BP41	B	Fever, Cold	20-Aug-17	21-Aug-17	Single	Mild	No	Resolved after treatment	Not related	AE not related to IP
BP54	A	Cough Cold	18-Jun-17	20-Jun-17	Single	Moderate	No	Resolved after treatment	Unknown	Resolved on 20/06/2017,after taking medication for 2 days
BP71	B	Fever And Cold	02-Sep-17	04-Sep-17	Single	Mild	No	Resolved after treatment	Not related	-
BP78	B	Fever	12-Aug-17	14-Aug-17	Single	Mild	No	Resolved after treatment	Not related	-

Also, the IP accountability and IP compliance recorded during the study complies with the set limits and further assures the sufficient IP consumption (> 80 %) by the study participants. The details have been presented in **Table 19** and **20**.

Table 19. Profile of IP Accountability

Time Points	Placebo (N = 39)		Brain Pill™ (N = 40)	
	Unused	Used	Unused	Used
Day 28	12.10 ± 6.85	108.05 ± 9.11	11.95 ± 9.11	107.90 ± 6.85
Day 56	10.33 ± 7.93	109.10 ± 10.14	10.90 ± 10.14	109.67 ± 7.93
Day 84	10.67 ± 7.74	109.98 ± 8.61	10.03 ± 8.61	109.33 ± 7.74

Table 20. Profile of IP Compliance

Time Points	Placebo (N = 39)	Brain Pill™ (N = 40)
Day 28	92.20 ± 4.74	90.38 ± 5.82
Day 56	92.35 ± 5.51	90.87 ± 7.61
Day 84	92.12 ± 4.99	92.84 ± 4.75

6 DISCUSSION

In this double-blind, placebo-controlled, parallel group, exploratory study, we sought to assess effect of moderate-term supplementation with Brain Pill™ on working memory capacity and mood disturbances. This proprietary product is being marketed in USA as a memory boosting pill and holds claims such as increases working memory, increases performance at work or school, speeds up information processing, improves mind clarity with reduced brain fog, distraction and stress, mentally prepares for exams or projects, improves performance under fatigue, efficient decision making and acquires new skills more easily. These claims have been proposed based on a published literature pertaining to the bioactive ingredients of the investigational product.

The current study attempted to assess the effect of the investigational product (Brain Pill™) on various aspects of working memory (verbal /visuospatial memory, focus, and concentration) and on the mood disturbances. The participants were screened on the basis of subjective memory lapse and mild mood disturbances. Statistical analyses on ITT and PP population with age range of 18-60 years did not achieve significant results in any of the efficacy parameters.

Based on the Jean Piaget's theory of cognitive development[20] which states that the cognition begins to stabilize, reaching a peak around the age of 35 and the establishment of formal operational thinking occurs during early adolescence and continues through adulthood, we decided to analyze the study data of younger population to assess the influence of age factor on the current study's efficacy variable.

Working memory (WM) span tasks have been shown to predict performance in both higher order and lower order cognitive tasks.[21] WMC is measured by complex span tasks that require simultaneous short-term storage of information while processing additional, and sometimes unrelated, information. According to domain-general accounts of working memory, the processing aspect of the task is controlled by a centralized component (i.e., the central executive or controlled attention), while the short-term storage aspect is supported by a domain-specific component (i.e., verbal or visuospatial store). From a domain-specific perspective, performance in complex tasks is a function of efficiency in either verbal or visuospatial abilities.[22] Hence, in

the current study, working memory was assessed by employing a working memory battery, comprised of four different cognitive tasks: digit span, matrix span, operation span and symmetry span. The first two of these are simple tasks whereas the last two are complex tasks. These computer-based tasks developed by Stone et al[23] provide estimates of short-term and working memory incorporating both visuospatial and verbal material. These tasks are built to be simple to use, flexible to adapt to the specific needs of the research design, and are open source.

