NeuroScientific
BIOPHARMACEUTICALS
ASX:NSB

ASX ANNOUNCEMENT
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New Biomarker Data Highlights Potential for EmtinB™ as an Effective Treatment for Multiple Sclerosis

HIGHLIGHTS

- **Treatment with EmtinB™ significantly reduced CXCL10/IP-10, IgG and MMP-9 immune biomarkers in *in vitro* human primary cell-based models of inflammation**
- **EmtinB™ has potential to address significant unmet medical need in treatment of MS, demonstrating disease modifying activity across immune-modulation, neuroprotection and remyelination**
- **Global sales for MS drugs in 2020 was US$22 billion**
- **Neuroscientific intends to assess EmtinB™ for MS in future planned Phase 2 studies**

NeuroScientific Biopharmaceuticals Ltd (ASX: **NSB**) (**"NeuroScientific"** or **"the company"**) is pleased to announce that EmtinB™ significantly reduced biomarkers for key drivers of dysfunctional immune responses in Multiple sclerosis (MS), specifically related to inflammation, immunomodulation, and cell migration. These significant results add to the growing body of impressive data that supports development of EmtinB™ as a potential disease-modifying treatment for MS. The preclinical biomarker study was conducted in human primary cell-based systems (BioMAP) by leading independent contract research organisation Eurofins, US.

NeuroScientific is developing its lead drug candidate EmtinB™ as a therapeutic treatment for neurodegenerative conditions, including Alzheimer's disease and MS. The Company has previously reported highly significant results from completed studies in MS (see announcements from 18 March 2020, 14 July 2020, and 4 August 2020) which demonstrated that EmtinB™ increased survival of neurons (neuroprotection), regenerated axons of neurons, and upregulated the process of remyelination (the protective sheath around axons that is degraded in MS). Additionally, EmtinB™ increased myelin formation by >30% in comparison to leading MS drug Copaxone™, which generated peak sales revenue of US$4 billion.

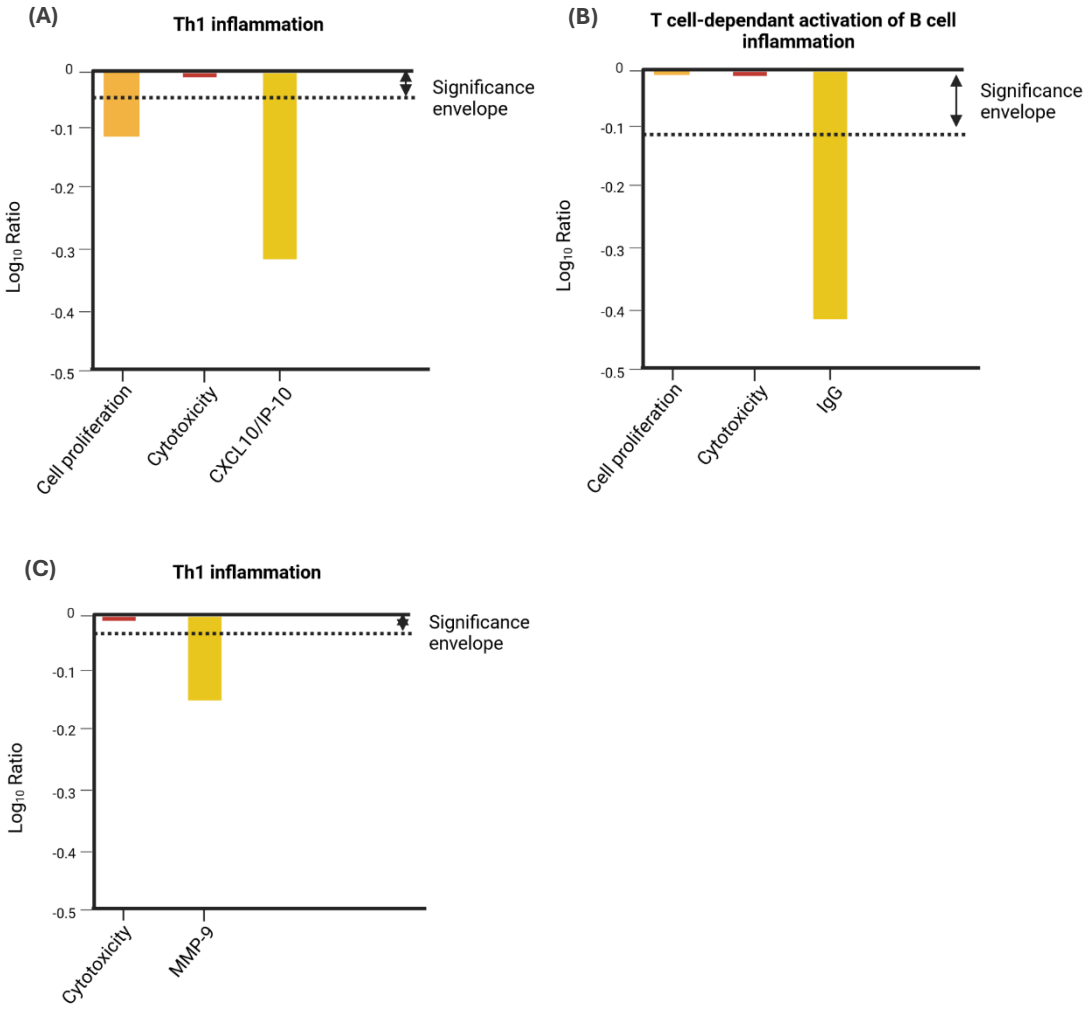
NeuroScientific's Managing Director Matt Liddelow commented: *"It is incredibly exciting to continue to explore the many potential therapeutic benefits of EmtinB™ and these current results from our biomarker studies further validate the disease modifying potential of EmtinB™ as a treatment for Multiple sclerosis. Unlike currently available drugs for MS, EmtinB™ has the potential to regulate immune processes, protect and regenerate nerve cells, and upregulate myelination".*

