Technical Report for Ceretrophin™ Clinical Study*

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**Ceretrophin™ is the technical name for BriteSMART™*

Study Objectives

This technical report describes the results of a study that was conducted in healthy human participants by the Brain Sciences Institute, Swinburne University in Australia on Ceretrophin™ which is a proprietary blend of:

Huperzine A
Vinpocetine
Acetyl-L-Carnitine
R-Alpha Lipoic Acid
Rhodiola Rosea
Biotin

The study was conducted to provide the first evidence on whether one month administration of Ceretrophin improves cognitive functioning in healthy human participants. Approximately 100 participants were initially enrolled into the clinical study. Human cognition is complex but can be measured using standardised tests of information processing, reaction time, attention, concentration, working memory, long term memory and decision making. These standardised measures relate to how we perform simple and complex tasks in real life. By assessing a range of cognitive measures before and after one month administration of either Ceretrophin or placebo it is possible for us to gauge whether Ceretrophin has a positive effect in improving human cognition.

Literature Support for Ceretrophin™

Based on the ingredients found in the Ceretrophin formulation there was evidence from previous research to support a hypothesis that treatment with the Ceretrophin formulation would improve cognition and mood. Following is a brief analysis of the literature supporting this hypothesis:

Huperzine A (HupA)

Huperzine A (HupA), isolated from Chinese herb huperzia serrata, has been considered by researchers to be a promising agent in the treatment of Alzheimer's Disease (AD; Zhang & Hu, 2001). Current pharmacotherapy used to treat AD includes acetylcholinesterase inhibitors and more recently N-methyl-D-aspartate (NMDA) antagonists (Lleo, et al., 2006). Recent studies have revealed that HupA functions as reversible inhibitor of acetylcholinesterase (Wang and Tang, 2004). Additionally, based on observations in the rat cerebral cortex, Zhang et al (2002) have proposed HupA to function as a non-competitive antagonist of NMDA receptors. HupA has been found to reverse or attenuate cognitive deficits in a broad range of animal models (Wang et al., 2001).

Numerous clinical trials have demonstrated that Hup A is effective in relieving memory deficits associated with college students, (Sun, et al, 1999), the elderly

and Alzheimer's disease without any serious adverse side effects (Wang, et al., 2001) and is considered to be a safe supplement (Si-Sun X, et al., 1995).

Vinpocetine (VIN)

Vinpocetine (VIN), derived from the periwinkle plant (vinca minor) (Szatmari and Whitehouse, 2003) has been highly researched and is widely used as a neuroprotective agent (Pereira, et al., 2003; Dezsi, et al., 2002; Santos, et al., 2000; Vas and Gulyas, 2005). VIN's primary actions are to enhance cerebral vascular blood flow, brain energy metabolism (Gulyas et al., 2002; Vas, et al., 2002; Szakacs, et al., 2001; Vas and Gulyas, 2005) and increase the neuronal uptake of glucose and oxygen (Shibota, et al., 1982; Vas and Gulyas, 2005; Tohgi, et al., 1990). VIN has been shown to improve speed of memory learning and recall cognitively healthy subjects (Polich, et al 2001; Hindmarch, 1985); and in cognitively compromised subjects (Szatmari, et al 2003; Wollschlaeger, 2001; Nicholson, et al 1990). It is due to these beneficial actions that VIN has been used in the prevention and treatment of diseases associated with compromised cognitive function (Vas and Gulyas, 2005; Kidd, 1999).

Acetyl-L-carnitine (ALC)

Acetyl-l-carnitine (ALC) is naturally synthesized in the human brain, liver and kidney (Rebouche, 2004; No authors listed, 1999) and may have beneficial properties in treating age related disorders such as Alzheimer's dementia (Dhitavat et al., 2002; Pettegrew et al., 2000; Kalaria and Harick, 1992). Further, studies have shown that ALC may be beneficial in the treatment of depression (Cavallini et al., 2004; Pettegrew et al., 2002), attention deficit disorders (Adriani et al., 2004; Torrioli et al., 1999) and cognitive impairment induced by alcohol (Tempesta, 1990). ALC plays an essential role in energy production by facilitating the uptake of acetyl CoA into the mitochondria during fatty acid oxidation (Mingrone, 2004; Spryet et al., 1992) and increases ATP energy production (Aureli et al., 1994). ALC also enhances acetylcholine synthesis, (Whites and Scates, 1990; Dolezal and Tucek, 1981) and enhances cerebral vascular blood flow (Kido et al., 2001; Rosadini et al., 1990), which are implicated in age related normal and abnormal states of cognitive decline, such as Alzheimer's disease.