The primary efficacy variable was based on the outcomes of the complex task, operation span due to its highest validity among all other tasks.[xv] The results obtained suggest that the participants from Brain Pill™ group experienced an improvement in verbal memory as evident from the statistically significant increase in accuracy factor of the digit recall phase of the operation span. This beneficial effect became visible as early as day 56 and maintained its statistical significance till day 84. Though the number of correct hits increased, the corresponding mean response time (MRT) did not decrease significantly in comparison with placebo. One confounding factor responsible for this result might be the default setting of the software-based task which does not switch to the next recall trial until indicated by the participant and hence extra dwelling time as well while calculating the MRT. The cumulative analysis of accuracy and mean response time in terms of composite Z score, exhibited a significant improvement (p= **0.044**) of participant belonging to active group, thus substantiating the claim of improvement in working memory capacity. Hence, we determined the Cohen's d and found to be equal to **0.628** which belongs to medium effect size range.

The second step in operation span task is mathematical problem solving. This efficacy variable did not show statistically significant difference between the group analyses, but showed remarkable within group improvement in mean response time. However the same trend could not observed in case of accuracy factor which can be justified on the basis of different intellectual as well as educational backgrounds of the study participants.

Out of other three remaining tasks of WMB, only the matrix span task exhibited beneficial results in terms of accuracy factor with a significant p = **0.001**. This finding further ascertains that the investigational product is indeed bears an efficacy to enhance visuospatial memory. The Cohen's d for this efficacy variable at day 84 was found to be **1.034**, indicating larger effect size.

Working memory capacity has been shown to correlate reliably with other cognitive abilities associated with day to day activities such as fluid intelligence[24], arithmetic[25], the ability to prevent mind wandering during tasks requiring focus[26], executive attention[27], general learning disabilities[28] and many more. These all action requires active maintenance and executive control of various working memory components.

As Brain Pill™ contains ingredients which have been clinically proven to improve the focus and attention (Citicoline),[29] we decided to assess this effect by a simple reaction time task using an online picture recognition test. The processing speed, which is measured by the response or reaction time to completely recognize, process and make decisions after a visual stimulus, is linked with other cognitive functions (including long and short-term memory). It was measured under pressure to maintain the focused attention. Statistically significant reduction in mean reaction time in **Brain Pill™** group at the end of day 28 (p=**0.019**) and day 56 (p=**0.031**) proves that the memory boosting supplement is able to improve a person's ability to learn and experience clearer focus and improved ability to absorb and retain the information with a decreased forgetfulness. The efficacy variable experienced an insignificant change at the end of day 84 (p=0.476), and can be attributed to the placebo effect or the logistic study design. Also, it is noteworthy that there is no accuracy tradeoff as the accuracy in terms of % correct hits increased over the span of 84 days. The Cohen's d for this efficacy variable at day 56 was found to be **0.665**, indicating medium effect size. These results are in coherence with those published by McGlade et al[30] who have reported that the adolescent males receiving 28 days of Cognizin® citicoline supplement showed improved attention and psychomotor speed compared to adolescent males who received placebo.

The BRUMS-TMD score used as a measure of mood disturbances could not achieve statistical significance in intergroup analysis. Though, there is a decreasing trend in TMD score in active group, no statistically significant difference was obtained between the groups for this mood assessment due to placebo effect. The subjective nature of the questionnaire might have confounded the results pertaining to this efficacy variable. Hence, it cannot be concluded that participants included in active group are benefitting from the active treatment via reduced stress and positive mood behavior.

With respect to safety evaluation, the investigational product and placebo were found to be equally safe as pulse rate and blood pressure were reported to be clinically safe range throughout the study period. Also, the adverse events were of mild to moderate nature and none of them can be correlated directly with the ingredients of the IPs.

As evident from the study results, the various efficient ingredients of Brain Pill™ are able to synergistically improve the verbal and visuospatial memory with enhanced processing speed and accuracy. Also, it is capable of maintaining the focused attention without any compromise with accuracy. It is as safe as placebo and without any side effects as affirmed by the safe use during the moderate period of 84 days (12 weeks). Hence, the younger population with diverse backgrounds ranging from the college goers to professionals can benefit from supplementation with Brain Pill™.

