Phase I/II PANDAS/PANS Clinical Trial Meets Primary Endpoints

Key Points:

- **First ever clinical trial to show highly significant clinical improvements in PANDAS/PANS patients (n=15) with a broad spectrum cannabinoid drug therapy (NTI164) with excellent safety**
- **Statistically significant and clinically meaningful improvements shown across a range of gold-standard, clinically validated assessments over 12 weeks of NTI164 treatment**
- **Primary endpoint of anxiety and depression (RCADS-P) met (p=0.016) with a 30% improvement in overall symptoms from high severity at baseline to low severity from week 4 onwards**
- **Primary endpoint of severity of illness: Children re-classified from markedly ill at baseline (CGI-S: 5.0) to moderately ill at 12 weeks (CGI-S: 4.1), an 18% improvement (p=0.0005)**
- **Second neurological disorder in children where NTI164 has shown strong benefits, alongside autism**

The Company will host an investor conference call at 12.00pm AEDT today with Dr Thomas Duthy, Executive Director. Details below.

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

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 *"I am very pleased with the clinical results reported to date and wish to thank all patients and their families for participating in this novel clinical trial. I have observed quite profound improvements in a number of my patients with NTI164, making it the first trial of its kind with a broad-spectrum cannabinoid therapy showing initial clinical utility like this with excellent safety. In addition, we await further evidence of genomic molecular changes from baseline measures and after 12 weeks of treatment to correlate this meaningful clinical response we have seen with biological evidence of effect. This would be a major step-forward for PANDAS/PANS patients and assist in identifying relevant biomarkers of the disease."*

The NTIPANS1 clinical trial was designed to examine safety, and gold standard measures of clinical symptoms associated with PANDAS/PANS, relating to the severity of their condition, important measures relating to anxiety, depression, obsessive compulsive disorders and physical tic movements at 12 weeks compared to baseline measures. NTI164 showed clinically significant and meaningful improvements in clinical function, with excellent safety and tolerability over 12 weeks of daily oral treatment.

Mr James Fletcher, President of the non-profit organisation PANS Australia and New Zealand Advocacy and Support Inc. said *"We here at PANS Australia and New Zealand Advocacy and Support Inc are very pleased to see the results of the Neurotech Clinical Trial regarding the use of NTI164 for children diagnosed with PANS. As our researchers continue to expand their understanding of PANS, they also help us to raise awareness of PANS within the general medical community. This in turn leads to earlier intervention and better long-term outcomes for children and adults with PANS. A targeted treatment for PANS in the form of NTI164 is a very exciting development indeed. Many thanks to the researchers for their work on this therapy and to the children and families who participated in the study."*

Dr Thomas Duthy, Executive Director of Neurotech said *"We commenced this clinical trial based on a small number of scientific publications that highlighted recurring, neuroinflammatory processes in these difficult to treat patients. With our established evidence in autism and supportive pre-clinical data we took the decision to run this world-first trial of NTI164 with Professor Dale and Professor Fahey, which has shown very strong benefits for these children over 12 weeks of daily treatment. Given the lack of safe and effective treatments for PANDAS/PANS with associated distressing symptoms and significant caregiver burden we remain very hopeful of an accelerated development plan for NTI164 to bring this therapy to market."*

Clinical Results

Safety

There were no serious adverse events recorded.

Across the 12 weeks of the trial a total of 9 adverse events were recorded from three (3) participants. Of these 9, 6 were possibly related to the study medication and included vomiting (4 events, 50%) and nausea (2 events, 22%). The remaining 3 reactions were viral infections unrelated to the study drug (3 events, 33%).

None of these adverse events were serious and were not considered to interfere with the patient's functioning. No additional treatment was required, except for the viral infection requiring pain relief and saline mouth wash). Normal blood chemistry, normal kidney and liver function and vital signs were recorded across the 12 weeks.

Efficacy

15 paediatric patients remained on daily treatment of NTI164 for the full duration of the 12 week period and were therefore evaluable for the analysis. As announced previously, all patients are continuing to receive treatment under the extension phase (54 weeks) of the trial protocol, and the Company successfully achieved an HREC extension to allow patients to be treated until 20 years of age.

The primary endpoint of the trial was the change in the Revised Child Anxiety and Depression Scale – Parent Version (RCADS-P), which is a 47-item parent-report questionnaire of youth anxiety and depression. The mean total T-score for the 15 patients after 12 weeks of NTI164 treatment was 58.2 which is a significant improvement (30%) from baseline where it was 83.7 (mean difference of -25.5, p value=0.016).

