

NTI164 Reverses Immune Dysregulation in PANDAS/PANS Children

Highlights:

- New proteomic insights into the biological effects of NTI164 in PANDAS/PANS patients which correlates to the significant clinical benefits observed in the Phase I/II clinical trial at 12 weeks
- NTI164 shown to positively modify immune cell function and gene translation dysregulation, improving overall health and functional outcomes of children
- Certain important dysregulated pathways associated with immune function and gene translation significantly reversed with NTI164, including MECP2 (the defective gene in Rett Syndrome)
- The disease-modifying potential of NTI164 may improve children with PANDAS/PANS by normalising their immune function and gene translation profiles
- Additional patent applications filed on this novel finding. Genomic analysis pending.

Neurotech International Limited (ASX: NTI) ('Neurotech', 'NTI' or 'the Company') a clinical-stage biopharmaceutical development company focused predominately on paediatric neurological disorders, today announces the results of the genomic analysis undertaken as part of the 15 patient, open-label Phase I/II clinical trial of NTI164 ("NTIPANS1") in children diagnosed with Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Paediatric Acute-Onset Neuropsychiatric Syndrome (PANS).

The NTIPANS1 trial, which reported statistically significant and clinically meaningful improvements in patients related to the severity of their illness, anxiety and depression at 12, 24 and 52 weeks¹ included an exploratory endpoint at 12 weeks, which aimed to elucidate potential biomarkers of disease based on changes to the proteomic and genomic profile of patients who received NTI164 versus baseline and a normative control group.

The scientific thesis is that PANDAS/PANS is an epigenetic gene regulation syndrome affecting the peripheral immune system and brain that is positively modulated by NTI164. Epigenetic neuroimmunology research using single cell RNA sequencing and proteomics was used to identify cellular dysregulation and determine the effects of treatments in patients (ex vivo). Epigenetics is the study of how gene activity within a cell is controlled, without changing the DNA sequence (e.g. through methylation) determine whether a gene is expressed or not.

Professor Russell Dale, Professor of Paediatric Neurology, University of Sydney and Children's Hospital at Westmead and Co-Principal investigator of the NTIPANS1 trial said "My research group hypothesises PANDAS/PANS is the result of gene-environment (epigenetic) neuroimmune dysregulation leading to persistent or progressive neuroinflammation. Currently most patients are symptomatically managed, whereas NTI164's anti-neuroinflammatory properties have now been shown to induce important epigenetic and proteomic changes in immune cells collected from patients at baseline (day zero) and after 12 weeks of treatment. This data is exciting as it demonstrates that the biological aspects of this debilitating condition can be modified by NTI164, including immune and epigenetic dysregulation, improving overall health and functional outcomes of children with PANDAS/PANS. We eagerly await further genomic analysis from these same patients."

¹ ASX releases 6 October 2023, 21 February 2024 and 6 June 2024

The proteome is the complete set of proteins expressed by an organism (in this case, each child), and proteomics analysis allows the study of interactions, functions, and changes in expression of these proteins over time. In this proteomics analysis, the quantity of all proteins was measured and compared between patients and controls (children without neurodevelopmental disorders).

The key results of the analysis to date are:

1. Protein expression of genes relating to immune cell function can be modulated by NTI164

- At baseline, protein expression of several genes relating to immune cell function were significantly upregulated in patients.
- After 12 weeks protein expression was modified for many of these genes in patients treated with NTI164 compared to their baseline levels.
- Most significant changes (i.e. high/low at baseline, reversed significantly after 12 weeks) included SERPING1 (C1 inhibitor) – a pro-inflammatory protein controlling a range of processes involved in maintaining blood vessels, including inflammation.

2. PANDAS/PANS patients show dysregulation in gene translation and immune function, which is modified by NTI164

- Dysregulation in the proteome of patients was in two main areas: gene translation and immune function.
- At baseline, all significantly up-regulated pathways relate to immune function, while the most significantly down-regulated pathways related to gene translation processes or post-translation modifications compared to healthy control children.
- After 12 weeks of NTI164 treatment, pathways relating to immune function were significantly down-regulated, while those relating to gene translation and epigenetic modulation became significantly up-regulated.