7 CONCLUSION

The outcomes related to working memory capacity assessments prove that **Brain Pill™** is capable of benefitting various components of the working memory. Supplementation had a significant positive effect on some measures of memory performance only, and no effect on mood. The efficacy of this product for minimizing the mood disturbances can be further assessed in a population with moderate severity by an alternative tool to enhance the effect size.

8 ACKNOWLEDGEMENT

Vedic Lifescience thanks Mr. Doug Mackay, for his suggestions and inputs throughout the study. We also thanks the below listed team members for their help in conceptualization, conduct, & reporting of this study:

Vedic Team for BrainPill Project:	
Name of Responsible Person	**Role**
Mr. Jayesh Chaudhary	CEO
Dr. Sachin Dighe	Clinical Operations
Dr. Sonal Raote	
Pritesh Shah	
Aditi Pradhan	
Monali Patil	
Divya Patel	
Pankaj Dalal	
Neethi Menon	
Dr. Surekha Pimple	Medical Writing
Zubair Ansari	IP Supply and Management
Anil Yadav	Quality Assurance
Mahesh Janjani	Admin and Logistic support
Sanket	
Dr. Sonal Raote	Study Investigator
Dr. Vivek Singh	
Dr. Harshad Thakur	Bio-Statistician

9 REFERENCES

[1]Kane MJ, Conway ARA, Hambrick DZ, & Engle RW (2007). Variation in working-memory capacity as variation in executive attention and control. In A. R. A. Conway, C. Jarrold, M. J. Kane, A. Miyake, & J. N. Towse (Eds.), Variation in working memory (pp. 21–48). New York: Oxford University Press.

[2] Baddeley AD & Hitch G. Working memory. In G.H. Bower (Ed.), The psychology of learning and motivation: Advances in research and theory 1974 (Vol. 8, pp. 47–89). New York: Academic Press.

[3] Baddeley AD & Lieberman K. (1980). Spatial working memory. ln R. Nickerson. Attention and Performance, VIII. Hillsdale, N): Erlbaum.

[4]Ackerman PL, Beier ME, Boyle MO. Working memory and intelligence: The same or different constructs? Psychological Bulletin 2005, 131, 30 – 60.

[5] https://www.brainpill.com/

[vi]Stone JM and Towse JN. A Working Memory Test Battery: Java-Based Collection of Seven Working Memory Tasks. Journal of Open Research Software, 3: e5,

[vii]Brandt R. The Brunel Mood Scale Rating in Mental Health for Physically Active and Apparently Healthy Populations. Health, 2016, 8, 125-132.

[viii] McGlade E, Agoston AM, DiMuzio J et al. The Effect of Citicoline Supplementation on Motor Speed and Attention in Adolescent Males. J Atten Disord. 2015 Jul 15. pii: 1087054715593633.

[ix] McGlade E, Locatelli A, Hardy J, Toshikazu Kamiya, Masahiko Morita, Koji Morishita, Yoichiro Sugimura, Deborah Yurgelun-Todd. Improved Attentional Performance Following Citicoline Administration in Healthy Adult Women . Food and Nutrition Sciences, 2012, 3, 769-773.

[x] Silveri M, Dikan J, Ross AJ et al. Citicoline enhances frontal lobe bioenergetics as measured by phosphorus magnetic resonance spectroscopy. NMR Biomed. 2008 Nov;21(10):1066-75. doi: 10.1002/nbm.1281.

[xi] Solomon PR, Adams F, Silver A et al. Ginkgo for memory enhancement: a randomized controlled trial. JAMA. 2002 Aug 21;288(7):835-40.

[xii] Richter Y, Herzog Y, Cohen T et al. The effect of phosphatidylserine-containing omega-3 fatty acids on memory abilities in subjects with subjective memory complaints: a pilot study. Clin Interv Aging. 2010 Nov 2;5:313-6. doi: 10.2147/CIA.S13432.

[xiii] Yurko-Mauro K, Alexander DD, Van Elswyk ME. Docosahexaenoic acid and adult memory: a systematic review and meta-analysis. PLoS One. 2015 Mar 18;10(3):e0120391. doi: 10.1371/journal.pone.0120391. eCollection 2015.

