Preclinical Success with Targeted Combination Therapies: Prednisone + NTI164

- **NTI continues to expand and validate its preclinical program using lead NTI164. NTI164 is a novel cannabis strain developed by Dolce Cann Global that contains full spectrum plant composition with high levels of minor cannabinoids and less than 0.3% THC.**
- **Prednisone belongs to a $5B annual sales class of drugs known as Corticosteroids. Prednisone medication is used to treat a large variety of conditions: autoimmune disorders, neurological disorders, rheumatoid arthritis, and multiple sclerosis. Whilst extremely effective, there are many adverse side effects that limit the use of corticosteroids, particularly long-term use.**
- **Preclinical studies conducted in human neuronal cells have demonstrated that NTI164, when combined with prednisone, is able to significantly reduce and normalise the levels of key inflammatory markers such as Tumour Necrosis Factor (TNF)-alpha, COX-2 expression, Interleukin -6 (IL-6), Interleukin – 1A (IL-1a), granulocyte-macrophage colony-stimulating factor (GM-CSF) levels. Prednisone alone had a limited effect on these markers.**
- **When combined with NTI164, prednisone efficacy was significantly increased, showing a 33% in the reduction of TNF-alpha and 87% reduction in the suppression of IL-6.**
- **These key biomarkers/cytokines all play vital roles in the onset, development and progression of multiple neuro-inflammatory disorders such as Multiple Sclerosis, Alzheimer's Disease and Rheumatoid Arthritis.**
- **Reducing the prednisone dose whilst achieving increased efficacy (with NTI164 compared to prednisone alone) could overcome many of the adverse side effects that are directly related to the dosage of prednisone. The results provide NTI with an ideal platform to progress strategic partnerships and further expand its clinical trial portfolio.**

Neurotech International Limited (ASX: NTI) ("Neurotech" or "the Company") is pleased to advise that preclinical studies demonstrate that NTI164 can improve the efficacy of prednisone at low doses (i.e. 5uM and 25uM). Significant anti-inflammatory synergistic activity was observed when NTI164 was combined with prednisone (at the low doses). These findings may have significant applications with regards to the use of prednisone across a variety of indications. Importantly, the combination treatment and formulation fall under NTI's recently lodged patent applications (refer ASX announcement 14 October 2021).

As mentioned above, reducing the prednisone dose whilst achieving increased efficacy (with NTI164 compared to prednisone alone) could overcome many of the adverse side effects that are directly related to the dosage of prednisone[1]. The results provide NTI with an ideal platform to progress strategic

[1] https://www.medicalnewstoday.com/articles/prednisone-oral-tablet

partnerships and further expand its clinical trial portfolio. The prednisone / NTI164 study further expands NTI's preclinical portfolio allowing the Company to develop a solid pipeline of combination products using major off patent generic actives with proven efficacy without side effects.

The Company will look to fast-track commercial negotiations with strategic partners to further develop and commercialise the most common worldwide off patent actives used in combination with NTI164 across multiple indications.

Brian Leedman, Chairman of Neurotech International commented:

"From a Company development perspective, we can't understate the clinical significance of these results. We have prednisone, one of the world's most commonly used off patent pharmaceutical drugs for neuroinflammatory disorders (including Rheumatoid Arthritis, Alzheimer's and MS)[1], demonstrating significant improvement in efficacy using anywhere from 70% to 90% less active dosage when used in combination with NTI164. Given the very well documented adverse side effects of prednisone usage, the potential to create a combination treatment with NTI164 and prednisone which increases efficacy and significantly reduces side effects is now a major driver for the Company. We are now pursuing other synergistic opportunities with blockbuster generics and other unique combination therapies. An all-natural, no THC combination treatment option will put NTI at the forefront of full spectrum cannabis strain development and commercialisation and we look forward to updating stakeholders with progress on an ongoing basis."

Neurotech International Non-Executive Director, Prof. Emeritus Allan Cripps said:

"The synergistic suppression of the inflammatory response with combined prednisone and NTI164 treatment in the preclinical in-vitro studies is a very exciting finding. Clearly, we are seeing the applications of the "entourage effect" of our full spectrum cannabis strains. If this can be translated to human studies; better clinical outcomes with less side effects would be expected for the treatment of diseases associated immune inflammation. The Company is looking forward to seeing the results of the recently commissioned combination preclinical studies utilising other major off-patent anti-inflammatory drugs such as Diclofenac and Celebrex which also have significant adverse side effects."

Table: A Summary of Results

Biomarker Analysis	**Control PBS buffer**	**Inflammation only: Interleukin & Interferon activation**	**PDN 5uM concentration**	**PDN (5uM)+ NTI164 (7.5ug/ml)**	**Significance** PDN vs PDN+NTI164	**% Reduction in inflammation using combination therapy versus PDN alone**
COX-2 Protein	0.799	1	0.888	0.586	P=0.0210 Significant	**34%**
+/- SEM	0.075	0	0.057	0.200		
TNF-a	20.33	45	30.17	20.33	P=0.0105 Significant	**33%**
+/- SEM	5.01	8.35	1.53	2.02		
IL-6	9.50	366.33	228.50	30.33	P=0.0002 Highly Significant	**87%**
+/- SEM	2.77	60.41	11.53	25.27		
IL-1a	77.5	154.83	144.5	69.00	P= 0.0213 Significant	**53%**
+/- SEM	38.66	33.11	27.54	22.52		
GM-CSF	168.80	768.13	611.97	278.97	P=0.0398 Significant	**54%**
+/- SEM	83.29	294.36	375.14	138.58		

Results are expressed as: Average +/- SEM (standard error of mean)
Treatment groups include:

Control: PBS Buffer
Positive control: Inflammatory stimulation by Interferon gamma and Interleukin – 1B activation
Prednisone (PDN) concentration 5uM
Combination therapy: Prednisone (PDN) 5uM + NTI164 concentration 7.5ug/ml

Result Analysis:
Calculated as % reduction in inflammation, PDN versus Combination therapy (prednisone 5uM + NTI164 concentration 7.5ug/ml).