MS is a progressive neurodegenerative disease characterised by chronic inflammatory responses, whereby activated immune cells migrate into the central nervous system (CNS) and attack the myelin sheath that surrounds nerve fibres and damage neurons, leading to

disruption of normal cognitive, sensory, and motor function. Cell signalling chemicals, called cytokines and chemokines, are key drivers of the immune responses in MS and are often used as biomarkers to assess treatment effect.[1] Global sales for approved MS drugs in 2020 was approximately US$22 billion.[2]

EmtinB™ significantly reduced important MS-related biomarkers Interferon gamma inducible protein-10 (**CXCL10/IP-10**), Immunoglobulin G (**IgG**), and matrix metalloproteinase-9 (**MMP-9**) (**Figure 1**). EmtinB™ reduced cell proliferation in Th1-type inflammation and did not cause any cytotoxicity. Since these biomarkers are significantly elevated in MS and associated with the pathophysiology of the disease, their down regulation by EmtinB™ indicates the strong therapeutic potential of EmtinB™ as a treatment for MS.

Figure 1: EmtinB™ significantly decreased biomarkers (A) CXCL10/IP-10, (B) IgG and (C) MMP-9, decreased Th1-mediated cell proliferation (A), and was not cytotoxic in *in vitro* human primary cell-based systems of inflammation



[1] International Immunopharmacolgy 2020; 83: 106314
[2] www.biomedtracker.com

Interferon gamma inducible protein-10 (CXCL10/IP-10)
CXCL10/IP-10 is a major chemokine that influences processes of inflammation and the migration of immune cells to sites of inflammation. CXCL/IP-10 is elevated in the serum and cerebral spinal fluid (CSF) of MS patients.[3] Studies involving the deletion of LRP-1, the binding target for EmtinB™, significantly increased CXCL10/IP-10.[4]

Immunoglobulin G (IgG)
IgG is an antibody that mediates various immune responses in the body and is excessively present in the CNS of MS patients, suggesting a significant role in the pathology of MS.[5]

Matrix Metalloproteinase-9 (MMP-9)
MMP-9 is an enzyme associated with tissue remodelling and transmigration of immune cells. In MS, MMP-9 mediates the infiltration of activated immune cells across the blood brain barrier (BBB), contributing to a key process in the cascade of abnormal immune responses identified in MS.[6] EmtinB™ target receptor LRP-1 has also been shown to regulate MMP-9.[7]

Biomarker activities were annotated when 2 or more consecutive concentrations changed in the same direction relative to vehicle controls, were outside of the significance envelope and had at least one concentration with an effect size > 20% ($|\log_{10}$ ratio$|$ >0.1). The significance envelopes were calculated using historical controls (95% confidence interval). Log_{10}ratio values have been collected by Eurofins over time (>3 years, >100 experiments) to generate a historical envelope of negative control values. The 95% significance envelope was the symmetrical upper and lower bound values of 95% of historical vehicle controls.