[xiv] Yesavage JA, Friedman L, Ashford JW et al. Acetylcholinesterase inhibitor in combination with cognitive training in older adults. J Gerontol B Psychol Sci Soc Sci. 2008 Sep;63(5):P288-94.

[xv] Unsworth N, Heitz RP. An automated version of the operation span task. Behavior Research Methods 2005, 37 (3), 498-505.

[xvi] Morcom AM, Catriona D, Richard G et al. Age effects on the neural correlates of successful memory encoding. Brain, Volume 126, Issue 1, 1 January 2003, Pages 213–229, https://doi.org/10.1093/brain/awg020.

[xvii] Salthouse TA, Meinz EJ: Aging, inhibition, working memory, and speed. J Gerontol B Psychol Sci Soc Sci 1995, 50:297–306.

[xviii] McGlade A, Locatelli A, Hardy J et al. Improved Attentional Performance Following Citicoline Administration in Healthy Adult Women. Food and Nutrition Sciences, 2012, 3, 769-773, doi:10.4236/fns.2012.36103 Published Online June 2012 (http://www.SciRP.org/journal/fns)

[xix] Carney E, Canada T. Dietary Folate and Vitamin B12 Intake and Cognitive Decline Among Community-Dwelling Older Persons. Nutr Clin Pract. 2006 Apr;21(2):188-189. doi: 10.1177/0115426506021002188.

[20] McLeod, S. A. "Piaget | Cognitive Theory". Simply Psychology. Retrieved 18 September 2012.

[21] Redick TS, Broadway JM, Matt Eet al. Measuring Working Memory Capacity With Automated Complex Span Tasks. European Journal of Psychological Assessment 2012; Vol. 28(3):164–171

[22] Friedman NP, Miyake A. Differential roles for visuospatial and verbal working memory in situation model construction. Journal of Experimental Psychology: General 2000, 129, 61 – 83.

[23] Stone J M and Towse J N. A Working Memory Test Battery: Java-Based Collection of Seven Working Memory Tasks. Journal of Open Research Software, 2015, 3: e5, DOI: http://dx.doi.org/10.5334/jors.br.

[27]Conway AR, Cowan N, Bunting MF et al. A latent variable analysis of work working memory capacity, short-term memory capacity, processing speed, and general fluid intelligence. Intelligence, 2002, 30(2): 163–183. DOI: http://dx.doi.org/10.1016/ S0160-2896(01)00096-4

[25] McLean JF, Hitch GJ. Working memory impairments in children with specific arithmetic learning difficulties. Journal of Experimental Child Psychology 1999, 74(3): 240–260. DOI: http://dx.doi.org/10.1006/ jecp.1999.2516

[26] Kane MJ, Hambrick DZ, Tuholski SW et al. The generality of working memory capacity: a latent variable approach to verbal and visuospatial memory span and reasoning. Journal of Experimental Psychology: General 2004, 133(2): 189–217. DOI: http://dx.doi. org/10.1037/0096-3445.133.2.189

[27] Kane MJ, Engle RW. Working-memory capacity and the control of attention: the contributions of goal neglect, response competition, and task set to stroop interference. Journal of experimental psychology: General 2003, 132(1): 47–70. DOI: http://dx.doi. org/10.1037/0096-3445.132.1.47

[28] Alloway TP. Working memory, but not IQ, predicts subsequent learning in children with learning difficulties. European Journal of Psychological Assessment 2009, 25(2): 92–98. DOI: http://dx.doi.org/10.1027/1015- 5759.25.2.92

[29] McGlade E, Locatelli A, Hardy J et al. Improved Attentional Performance Following Citicoline Administration in Healthy Adult Women. Food and Nutrition Sciences, 2012, 3, 769-773.

[30] McGlade E, Agoston AM, DiMuzio J et al. The Effect of Citicoline Supplementation on Motor Speed and Attention in Adolescent Males. J Atten Disord. 2015 Jul 15. pii: 1087054715593633.