This clinically meaningful improvement of 30% results in these patients being re-classified as low severity (<65) versus high severity (>70). To put this into perspective, only 2% of youth in the general population have T-scores of 70 or higher. Upon commencement with NTI164, all sub-domains of RCADS-P all improved significantly at 12 weeks: social phobia (32%), panic disorder (28%), major depression (15%), separation anxiety (36%), general anxiety (42%) and obsessive-compulsive behaviours (47%).

The second primary efficacy endpoint was Clinical Global Impression-Severity of illness (CGI-S). The CGI-S scale is clinician administered and ranks from 1 (Normal) to 7 (Extremely ill). At 12 weeks of treatment, the mean severity of illness rating of the patients was 4.1, representing an improvement of 18% from baseline (CGI-S: 5.0), p=0.0005. At baseline, 20% of patients were classified as extremely ill, 60% were markedly ill and 20% were moderately ill. By week 12, patients were classified as mildly ill (20%), moderately ill (73%) and one patient (7%) was classified as markedly ill. This patient acquired a significant infection during the trial, which may have been a factor in their response.

CGI- Improvement (CGI-I) was strong, showing that after 4 weeks of treatment with NTI164, 33% of patients were much improved, 67% minimally improved. After 12 weeks of daily treatment with NTI164, 53% of patients were much improved, 40% minimally improved and one patient (7%) had no change (same patient as above). CGI-I does not provide for statistical p values from the change (no improvement assumed at baseline).

CGI-Therapeutic Effect after 4 weeks of daily NTI164 treatment, 67% of patients demonstrated a Moderate improvement and 33% demonstrated a Minimal improvement. After 12 weeks, 53% demonstrated a Moderate improvement, 40% Minimal and 7% (n=1) No Change. CGI-Therapeutic Effect does not provide for statistical p values (no therapeutic effect assumed at baseline).

Reductions in clinically used, gold-standard measures of function and neuropsychiatric symptoms were the secondary outcome measures / endpoints, which are described below. The trial was not statistically powered for any secondary endpoints.

The Yale Global Tic Severity Scale (YGTSS) is a clinician-rated instrument considered as the gold standard for assessing tics in patients with Tourette's Syndrome and other tic disorders, including PANDAS/PANS. Although tics are not part of a core definition of PANDAS/PANS, approximately 70% of people with PANDAS/PANS have tics (motor/verbal).

The mean total severity score for the 15 patients after 12 weeks of NTI164 treatment was 44.7 which is a material improvement of 14% from baseline where it was 52.0 (mean difference of -7.3, p =0.07). Patient tics overall were classified as mild under YGTSS. Motor tic severity (a sub domain of YGTSS) improved by 32% (mean change of -3.1 from baseline score of 15.8) and was borderline statistically significant (p=0.05).

The Conners Scale measures attention-deficit hyperactivity disorder (ADHD) symptoms such as attention deficits and hyperactivity or impulsivity symptoms. The mean total T-score for the 15 patients after 12 weeks of NTI164 treatment was 17.3 which is a significant improvement (16%) from baseline where it was 20.6 (mean difference of -3.3, p =0.08).

Patient's quality of life as measured by the EQ-5D-Y assessment improved considerably between baseline and 12 weeks of treatment with NTI164. The mean total T-score after 12 weeks of NTI164 treatment was 83.5 which is an 18% improvement from baseline where it was 70.6 (mean difference of 12.9, p value=0.05). The change was borderline statistically significant.

The Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) designed to rate the severity of obsessive and compulsive symptoms in children and adolescents, ages 6 to 17 years. PANDAS/PANS paediatric patients exhibit severe forms of obsessive-compulsive disorder (OCD) that appear suddenly (acute onset), accompanied by other confusing and distressing symptoms. The mean total T-score for the 15 patients after 12 weeks of NTI164 treatment was 30.0 which was an improvement (10%) from baseline where it was 33.0 (mean difference of -3.0, p=0.96). The children were down-staged from extreme symptoms to severe symptoms on the basis of this scale change.

Conclusions

The current approach to PANDAS/PANS treatment emphasizes immunomodulation/anti-inflammatory treatments in association with both psychotropic and cognitive-behavioural therapies, while antibiotics are suggested when an active bacterial infection is established.[1] Although this treatment approach is endorsed in consensus treatment guidelines, these agents are not specifically approved for PANDAS/PANS treatment.

NTI164 has shown to be safe and well tolerated up to doses of 20/mg/kg/day. The side effects reported were not serious or severe and did not significantly interfere with patients' functioning. No clinically significant abnormal laboratory values were reported.

