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BIOPHARMACEUTICALS

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Data from CVN Mouse Model Indicates Neuroprotective Properties of EmtinB

- **1-H MRS data shows that EmtinB regulates levels of choline metabolites in the diseased brain, and reverses pathological pattern to normal state, indicative of increased synaptic brain activity**
- **Neuroprotective effect of EmtinB is not dependent on its ability to modulate neuroinflamation**
- **CVN model did not clearly demonstate the phenototypical difference in cognition between non-diseased animals and diseased animals irrespective of treatment with EmtinB.**
- **Data demonstrates trends in ability of EmtinB to downregulate GABA, the chief neurinhibitory transmiter in the brain, and reverse increased amount of Tau, one of the main markers of AD pathology.**
- **Data reads well for our ophtalmology program that aims to demonstrate neuroprotective properties of EmtinB in the optic nerve**

Perth, Australia; 6 December 2019: Drug development company NeuroScientific Biopharmaceuticals Ltd (ASX:NSB, "NSB" or the "Company") is pleased to report the data from its preclinical study of EmtinB in the CVN mouse model of Alzheimer's Disease ("AD").

One of the biggest issues identified as negatively impacting the translation of preclinical Alzheimer's research into effective drug treatments is the lack of animal models that replicate the disease as it occurs in humans. Different models replicate various traits of the Alzheimer's pathology. The Company strongly believes that before progressing any lead compound into Alzheimer's clinical studies, it is important for any drug developer to "stress test" the idea and theory behind that compound in environments that prove neuroprotective effects, neuroinflammatory modulation, synaptic plasticity modulation and amyloid plaque production.

We have previously demonstrated the ability of EmtinB to reduce cognitive impairment in the APPswe/PS1dE9 (i.e. "plaque model") model of disease. The purpose of the current study was to investigate potential neuroprotective and neuroinflammatory mechanism of action of EmtinB in Alzheimer's Disease. Data from this study provided valuable information with regards to future design of our clinical studies in neurodegenerative diseases, including Alzheimer's, as well as potential use of brain metabolites and biomarkers in patients.

"A vast amount of data is available on metallothionein's involvement in neuroprotection and Alzheimer's pathology and yet we are missing some important information about the ability of EmtinB to replicate the same characteristics. While the cognitive data set appears inconclusive, we are pleased with the results on the whole as it builds our deeper understanding of this unique molecule and its correct application in the neuroscience field," said Matthew Liddelow, CEO and Managing Director.

"Given this new set of data enhances our view of EmtinB as a potent neuroprotective drug, we are looking forward to receiving the data from our Glaucoma pig model by the end of the calendar year," said Brian Leedman, Chairman.

Key Outcomes from the Study

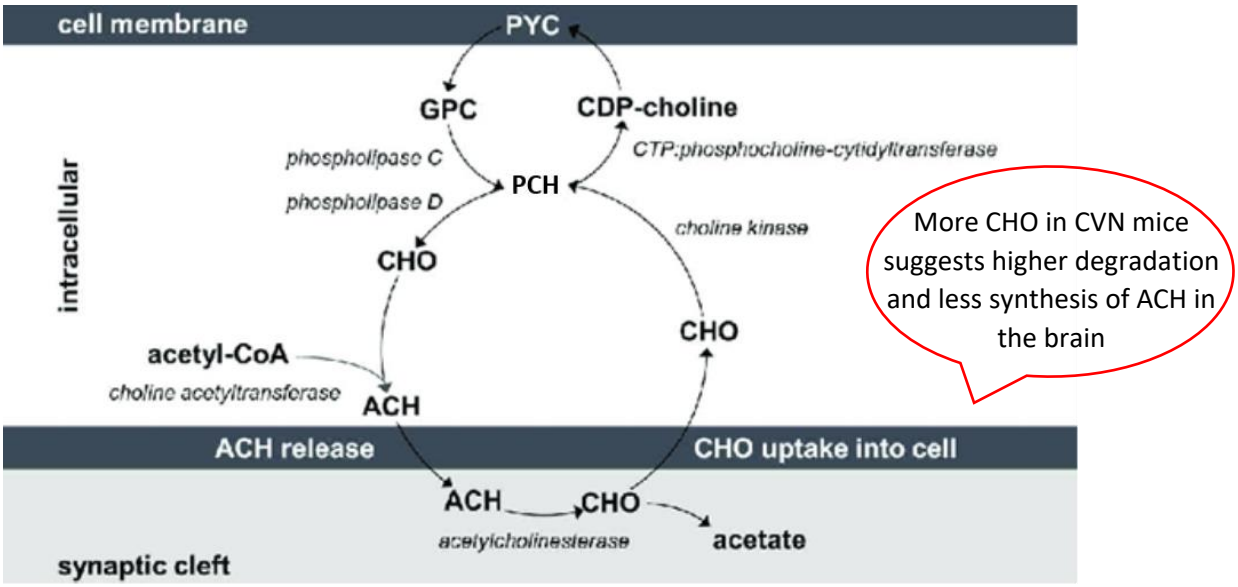
1-H MRS Data shows EmtinB regulates levels of Choline Metabolites in the diseased brain, and reverses pathological pattern to normal State, indicative of increased synaptic brain activity