Alpha Lipoic Acid (ALA)

Alpha-lipoic acid (ALA), also known as thioctic acid, is a disulfide compound that is a cofactor in vital energy-producing reactions in the body. ALA is a naturally-occurring coenzyme for a group of enzymes (i.e. biological catalysts) responsible for the conversion of fats, carbohydrates and proteins in to biological energy (i.e.

adenosine triphosphate or ATP; Packer et al, 1995). ALA occurs in two forms, i.e. isomers called R and S, R being the natural and more therapeutically active form. ALA is both lipid (fat)-soluble and water-soluble. This confers certain unique physicochemical characteristics and provides a distinct advantage over other antioxidants. Alpha-lipoic acid has two important functions in our body. First, it serves as a coenzyme (i.e. facilitating the action of enzymes) in several metabolic pathways. Second, it is an important antioxidant (Packer et al, 1995).

Since research suggests that the R form of ALA may be considerably more bio-active than the S form of ALA, and since most commercial forms of ALA are "racemic" containing both R & S forms, the Ceretrophin™ -AVH Plus™ formula uses 150 mg of the R form (R-ALA), believed to therapeutically interact with acetyl-l-carnitine to both improve cognitive function and to reduce oxidative (ROS) damage to mitochondria.

Alpha-lipoic acid has been the subject of a significant amount of research regarding its ability to work synergistically with acetyl-l-carnitine (ALC) to improve mitochondrial energy production of ATP while slowing down mitochondrial aging, if not reverses mitochondrial age (Hagen, et al., 2002a). ALA has been clinically shown to enhance memory function and in combination with ALC to reverse age-associated memory decline (Hagen, et al., 2002b; Liu, et al., 2002).

In general, alpha-lipoic acid doses of 600 mg/day have been well tolerated. Doses as high as 1,200 mg/day (600 mg, 2 times/day) for 2 years and 1,800 mg/day (600 mg, 3 times/day) for 3 weeks did not result in adverse effects when given to patients with diabetic neuropathy under medical supervision. There are no reports of toxicity from alpha-lipoic acid overdose in humans. In individuals with diabetes and/or impaired glucose tolerance, alpha-lipoic acid supplementation may lower blood glucose levels.

Rhodiola rosea

Rhodiola rosea is a popular plant in traditional medicinal systems in Eastern Europe and Asia with a reputation for stimulating the nervous system (Lazarova, et al., 1986), decreasing depression (Kelly, 2001), enhancing work performance (Azizov, 1998), eliminating fatigue (Darbinyan, et al., 2000), and preventing high altitude sickness (Petkov, et al., 1986). Rhodiola rosea has been categorised as an adaptogen by Russian researchers due to its observed ability to increase resistance to a variety of chemical, biological and physical stressors (Kelly, 2001). Claims have been made to suggest that Rhodiola rosea has antidepressant, anticancer (Udintsev and Shakhov, 1991) and cardioprotective effects, (Maslova, et al., 1994), and also enhances central nervous system activity (Petkov, et al., 1986; Lazarova, et al., 1986).

The adaptogenic, cardiopulmonary protective and central nervous system activities of Rhodiola rosea have been attributed primarily in its ability to influence levels and activity of monoamines and opioid peptides, such as beta-endorphins (Kelly, 2001). These effects are believed to be a result of Rhodiola rosea inhibiting the activity of the enzymes responsible for monoamine degradation, monoamine oxidase and catechol-O-methyltransferase (Stancheva and Morsharrof, 1984). It is also believed that Rhodiola rosea facilitates the transport of neurotransmitters within the brain. In addition to these central effects on monoamines, Rhodiola rosea has been reported to prevent both catecholamine release and subsequent cAMP elevation in the myocardium, and the depletion of adrenal catecholamines by acute stress (Maslova, et al., 1994). In two double-blind clinical trials (Baranoy, 1982; Spanov, et al., 2000), the dose of a standardised Rhodiola rosea extract ranged from 100-170 mg per day. The content of rosavin consumed in these daily doses is approximately 3.6-6.14 mg. In another clinical study, forty students were randomised to receive either 50mg of Rhodiola rosea or placebo twice daily for a period of 20 days. The students receiving the standardised extract of Rhodiola rosea demonstrated significant improvements in physical fitness, psychomotor function, mental performance and general wellbeing. Subjects receiving the Rhodiola rosea extract also reported statistically significant reductions in mental fatigue, improved sleep patterns, a reduced need for sleep, greater mood stability and a greater motivation to study (Spasov, et al., 2000).