NTI164 has shown statistically significant efficacy in improving the symptoms associated with PANDAS/PANS after 12 weeks of daily therapy, with the trial meeting the key primary endpoints of anxiety and depression (RCADS-P) with a 30% improvement overall and severity of illness displaying an 18% improvement. Other efficacy measures also showed improvements over 12 weeks of treatment.

The Company eagerly awaits the multi-omic exploratory endpoint, which for the first time could elucidate potential biomarkers of disease. Neurotech's hypothesis is that NTI 164 will be anti- inflammatory and affect gene regulation, thereby improving clinical symptoms. Neurotech hypothesises that the transcriptomic signature can be modified with NTI164 treatment, corresponding with clinical improvements in neuropsychiatric (emotional) symptoms associated with PANDAS/PANS.

Conference Call / Webinar

The Company will host an interactive investor webinar /conference call at 12.00pm AEDT today with Dr Thomas Duthy, Executive Director.

The live presentation and audio can be accessed via the webcast link:

https://ccmediaframe.com/?id=iKrOImUU

To ask a question during the webinar, details of the call are set out below.

In order to pre-register for the conference call and avoid a queue when calling, please follow the link below. You will be given a unique pin number to enter when you call which will bypass the operator and give you immediate access to the event.

https://s1.c-conf.com/diamondpass/10033959-fh86y7.html

Alternatively, you may dial in with the following details, approximately five minutes before the scheduled start time and provide the Conference ID to an operator.

Conference ID: **10033959**

Participant Dial-in Numbers:

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

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About Neurotech

Neurotech International Limited (ASX:NTI) is a clinical-stage biopharmaceutical development company focused predominately on paediatric neurological disorders. Neurotech has completed a Phase I/II clinical trial in Autism Spectrum Disorder (ASD), which demonstrated excellent safety and efficacy results at 28 days, 20 weeks and 52 weeks of treatment with NTI164. The Company commenced Phase II/III randomised, double-blind, placebo-controlled clinical trial in ASD in Q4 CY2022. Neurotech is also conducting additional Phase I/II trials in Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Paediatric Acute-Onset Neuropsychiatric Syndrome (PANS), collectively PANDAS/PANS, along with Rett Syndrome and Cerebral Palsy during CY2023. Neurotech is also commercialising Mente, the world's first home therapy that is clinically proven to increase engagement and improve relaxation in autistic children with elevated Delta band brain activity.

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 is 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

APPENDIX - Study Details NTIPANS1 Clinical Trial Design

Title of Study	A Phase I/II Baseline Controlled Multi-Site Open-Label Study to Assess the Safety & Efficacy of NTI164 in Young People with Paediatric Acute-Onset Neuropsychiatric Disorder (PANS)
Co-Principal Investigators	Prof Russell Dale, Head, CHW Clinical School and Speciality of Child and Adolescent Health, The Children's Hospital at Westmead Prof Michael Fahey, Head of Paediatric Neurology, Monash Children's Hospital
Treatments	*Baseline/up-titration phase*: patients receive a baseline dose of 5mg/kg/day of NTI164 which will be increased weekly by 5mg/kg for a period of 4 weeks until the maximum tolerated dose or 20mg/kg is achieved. *Treatment phase:* patients will receive the maximum tolerated dose or 20mg/kg/day for 8 weeks, after which extension to 54 weeks will be offered if patients would like to continue (extension phase). *Down-titration phase (for patients not entering extension phase):* at the end of the 8 week treatment phase, patients will commence weaning of NTI164, gradually decreasing the maximum tolerated dose by 5mg/kg/week for a period of 4 weeks until the end of the study. *Extension phase:* Patients who choose to continue receiving the maximum tolerated dose beyond the 8 week treatment phase may do so for up to 54 weeks. Patients will undergo the down-titration phase at the end of their extension phase.
Primary Endpoints	<u>Revised Children's Anxiety and Depression Scale-Parent-rated (RCADS-P) score</u> RCADS-P is a 47 item parent-reported questionnaire that measures symptoms of depression and anxiety in children and adolescents aged 8–18. The RCADS-P consists of six subscales helpful in screening children for high prevalence disorders, including: separation anxiety disorder (SAD), social phobia (SP), generalized anxiety disorder (GAD), panic disorder (PD), obsessive