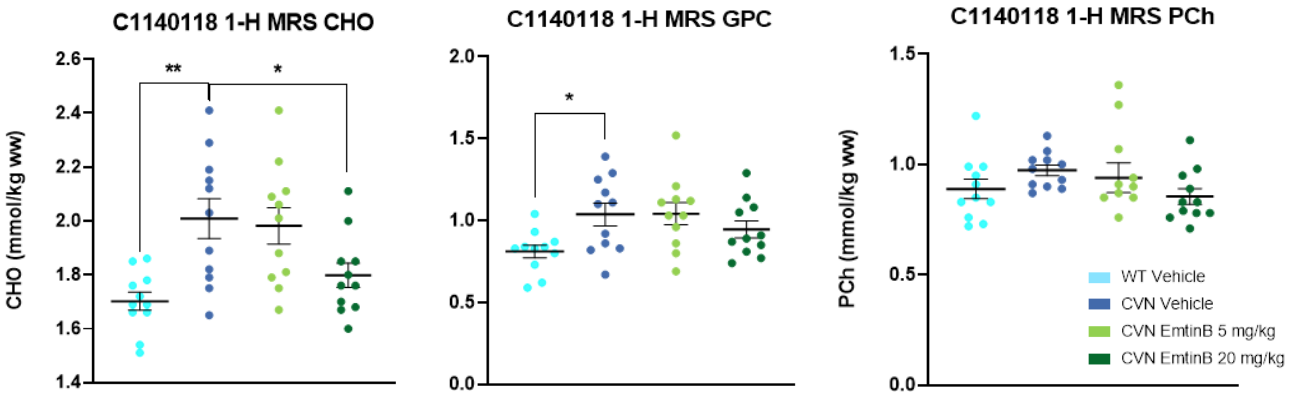
Experimental and clinical studies give evidence for the breakdown of membrane phospholipids during neurodegeneration. Patients with Alzheimer's disease had elevated levels of all choline metabolites (CHO, PCH, GPC) and less Acetylcholine (ACH) due to a lower activity of choline acetyltransferase.

There is a positive correlation between ACH deficit and cognitive impairment, indicating that ACH is an important neurotransmitter for memory. The market leading drug in Alzheimer's Disease, Donepezil, binds and reversibly inactivates the cholinesterases, thus inhibiting degradation of acetylcholine and increasing its concentrations at cholinergic synapses.

Our CVN animal study has demonstrated similar correlations (more Choline metabolites, suggesting less Acetylcholine) in CVN animals. Importantly, we were able to demonstrate that treatment with EmtinB reversed the increase in all choline metabolites in CVN mice to the levels of wild type animals. Data thus suggests that EmtinB shows patterns of reverse neurodegeneration resulting in better neurotransmission.

1-H MRS measurements were performed in mice aged at 13.5 months for all brain biomarkers. Data below presented as mean ± SEM. WT Vehicle, n = 11; CVN Vehicle, n = 11; CVN EmtinB 5 mg/kg, n = 11; CVN EmtinB 20 mg/kg, n = 11. Statistically significant changes / reversal was shown for CHO (choline, $p<0.05$), which is the immediate precursor for Acetylcholine and reversal trends were demonstrated for GPC (glycerophosphocholine) and PCH (phosphocholine).