Numerous controlled clinical trials have demonstrated improved cerebral performance from dietary supplementation with specific nutrients and botanicals, generally with a minimum degree of risk. In a double-blind, placebo-controlled, cross-over study of 45 young adult vegetarians, creatine (which plays a pivotal role in brain energy homeostasis) supplementation had a significant positive effect on both working memory (backward digit span) and intelligence (Raven's Advanced Progressive Matrices); both tasks that require speed of processing (Rae, et al., 2003). Similarly, a double blind, placebo-controlled trial revealed that a 3 month vitamin-mineral supplementation administration, modestly raised the nonverbal intelligence of some groups of Western schoolchildren, as measured by the measured by the Wechsler Intelligence Scale for Children-Revised (WISC-R). Further, since not all children in this trial were affected by supplementation, the authors suggested that this was presumably because the majority were already adequately nourished (Schoenthaler, et al., 2000).

While some nutrients and botanicals can benefit brain functioning when a systemic deficiency exists, only a few offer clinically significant benefits to memory and the allied cognitive functions. Previous studies focussing on Acetyl-L-carnitine (ALC), Vinpocetine (VIN), Huperzine A (Hup A), Alpha Lipioc Acid (ALA) and Rhodiola, have demonstrated efficacy for the use of these natural and nutritional supplements in age related cognitive decline. Since these natural supplements have specific biological functions, which have been associated with

delaying the progression of associated cognitive dysfunctions, they may also improve aspects of learning and memory.

Research on each of the aforementioned natural products has provided evidence to suggest that the use of these compounds, in combination, may possibly have stronger effects on improving cognitive functioning, attention, energy levels, stress and mood. Furthermore, given that previous studies have shown that ALC, VIN, Hup A, ALA and Rhodiola nutritional supplements may improve cognitive functioning due to their ability to affect neurological mechanisms, this study will aim to determine whether supplementation with these natural products can also influence IQ scores in healthy subjects.

The special nutritional formulation, Ceretrophin comprises a combination of these natural ingredients and has been devised based on clinically validated recommended daily doses.

Study Methodology

The study was a randomized, double-blind, placebo controlled study examining the effects of a special nutritional formulation Ceretrophin vs placebo on cognitive function and mood. This means that the participants were randomly allocated to either a placebo or Ceretrophin group in which they were administered either placebo or Ceretrophin tablets for one month. The study was double blind because both the experimenters and the human participants did not know which tablets they were taking.

Exclusion Criteria

1. Not currently taking prescription drugs affecting the brain or nervous system (e.g., Modafinil, acetylcholinesterase inhibitors, anti-cholinergics, stimulants, L-dopa, MAO inhibitors, NMDA receptor antagonists, methylphenidate, amphetamine, pseudo-ephedrine, SSRIs and other anti-depressant medication),

2. Not currently taking OTC medications affecting the brain (e.g., ephedra based diet pills),

3. Who have not used any supplements within the past 30 days that have an effect on cognitive function, memory, anxiety, depression (e.g. Ginseng, Gingko, Vinpocetine, 5HTP, Tryptophan, St. John's Wort, ephedrine (ephedra), alpha GPC, Citicoline, phosphatidylserine, acetyl-l-carnitine, Focus Factor™),

4. Not active Smokers

5. Not taking the following: anti-coagulant drugs (Warfarin, Heparin, Plavix); anti-cholinergics or acetylcholinesterase inhibitors (bethanechol (Ureholine), donepezil (Aricept), rivastigmine (Exelon), galantamine (Reminyl), edrophonium (Enoln, Reversol, Tensilon), neostigmine (Prostigmin)

6. Do not have any of the following health conditions: AIDS, HIV; Chronic Fatigue Syndrome, Epstein Barr, Fibromylagia, Lupis, Multiple Sclerosis, Thyroiditis, Ulcerative Colitis, Crohn's Disease, Irritable Bowel Syndrome, dementia including Alzheimer's and Parkinsons' disease, Type 1 or 2 Diabetes, Insomnia or Sleep Apnea, Narcolepsy

7. No history of head trauma

8. No neurological deficits

9. Not pregnant or lactating

10. Not anticipating any planned changes in lifestyle (e.g. exercise regimen) for the duration of the study

11. No known allergies to nuts

12. Must not be younger than 18 years of age or older than 65 years of age.

In addition participants were requested not to have alcohol or caffeine-containing food or beverages on the testing days (eg, coffee, tea, chocolate and energy drinks containing caffeine or guarana). Further to control for food intake participants they were also required to eat a light breakfast (eg, 2 pieces of toast or cereal with juice) on the testing days.