	compulsive disorder (OCD) and major depressive disorder (MDD). **[Timeframe: Baseline, Week 12]** Clinical Global Impression-Severity (CGI-S) Reflects clinician's impression of severity of illness on a 7-point scale ranging from 1=not at all to 7=among the most extremely ill. **[Timeframe: Baseline, Week 12]** Clinical Global Impression-Improvement (CGI-I) Reflects clinician's impression rates the total improvement whether or not, in the clinician's judgement, is due entirely to drug treatment on a 7-point scale ranging from 1=very much improved to 7=very much worse **[Timeframe: Baseline, Week 12]**
Secondary Endpoints	Yale Global Tic Severity Scale (YGTSS); gold-standard for clinical measurement of tics Children's Yale-Brown Obsessive-Compulsive Scale; gold-standard for clinical measurement of OCD symptoms and severity Conners Scale; gold-standard for clinical assessment of attention deficit hyperactivity disorder (ADHD) behaviours EQ-5D-Y; a globally accepted tool for measuring impairment in the domains of mobility, looking after oneself (e.g., personal hygiene habits), ability to perform usual/daily activities, having pain or discomfort, and feeling worried, sad, or unhappy Unique blood transcriptomic and/or epigenetic signature in children with PANS is improved with NTI164
Safety	Safety will be monitored and measured by full blood examinations, liver and kidney function tests. Adverse events will be assessed and evaluated by delegated study staff through discussions with the Participant at week 4 and via phone calls made to them throughout the study and by clinically significant lab results.
Multi-omic Studies	Transcriptomics – RNA Sequencing Methylomics Immune biomarker studies - Cytokines
Summary Inclusion Criteria	Participant is aged < 17 years

	Fulfil PANS criteria: Acute onset of OCD or severely restricted food intake Concurrent presentation of additional neuropsychiatric symptoms from at least 2 of the following 7 categories: anxiety, emotional lability/depression, irritability, aggression or severely oppositional behaviours, behavioural regression, deterioration in school performance, sensory or motor abnormalities (e.g. tics), somatic symptoms (e.g. sleep disturbances, enuresis or increase in urinary frequency) Symptoms not better explained by a known neurologic or medical disorder (e.g. Sydenham's chorea) RCADS-P scores of >65 (a scale of anxiety, social phobia, panic disorder, OCD, and low mood, a score of >65 infers moderate-significant impairment) Other patient medications (e.g. anti-psychotics) must be stable for at least 12 weeks prior to trial participation
Summary Exclusion Criteria	Infection and/or antibiotic use in the 2 weeks prior to trial participation (i.e. baseline blood tests and commencement of NTI164) Recent changes to other patient medication (e.g. addition or escalation of anxiolytics, anti-depressants etc; medication dosage must be stable for at least 12 weeks prior to trial participation) Intellectual disability preventing adequate assent from patient, or that would affect reporting throughout trial; patients with intellectual disability must still have the capacity to verbalise their symptoms/experiences Ongoing immunomodulating or immunosuppressive treatment use in the previous 12 weeks, including steroids, IVIG, antibiotics, low-dose naltrexone, mycophenolate, Rituximab etc. Currently using or has used recreational or medicinal cannabis or cannabinoid-based medications (e.g. Sativex ®, Epidiolex ®) in the previous 12 weeks and/or is unwilling or unable to abstain for the duration of the trial Underlying renal impairment, cardiovascular issues (e.g. arrhythmia), current or previous thrombosis Impaired hepatic function, defined as serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 x upper limit of normal (ULN) or total bilirubin (TBL) > 2 x ULN; this criterion can only be confirmed once baseline laboratory results are available and

	participants who fail this criterion will not proceed in this study Other diagnosed neurological condition likely to be contributing to OCD/neuropsychiatric symptoms (e.g. Huntington's disease)
Concomitant Care	Concomitant use of immune modulating or immunosuppressive therapies, including all forms of steroids (except topical), low dose naltrexone, mycophenolate, Rituximab etc. is prohibited during the trial period. Changes to the dose of existing medications (e.g. anti-anxiety or anti-psychotic treatment) is prohibited throughout the trial period. The addition of new medication, including anti-anxiety (selective serotonin reuptake inhibitors) or anti-psychotic treatments (e.g., Risperidone, Aripiprazole, Olanzapine, Quetiapine etc.) is prohibited and if a patient requires a new medication during the study period, they will be discontinued from the study

[1] Gagliano A, Carta A, Tanca MG, Sotgiu S. Pediatric Acute-Onset Neuropsychiatric Syndrome: Current Perspectives. Neuropsychiatr Dis Treat. 2023 May 24;19:1221-1250.