NeuroScientific
BIOPHARMACEUTICALS
ASX:NSB

ASX ANNOUNCEMENT
20 AUGUST 2021

CLARIFICATION ANNOUNCEMENT

NeuroScientific Biopharmaceuticals Ltd (ASX: **NSB**) notes that the following announcement serves as a clarification to the previously released announcement on the 19 August 2021, to provide further information regarding the specifics of the studies mentioned within the announcement.

HIGHLIGHTS

- **Treatment with EmtinB™ significantly reduced SAA, IP10, Eot3 biomarkers associated with severe COVID-19 in a panel of human primary cell-based systems**
- **Study results indicate EmtinB™'s therapeutic potential in preventing severe immune responses from COVID-19 infections**
- **Treatment with EmtinB™ was safe and well tolerated across all dose concentrations - suggesting it is safe to administer in future work**

NeuroScientific Biopharmaceuticals Ltd (ASX: **NSB**) (**"NeuroScientific"** or **"the company"**) is pleased to announce that EmtinB™ significantly reduced important biomarkers associated with severe COVID-19 and poor patient prognosis by more than 50% (vs. controls; $p<0.05$), indicating strong therapeutic potential for EmtinB™ in preventing severe immune responses resulting from COVID-19 infections. Additionally, EmtinB™ was shown to be safe and well-tolerated across all dose concentrations. The biomarker studies were undertaken by leading independent research organisation Eurofins, US across 12 assay panels consisting of human primary cell-based systems (BioMAP) designed to model various human disease states. Separate tissue screening studies to assess safety in human lung tissues was performed by The Institute for Respiratory Health, Aus.

Early diagnosis and appropriate treatment are essential in reducing the morbidity and mortality of COVID-19-infected patients. Severely ill COVID-19 patients require simultaneous management of oxygenation and inflammation without compromising viral clearance. While multiple tools are available to aid oxygenation, there is unmet medical need in in immunomodulatory therapy that can adjust inflammatory immune responses and prevent fatal cytokine storms across COVID disease stages.

For the first time the team at Neuroscientific Biopharmaceuticals demonstrated in human primary cell-based systems that model complex disease biology of acute and chronic inflammation in an *in vitro* format (BioMAP) that its lead drug candidate EmtinB™ can dramatically reduce major immune biomarkers identified in COVID-19 clinical studies as indicators of severe disease and poor patient prognosis[1,2,3]. Decreasing these immune biomarkers indicates that EmtinB™ may decrease inflammatory processes that are significantly elevated during severe COVID-19 infections.

NeuroScientific's Managing Director Matt Liddelow commented: *"These results demonstrate the significant therapeutic utility of EmtinB™ and its potential modulation of inflammatory processes outside of the central nervous system. For the first time, our team have demonstrated an EmtinB™-mediated effect on adaptive immune responses as evidenced by regulation of these inflammatory biomarkers".*

NeuroScientific's Non-Executive Chairman Paul Rennie said: *"These results demonstrate EmtinB™ is a true platform technology. Inflammation is now a well-recognised driver of disease progression in many diseases and Big Pharma Companies have a keen interest in this space. These data will demonstrate the wide range of potential clinical applications of EmtinB™ and therefore enhance the commercial interest in this compound".*

Among 148 clinical biomarkers tested in the human primary cell-based models, Serum Amyloid A (SAA), Interferon-gamma-inducible protein 10 (IP-10), and Eotaxin-3 (Eot3) immune markers were the most affected by EmtinB™ treatment, significantly reducing their expression (>50% vs. controls; $p<0.05$) and suggesting clinically meaningful outcomes in COVID-19 disease.

Inflammation
Inflammation is a response to a foreign organism such as viruses, bacteria, pollen, or dust particles. Ongoing studies have highlighted the role of inflammation in the progression of a variety of diseases such as cancer, atherosclerosis, asthma, and arthritis.

COVID-19 infection is accompanied by an aggressive inflammatory response with the release of a large amount of pro-inflammatory cytokines in an event known as "cytokine storm." The 'cytokine storm', is where uncontrolled levels of proinflammatory cytokines (proteins released by immune cells) which cause excessive inflammation which leads to a decrease in lung function.

Proinflammatory cytokines are produced predominantly by activated macrophages and are involved in the up-regulation of inflammatory responses. Measuring proinflammatory cytokines is a 'biomarker' of disease and its progression.

Serum Amyloid A (SAA)
SAA is a clinical biomarker for acute phase inflammation, more commonly associated with increased risk of cardiovascular events. In COVID-19 patients, high SAA concentrations are significantly associated with more severe COVID-19 disease and an increased risk of mortality in patients.[1] Therefore, regulation of SAA is important for stabilising the inflammatory processes that contribute to the severity of disease in COVID-19 patients.

Interferon-gamma-inducible protein 10 (IP-10)
Similarly to SAA, several recent publications have demonstrated IP-10 as a strong biomarker for COVID-19 disease progression and a target in preventing lung injury. Modulation of IP-10 is a suggested therapeutic strategy for treating acute respiratory distress syndrome associated with coronaviruses, including COVID-19.[2]

[1] International Journal of Infectious Disease 2021; 105: 101016
[2] Journal of Allergy & Clinical Immunology 2020; 146: 32360286

Eotaxin 3 (Eot3)
Eot3 modulates the migration of immune cells eosinophils and basophils to sites of tissue inflammation and is a clinical biomarker for airway eosinophilic inflammation in asthma.[3] In severe COVID-19 patients, during the second and third phases of the disease, eosinophils participate in a maladaptive immune response and directly contribute to worsening of disease symptoms. Down-regulating Eot3, and thus triggering the blockade of eosinophil activation, may aid in improving patient outcomes.[4]

These studies were conducted as part of NeuroScientific's exploratory R&D program to investigate EmtinB™ treatment of post-COVID lung fibrosis, with the program commencing in conjunction with the announcement of a collaborative partnership with The Institute for Respiratory Health (announced on 20 November 2020). The tissue screening studies undertaken by the Institute for Respiratory Health have been ongoing since January 2021. The biomarker study undertaken by Eurofins was conducted from June 2021 to August 2021.

Biomarker activities were annotated when 2 or more consecutive concentrations change 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-

For more information please contact:

Matthew Liddelow
CEO and Managing Director
ml@neuroscientific.com
+ 61 8 6382 1805

Lucas Robinson
Investor Relations
Corporate Storytime
lucas@corporatestorytime.com
+ 61 408 228 889

[3] International Journal of Inflammation 2015; 2015: 630637
[4] Frontiers in Pharmacology 2021; 12: 622554

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.