Test Parameters

The following neuropsychological tests were employed in the currents study:

The Cognitive Drug Research measure (CDR) is a well-validated test, which was used to assess attention, working memory and episodic secondary (longer term memory, or consolidation).

Inspection time (IT) is a measure speed of early information processing.
The Profile of Mood States (POMS) is a self-report designed to measure six dimensions of mood: tension-anxiety; depression-dejection; anger-hostility; vigor-activity; fatigue-inertia; and confusion-bewilderment (POMS: McNair, Lorr, & Droppelman, 1992).

IQ was assessed using the Raven's Progressive Matrices. This was done by administering the even items at baseline and the odd items at Week 4.

The UWIST Mood Adjective Checklist (UMACL; Matthews, Jones & Chamberlain, 1990) will be used to measure mood states and energy levels.

The Spielberger State-Trait Anxiety Inventory (STAI: Spielberger, 1983) is a 20-item questionnaire, to measure anxiety at the time of testing.

Perceived Stress Scale (PSS; Cohen, 1983) was used to measure stress symptoms and effective coping

Participants visited Swinburne University on 3 separate occasions
Visit 1: Health assessment, practice, baseline and acute testing
Visit 2: 1 week (7 days) following baseline testing and
Visit 3: 4 weeks (28 days) following baseline testing.

During the first visit, participants completed a general health assessment and were then allocated into one of three treatment groups for baseline and acute testing.

Results

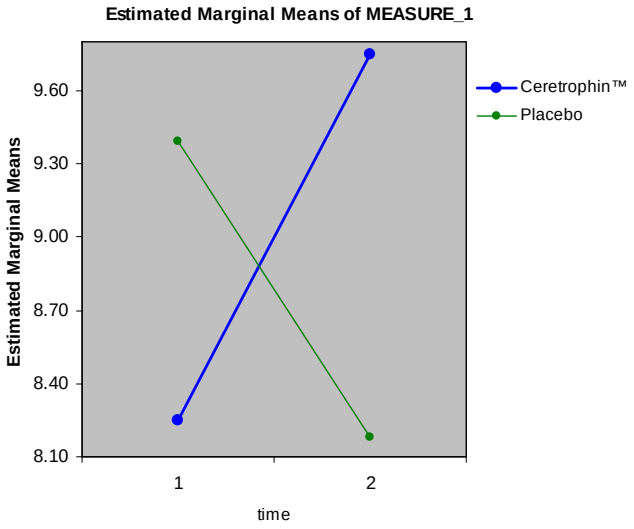
(1) Cognitive Measures

Raven Progressive Matrices (general intelligence IQ)

Participants in the Ceretrophin group statistically improved their performance on the Raven Progressive Matrices relative to the placebo group ($p<.001$). This was a very strong effect and equates to an IQ improvement of about 6 IQ points. The Raven Progressive Matrices is a well-validated non-verbal measure of general intelligence. To complete this task a participant must engage in several higher-order cognitive processes such as visualisation, spatial working memory, mental rotation, reasoning, and non-verbal problem solving. This is a remarkable result particularly given the statistical significance and effect size. This result supports the smaller improvements in accuracy of the less difficult tasks used in the CDR battery. It is of note that the most significant effect of Ceretrophin is seen with the most complex task. Future studies may wish to use highly complex cognitive tasks in order to ascertain the full potential of Ceretrophin on the brain and cognition.

Descriptive Statistics

	Condition	Mean	Std. Deviation	N
Raven's - advance progressive matrix - baseline	Ceretrophin	8.2500	3.34984	36
	Placebo	9.3929	3.77457	28
	Total	8.7500	3.55903	64
Raven's - advance progressive matrix - week 4	Ceretrophin	9.7500	3.47542	36
	Placebo	8.1786	4.49735	28
	Total	9.0625	3.99950	64



Simple Reaction Time

The speed of simple reaction time did not significantly improve due to the Ceretrophin treatment across the 4 weeks of administration. This is the simplest cognitive measure in the cognitive battery. This result is consistent with the results from the other main variables in so far as the Ceretrophin™ did not speed up neural processes but instead improved accuracy and reduced mistakes.