3. NTI164 modifies the phosphoproteome of children with PANDAS/PANS

- The phosphoproteome is the complete set of phosphorylated proteins within a cell. Phosphorylation modification plays a crucial role in regulating protein function, activity, interactions, localization, and stability, and is involved in numerous cellular processes such as signal transduction, cell cycle control, and metabolism.
- Analysis confirmed many abnormalities at baseline in children relating to cellular signalling compared to healthy controls.
- After 12 weeks of NTI164 administration, their profile is significantly modified with many pathways upregulated at baseline subsequently down-regulated, and those down-regulated at baseline up-regulated at week 12 with increases in expression in pathways relating to translation and epigenetics. The phosphoproteome of patients after 12 weeks of NTI164 showed a significant normalisation towards matched healthy normal controls.

The researchers concluded with evidence that PANDAS/PANS patients have inflammatory cellular environments due to gene dysregulation, and NTI164 normalises this. NTI164 appears to have both significant anti-inflammatory effects, as well as potential as an epigenetic modulator.

The data is expected to be published in a leading scientific journal in due course and is subject to new patent applications filed by Neurotech.

Authority

This announcement has been authorised for release by the Board of Neurotech International Limited.

Further Information

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About Neurotech

Neurotech International Limited (ASX:NTI) is a clinical-stage biopharmaceutical development company focused predominately on paediatric neurological disorders with a broad-spectrum oral cannabinoid drug therapy called NTI164. Neurotech has completed a Phase II/III randomised, double-blind, placebo-controlled clinical trial in Autism Spectrum Disorder (ASD) with clinically meaningful and statistically significant benefits reported across a number of clinically-validated measures and excellent safety. In addition, Neurotech has completed and reported statistically significant and clinically meaningful Phase I/II trials in ASD and Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Paediatric Acute-Onset Neuropsychiatric Syndrome (PANS), collectively PANDAS/PANS along with Rett Syndrome. Neurotech has received human ethics committee clearance for a Phase I/II clinical trial in spastic cerebral palsy.

For more information about Neurotech please visit <http://www.neurotechinternational.com>.

About NTI164

NTI164 is a proprietary drug formulation derived from a unique cannabis strain with low THC ($M<0.3\%$) and a novel combination of cannabinoids including CBDA, CBC, CBDP, CBDB and CBN. NTI164 has been exclusively licenced for neurological applications globally. Pre-clinical studies have demonstrated a potent anti-proliferative, anti-oxidative, anti-inflammatory and neuro-protective effects in human neuronal and microglial cells. NTI164 is being developed as a therapeutic drug product for a range of neurological disorders in children where neuroinflammation is involved.

About PANDAS/PANS

Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Paediatric Acute-Onset Neuropsychiatric Syndrome (PANS), collectively PANDAS/PANS, is a clinical diagnosis given to children who have a dramatic (typically within one day) onset of neuropsychiatric symptoms including Obsessive-Compulsive Disorder (OCD) and/or restrictive eating. Children may exhibit repetitive tic movements, become moody, irritable/aggressive and anxious and have difficulty with schoolwork. The cause of PANS is unknown in the majority of cases; however, the disorder is hypothesised to be triggered by infections, metabolic disturbances, and other inflammatory reactions. PANDAS is considered a subset of PANS.

About Neurotech PANDAS/PANS Phase I/II Clinical Trial

NTIPANS1 was a single-arm, open-label, Phase I/II clinical trial that recruited 15 paediatric patients with a clinical diagnosis of moderate to severe PANDAS/PANS to determine the efficacy and safety of orally administered NTI164 in these patients. The primary endpoints of the trial are the change from baseline at twelve (12) weeks for the Revised Children's Anxiety and Depression Scale-Parent-rated (RCADS-P) score and Clinical Global Impression (CGI) of severity (CGI-S) and improvement (CGI-I). Secondary clinical endpoints include other gold-standard, validated assessment tools: Yale Global Tic Severity Scale (YGTSS), Children's Yale-Brown Obsessive-Compulsive Scale, Conners Scale and EQ-5D-Y. Other secondary endpoints will examine the Safety and Tolerability of orally administered NTI164 (at 5,10,15 and 20 mg/kg/day). The trial enrolled children at two centres within Australia; the Children's Hospital at Westmead and the Paediatric Neurology Unit at Monash Medical Centre. The Phase I/II clinical trial has been registered on the Australian New Zealand Clinical Trials Registry (ANZCTR) under registration number: ACTRN12622001419752 or visit: <https://www.anzctr.org.au>