This announcement is authorised by the Board of NeuroScientific Biopharmaceuticals Ltd.

-ENDS-

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[3] Neuroimmunomodulation 2014;21: 322330
[4] Frontiers in Cardiovascular Medicine 2019;6:51
[5] Frontiers in Neurology 2020; 11: 533388
[6] Frontiers in Immunology 2019; 10:1564
[7] Frontiers in Cardiovascular Medicine 2019;6:51

About NeuroScientific Biopharmaceuticals Ltd
NeuroScientific Biopharmaceuticals Limited (ASX: NSB) is a company developing peptide-based pharmaceutical drugs that target a number of neurodegenerative conditions with high unmet medical demand. The company's product portfolio includes EmtinB™, a therapeutic peptide initially targeting Alzheimer's disease and glaucoma, as well as other Emtin peptides (EmtinAc, EmtinAn, and EmtinBn) which have demonstrated similar therapeutic potential as EmtinB™. For more information, please visit www.neuroscientific.com

About EmtinB™
EmtinB™ is a peptide-based compound that binds to surface-based cell receptors from the LDLR family, activating intracellular signalling pathways that stimulate neuroprotection, neuroregeneration and modulate neuroinflammation. EmtinB™ is modelled on a specific active domain of the complex human protein called Metallothionein-IIA, which is produced as part of the human body's innate immune response to cell injury.

Our preclinical research has established that EmtinB™ is highly specific and selective for its target receptor, safe and well tolerated at high concentrations, and is able to penetrate the blood brain barrier. A series of Phase I clinical studies will be conducted to establish the safety profile of EmtinB™ in humans.

About BioMAP Technology Platform
BioMAP panels consist of human primary cell-based systems designed to model different aspects of the human body in an in vitro format. The 12 systems in the panel allow test agent characterization in an unbiased way across a broad set of systems modelling various human disease states. BioMAP systems are constructed with one or more primary cell types from healthy human donors, with stimuli (such as cytokines or growth factors) added to capture relevant signalling networks that naturally occur in human tissue or pathological conditions. Vascular biology is modelled in both a Th1 (3C system) and a Th2 (4H system) inflammatory environment, as well as in a Th1 inflammatory state specific to arterial smooth muscle cells (CASM3C system). Additional systems recapitulate aspects of the systemic immune response including monocyte-driven Th1 inflammation (LPS system) or T cell stimulation (SAg system), chronic Th1 inflammation driven by macrophage activation (lMphg system) and the T cell-dependent activation of B cells that occurs in germinal centres (BT system). The BE3C system (Th1) and the BF4T system (Th2) represent airway inflammation of the lung, while the MyoF system models myofibroblast-lung tissue remodelling. Lastly, skin biology is addressed in the KF3CT system modelling Th1 cutaneous inflammation and the HDF3CGF system modelling wound healing. A subset of 8 of these BioMAP systems has previously been used in the U.S. Environmental Protection Agency (EPA)'s ToxCast™ program to characterize environmental chemicals, define mechanisms of toxicity and to develop predictive signatures of toxicity.

Each test agent generates a signature BioMAP profile that is created from the changes in protein biomarker readouts within individual system environments. Biomarker readouts (7 - 17 per system) are selected for therapeutic and biological relevance, are predictive for disease outcomes or specific drug effects and are validated using agents with known mechanism of action (MoA). Each readout is measured quantitatively by immune-based methods that detect protein (e.g., ELISA) or functional assays that measure proliferation and

viability. BioMAP readouts are diverse and include cell surface receptors, cytokines, chemokines, matrix molecules and enzymes. In total, the Diversity PLUS panel contains 148 biomarker readouts that capture biological changes that occur within the physiological context of the particular BioMAP system. Using custom-designed software containing data mining tools, a BioMAP profile can be compared against a proprietary reference database of > 4,000 BioMAP profiles of bioactive agents (biologics, approved drugs, chemicals and experimental agents) to classify and identify the most similar profiles. This robust data platform allows rapid evaluation and interpretation of BioMAP profiles by performing the unbiased mathematical identification of similar activities. Specific BioMAP activities have been correlated to in vivo biology, and multiparameter BioMAP profiles have been used to distinguish compounds based on MoA and target selectivity and can provide a predictive signature for in vivo toxicological outcomes (e.g., vascular toxicity, developmental toxicity, etc.) across diverse physiological systems.