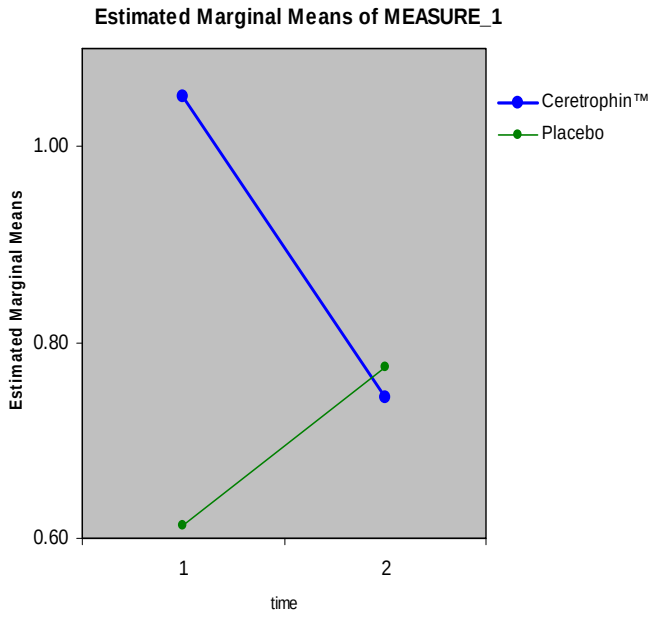
Digit Vigilance and Choice Reaction Time

The Ceretrophin treatment significantly (p=.05) decreased the number of false alarms (mistakes) during the Digit Vigilance task after 4 week administration.

Participants in the Ceretrophin group relative to the placebo group improved their attention/concentration. This was a relatively strong effect.

Descriptive Statistics

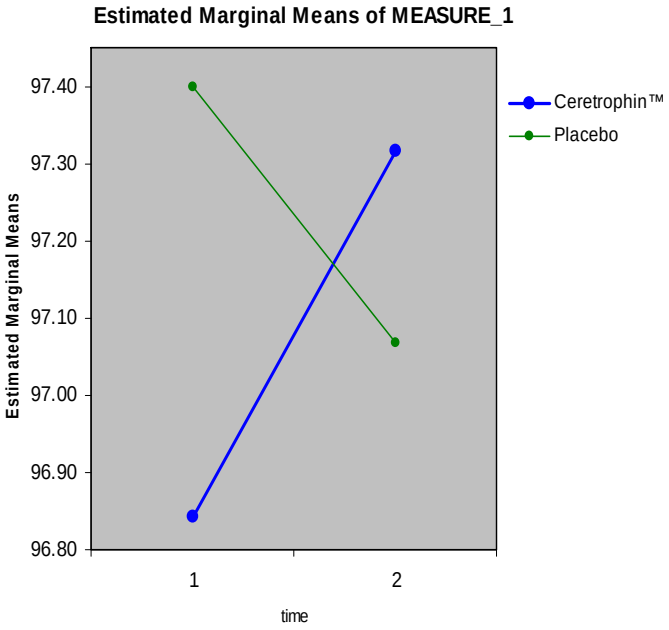
	Condition	Mean	Std. Deviation	N
Digit Vigilance - False Alarms - BASELINE	Ceretrophin	1.0513	1.19095	39
	Placebo	.6129	1.05443	31
	Total	.8571	1.14570	70
Digit Vigilance - False Alarms - Week 4	Ceretrophin	.7436	.78532	39
	Placebo	.7742	1.02338	31
	Total	.7571	.89176	70



Performance on the Choice Reaction Time Accuracy also improved due to the Ceretrophin™ and this result approached statistical significance (p=.11). The effects of the Ceretrophin was not to speed up the brain directly or to make participants quicker to respond to the discrimination but gave them better accuracy in discriminating between the stimulus alternatives. This indicates an improvement in the efficiency of decision making and information processing. Note that there was not a slowing of RT which led to an increase in accuracy. The increase in accuracy due to the Ceretrophin was not a consequence of a slowing of response time (increase in RT). Although approaching statistical significance this was not a strong effect.

Descriptive Statistics

	Condition	Mean	Std. Deviation	N
Choice Reaction Time - Accuracy - baseline	Ceretrophin	96.8421	2.73640	38
	Placebo	97.4000	2.58110	30
	Total	97.0882	2.66394	68
Choice Reaction Time - Accuracy - Week 4	Ceretrophin	97.3158	2.42849	38
	Placebo	97.0667	3.51287	30
	Total	97.2059	2.93491	68