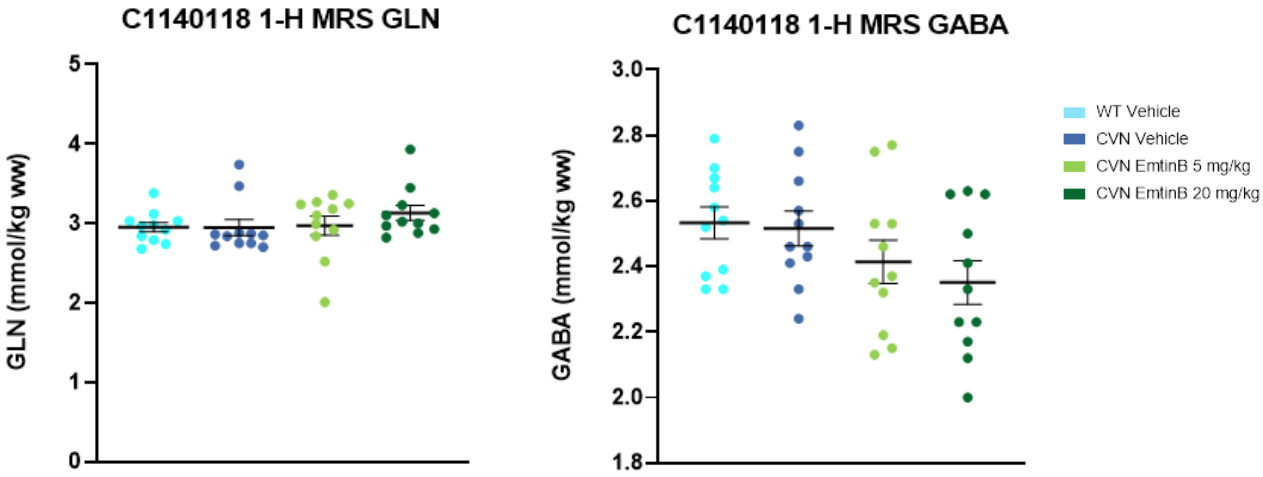


EmtinB could be reducing GABA, the chief inhibitory neurotransmitter in the brain, one of the biomarkers of Alzheimer's pathology

GLN (Glutamine) is the metabolic precursor of GABA (γ-aminobutyric acid), the main inhibitory neurotransmitter in the mammalian cerebral cortex. Increased GABA levels have also been described in patients with AD and Parkinson's Disease ("PD"). It has also been shown that the numbers of $GABA_A$ and $GABA_B$ receptors are increased in AD, and thus may become overactivated by the increased GABA levels observed in AD.

Data from CVN animal data demonstrates that although not statistically significant, treatment with EmtinB can cause remodeling of GABAergic neurotransmission as a compensatory response to neurodegeneration and a diminished number of active neurons (see below reduction in GABA 1-H MRS signal with EmtinB 20 mg/kg). Data below presented as mean ± SEM. WT Vehicle, n = 11; CVN Vehicle, n = 11; CVN EmtinB 5 mg/kg, n = 11; CVN EmtinB 20 mg/kg, n = 11. Moreover, we note that there were no trends in reduced levels of Glutamine, suggesting that EmtinB could stimulate GABA breakdown. Given the limited scope of currently available therapies in modifying the course of the Alzheimer's Disease, a better understanding of GABAergic remodeling in AD could open innovative and novel therapeutic opportunities.

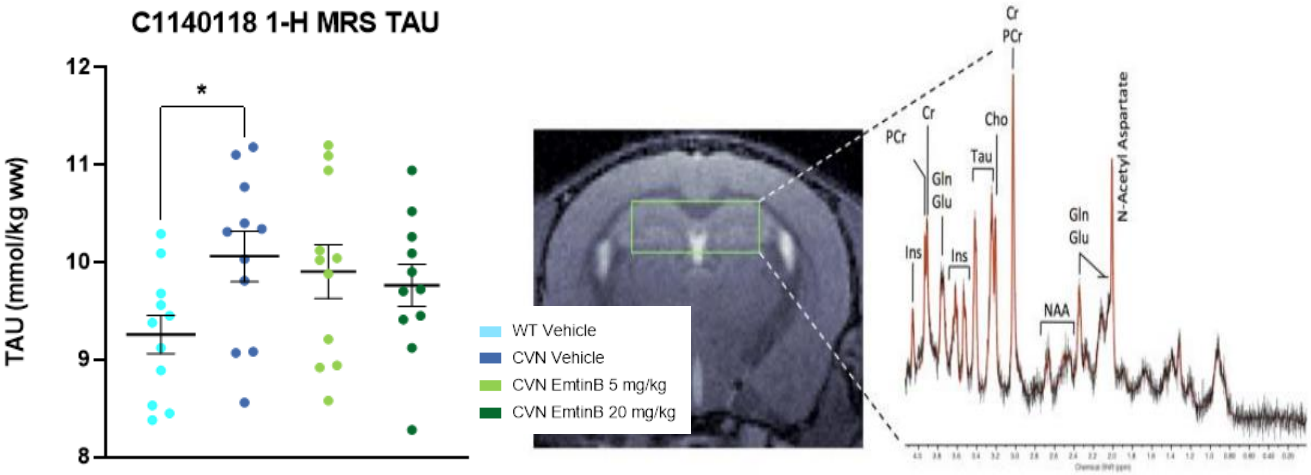
More studies will be required to confirm the ability of EmtinB to modulate GABAergic neurotransmission.