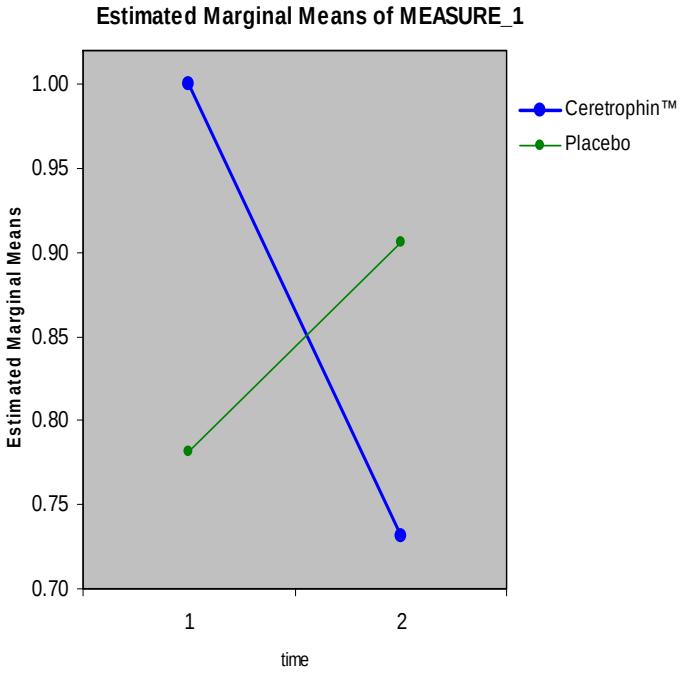


Spatial Working Memory

There was a trend towards significance for Spatial Working Memory Outliers (p=.13). Although not significant, the results (see mean values below) indicate that there was more of an improvement in the number of mistakes over the treatment duration for the Ceretrophin than for the placebo. Larger sample size may help this result become statistically significant. This result should be treated as a preliminary finding that should be subjected to replication in a larger sample.

Descriptive Statistics

	Condition	Mean	Std. Deviation	N
Spatial Working Memory - Outliers - baseline	Ceretrophin	1.0000	1.16190	41
	Placebo	.7813	.83219	32
	Total	.9041	1.02962	73
Spatial Working Memory - Outliers - week 4	Ceretrophin	.7317	1.04939	41
	Placebo	.9063	1.20106	32
	Total	.8082	1.11377	73

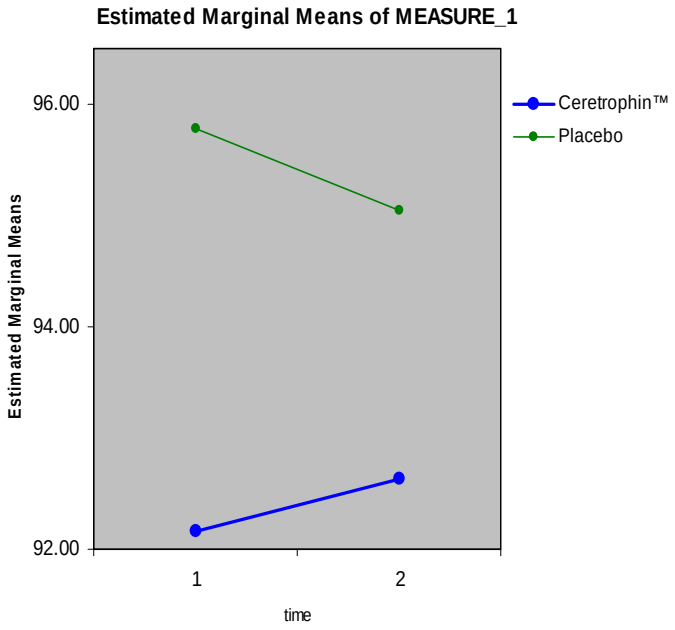


Numerical Working Memory

Participants on the Ceretrophin treatment showed an improvement (p=.18) in Numerical Working Memory Accuracy compared to placebo participants. This again approached statistical significance. The result indicates that there is some evidence that there is an improvement in holding numbers in working memory (immediate memory) from Baseline to Week four due to the Ceretrophin treatment. Increasing the sample size (statistical power) may result in this variable showing statistical significance. This is an interesting but preliminary finding.

Descriptive Statistics

	Condition	Mean	Std. Deviation	N
Numeric Working Memory Original Stimuli - Accuracy - baseline	Ceretrophin	92.1645	7.24746	38
	Placebo	95.7787	5.26386	30
	Total	93.7590	6.65344	68
Numeric Working Memory Original Stimuli - Accuracy - week 4	Ceretrophin	92.6326	7.80322	38
	Placebo	95.0380	3.94556	30
	Total	93.6938	6.46620	68



Picture Recognition

There was no significant change in performance in Picture Recognition over the 4 week trial attributable to either Placebo or Ceretrophin treatment.

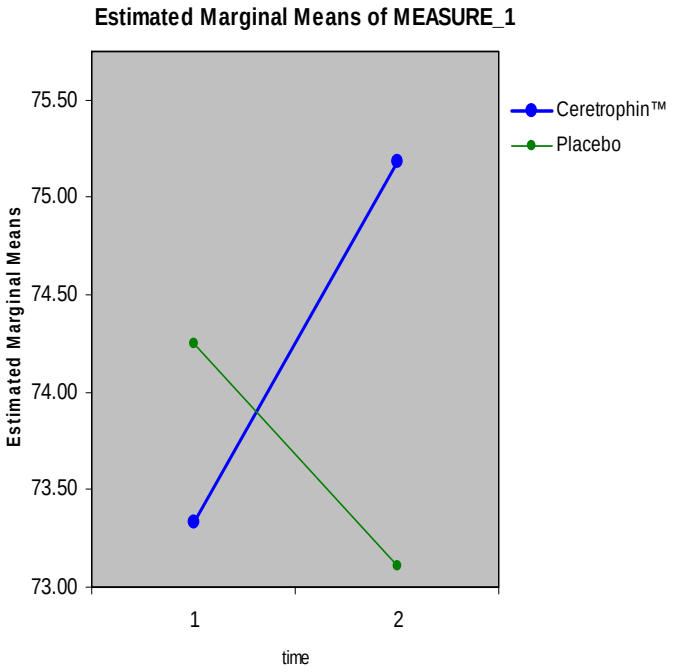
Word Recognition

Word Recognition Accuracy improved for the Ceretrophin participant group but decreased for the Placebo participant group across the 4 weeks of the trial. Although this only approached statistical significance (p=.12) the results provides some evidence that Ceretrophin treatment improves the accuracy of memory consolidation of words. Again a systematic picture of results is emerging with many variables showing improvement in accuracy rather than speed, and that this improvement in accuracy is not a consequence of a slowing of RT (or more

cautious responding). Overall the changes to the different accuracy variables suggest that the Ceretrophin improves efficiency by reducing the number of errors of neural processing of cognitive measures.

Descriptive Statistics

	Condition	Mean	Std. Deviation	N
Word Recognition Original Stimuli - Accuracy - baseline	Ceretrophin	73.3336	16.25226	36
	Placebo	74.2534	14.87757	29
	Total	73.7440	15.54023	65
Word Recognition Original Stimuli - Accuracy - week 4	Ceretrophin™	75.1853	15.50148	36
	Placebo	73.1038	14.19566	29
	Total	74.2566	14.85472	65



Inspection Time

A smaller sub-set of participants completed this task. No differences were observed between the Ceretrophin and placebo groups but this may be due to the low sample size.

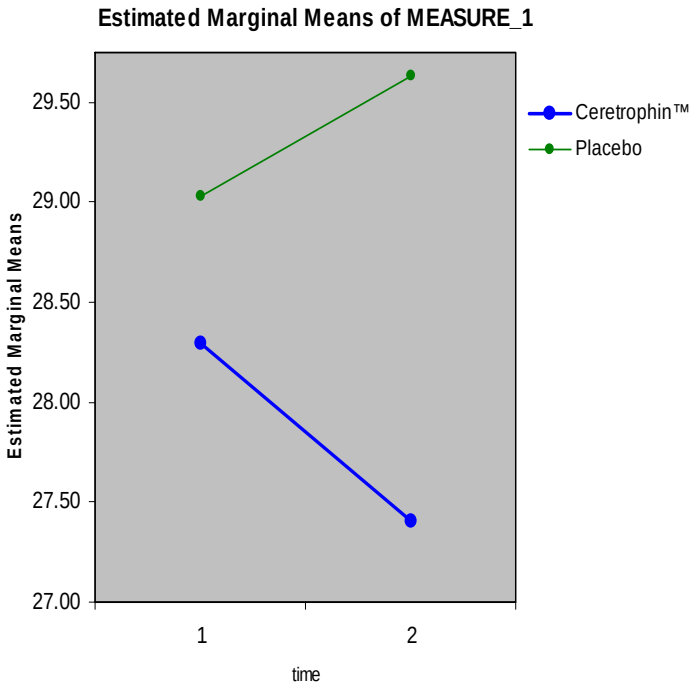
(2) Mood Measures

Perceived Stress (p<.05)

Four week treatment of Ceretrophin showed a small reduction in the levels of stress perceived by participants relative to the placebo group. It is also noteworthy that participant recruitment did not involve highly stressed or anxious individuals but just normal population levels of stress and other moods. This effect may be even more pronounced if a more clinical population was tested.