CVN animals demonstrate statistically significant increase in Tau protein, treatment with EmtinB demonstrates trends in reducing its levels

A pronounced increase in CSF Tau protein (Tau) is found in most patients with Alzheimer's Disease. In line with our 1-H MRS data in CVN model has demonstrated a statistically significant increase in Tau protein in CVN animals when compared to wild type animals ($p<0.05$). Treatment with EmtinB has shown a dose dependent decrease in Tau brain markers in CVN animals, indicative of EmtinB's neuroprotective effect.

Data below presented as mean ± SEM. WT Vehicle, n = 11; CVN Vehicle, n = 11; CVN EmtinB 5 mg/kg, n = 11; CVN EmtinB 20 mg/kg, n = 11. More studies will be required to confirm the ability of EmtinB to regulate levels of Tau production in Alzheimer's Disease.



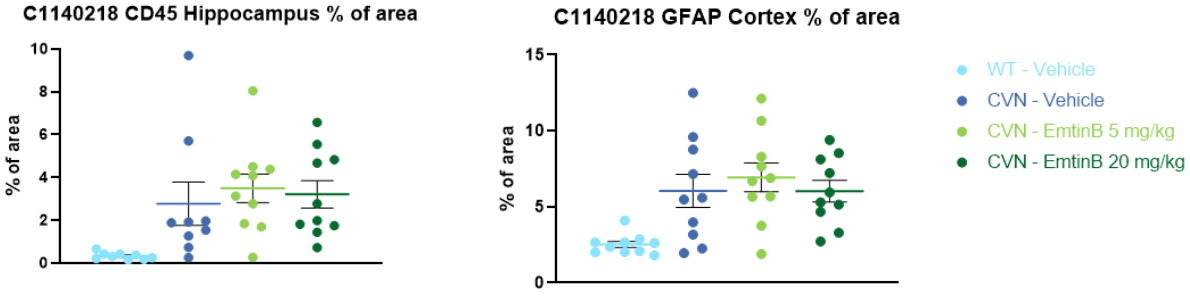
EmtinB showed no effect on reducing neuroinflammatory markers in the Cortex and Hippocampus areas of CVN animals

The pathogenesis of Alzheimer's Disease is a critical unsolved question with the neuroinflammation component representing the newest and most "undecided" parameter.

A recently published study has demonstrated an inhibitory effect of MTII (metallothionein II, EmtinB is modeled on the active domain of MTII) on activated microglia. MTII was able to reduce cytokine-stimulated activation of microglia, demonstrating immunosuppressive effect.

To test whether EmtinB has similar immunosuppressive traits we compared the levels of CD45 and GFAP, inflammatory markers in the brain. There was a strong phenotypic difference between wild type and CVN untreated animals in both markers. To our surprise, we have not observed any changes in CD45 or GFAP upon treatment with EmtinB, indicating that observed neuroprotective properties of EmtinB are not associated with its ability to modulate inflammatory response in the brain.

Further studies will be required to determine whether EmtinB can regulate microglia and astrocyte activation as part of the neuroinflammatory cascade.



Inconclusive data on cognitive response in CVN model; no phenotypic difference between wild type and CVN untreated animals

We have previously demonstrated the ability of EmtinB to reduce cognitive impairment in the APPswe/PS1dE9 (i.e. “plaque model”) model of disease. The CVN model was used to test whether, in a different animal model where Alzheimer’s pathology is driven by neuroinflammatory modulation, we can still observe positive effect of EmtinB on cognition.

Using same groups of animals that were used for 1H-MRS Biomarker studies (approx. 13.5 months of age), we analyzed data from radial arm water maze measurements (the standard cognitive test in mouse models). While there was a trend towards phenotypic differences between wild type and CVN animals, the statistical significance was not achieved making it hard to judge the ability or inability of EmtinB to improve cognitive function in this mouse model of Alzheimers.

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About NeuroScientific Biopharmaceuticals Ltd

NSB (ASX:NSB) is a drug development company focused on developing peptide-based pharmaceutical drugs for the treatment of neurodegenerative conditions with high unmet medical need. The Company’s product portfolio includes EmtinB, a novel therapeutic peptide most advanced as a treatment for Alzheimer’s disease; and other related peptides (EmtinAc, EmtinAn, and EmtinBn) which have demonstrated similar therapeutic potential as EmtinB. For more information, please visit www.neuroscientific.com

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