Descriptive Statistics

	Treatment	Mean	Std. Deviation	N
Perceived Stress Scale baseline	Ceretrophin	28.2973	3.02641	37
	Placebo	29.0333	3.87283	30
	Total	28.6269	3.42378	67
Perceived Stress Scale Week 4	Ceretrophin	27.4054	3.24431	37
	Placebo	29.6333	3.83705	30
	Total	28.4030	3.66829	67

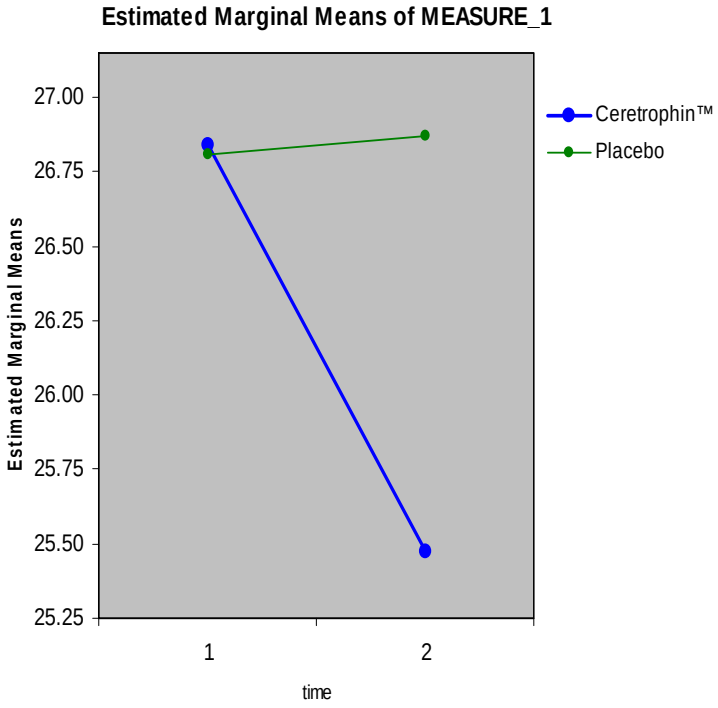


Tense Arousal (p=.12)

Consistent with the reduction in the level of stress, we observed a reduction in the level of tense arousal. This was not statistically significant and a larger sample would increase the statistical power with this variable.

Descriptive Statistics

	Treatment	Mean	Std. Deviation	N
tense arousal baseline (UMACL)	Ceretrophin	26.8421	3.90790	38
	Placebo	26.8065	4.30828	31
	Total	26.8261	4.06186	69
tense arousal Week 4 (UMACL)	Ceretrophin	25.4737	5.43132	38
	Placebo	26.8710	4.90403	31
	Total	26.1014	5.21069	69



Safety

There were no statistically significant side-effects after 4 weeks of testing.

Conclusions

This was the first double blind placebo controlled study to examine the effect of one month administration of Ceretrophin on cognitive and mood variables. The data from this trial provide evidence that this is an interesting and exciting compound that improves a range of cognitive and mood variables in healthy adults.

In terms of the cognitive variables, there is evidence that Ceretrophin improves functioning during highly complex cognitive tasks that assess general reasoning and problem solving. There was also some evidence that Ceretrophin improved working memory variables. The results if taken together do also suggest an improvement in the efficiency of information processing and decision making such as in improving accuracy and reducing cognitive errors. The reduction in errors and improvement in accuracy was seen in nearly all tasks. There are some issues of statistical power (i.e. the sample size). With effect sizes of 5-10% a larger sample than in the present study is needed to obtain statistically significant results. The highly statistically significant improvement in general intelligence from the Raven Progressive Matrices was larger than the other cognitive variables and so was easier to observe statistically.

In terms of mood, Ceretrophin appears to reduce stress and tension. Given the increase in occupational stress seen throughout the western world this is an important finding. Again a larger sample would be useful in better understanding the changes in mood due to treatment in Ceretrophin.

Overall the results suggest that Ceretrophin is a unique compound that exerts beneficial effects to both cognition and mood, particularly in general intelligence and during complex cognitive reasoning tasks/decision making. Future larger scale trials should be undertaken and completed as a matter of priority.

Statistically significant improvements in several variables relative to placebo could be attributed to the 4 week administration of Ceretrophin

- Raven Progressive Matrices (working memory, general intelligence)
- Digit Vigilance Errors (attention)
- Stress (mood)

The study also found some evidence (approaching statistical significance) of the following measures to be improved due to the 4 week Ceretrophin treatment

- Spatial Working Memory Errors (working memory)
- Numerical Working Memory Accuracy (working memory)
- Word Recognition Accuracy Original Stimuli (memory consolidation)
- Tension (mood)