Student's t-test was used for statistical analysis.

Background Information

Prednisone belongs to a class of drugs known as Corticosteroids. Corticosteroids are drugs used in the management and treatment of almost all areas of medicine.

Prednisone medication is used to treat a large variety of immune inflammatory conditions such as; autoimmune disorders, neurological disorders, rheumatoid arthritis and multiple sclerosis.

The corticosteroids market is expected to witness a CAGR of 4.3%, during the forecast period (2020-2025). Current market size is estimated at $5Billion USD. The major factors accounting for the growth of the corticosteroid market are increasing the incidence of chronic diseases, growing geriatric population and surging investment in research and development. The United Nations forecast human population is expected to increase from 7.2 billion today to 8.2 billion by 2025. This will increase the burden of chronic diseases to 57% worldwide according to WHO by the end of 2020 and is expected to increase further during the forecast period. Hence, this uninterrupted incidence and prevalence of chronic diseases lead to the growth of the Corticosteroids market during the forecast period[2].

Prednisone Use and Side Effects

Despite its significant efficacy, the many adverse effects limit the utility of prednisone and corticosteroids. Adverse effects appear to be related to both their average dose and cumulative duration.

High dose use is commonly associated with[2]:

- Elevated pressure in the eyes (glaucoma).
- Clouding of the lens in one or both eyes (cataracts).
- High blood sugar, which can trigger or worsen diabetes.
- Increased risk of infections, especially with common bacterial, viral and fungal microorganisms.
- Thinning bones (osteoporosis) and fractures.
- Suppressed adrenal gland hormone production that may result in a variety of signs and symptoms, including severe fatigue, loss of appetite, nausea and muscle weakness.
- Thin skin, bruising and slower wound healing.
- Significant weight gain.

Therefore, being able to reduce the dose whilst providing high level efficacy can be a breakthrough in the use of prednisone and related corticosteroids.

[2]https://www.mordorintelligence.com/industry-reports/corticosteroids

Preclinical studies conducted in human neuronal cells have demonstrated that prednisone formulated with NTI164:

- Lower doses of prednisone are required to achieve maximum efficacy.
- Studies were focused on key inflammatory biomarkers as well as cytokines that are directly involved in the progression of inflammation and various chronic neuro-inflammatory disorders.
- TNF-alpha, COX-2 and cell mitochondria output were assessed using prednisone alone, NTI164 alone and prednisone + NTI164 across a number of doses.

Results

- Across all the preclinical studies prednisone had a modest effect in suppressing / reducing these key biomarkers and cytokines.
- When combined with NTI164, prednisone + NTI164 proprietary combination formulation were able to reduce and normalise the levels of TNF-alpha, COX-2, IL-6, IL-1A and GSCMF.
- These results demonstrate a significant combination | synergistic output between NTI164 and prednisone.

NTI164 can improve the efficacy of prednisone whilst being able to use minimum dosage. These findings may have significant applications with regards to the use of prednisone across a variety of indications.

Reducing the prednisone dose whilst achieving increased efficacy (with NTI164 compared to prednisone alone) could overcome many of the unwanted and dangerous side effects that are directly related to the dosage of prednisone.

These results reconfirm the potent anti-inflammatory, neuro-regulatory effects of NTI164.

Combination therapy development and applications have been increasing over the past 5 years[3, 4]. The rationale for combination therapy is **to use drugs that work by different mechanisms, thereby decreasing the likelihood that resistant cells will develop**. When drugs with different effects are combined, each drug can be used at its optimal dose, without intolerable side effects, thereby providing the best outcomes for patients.

For example, TNF-alpha inhibitors (eg. Infliximab) combined with anti-seizure meds (eg. Lamotrigine) have proven to be very effective in managing seizures and related inflammatory conditions*.

In the case of prednisone + NTI164 combination, prednisone mimics the effects of hormones your body naturally produces in your adrenal gland. When prescribed in doses higher than your body's usual levels, prednisone dampens inflammation. Preclinical studies have shown that NTI164 is able to regulate multiple pathways ie., Arginase-1, Beta-tubulin and iNOS pathways. As previously announced to the ASX (date: November 2020) results have demonstrated that the NTI strains may regulate and suppress inflammation by acting on these pathways which are directly involved in complex anti-inflammatory processes relating to immunity and natural defence mechanisms.

[3]: Treatment approaches to patients with multiple sclerosis and coexisting autoimmune disorders
https://doi.org/10.1177/17562864211035542

[4]It's Time For Combination Therapies: in Multiple Sclerosis

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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 is a medical device and solutions company conducting clinical studies to assess the neuro-protective, anti-inflammatory and neuro-modulatory activities of our proprietary NTI/Dolce cannabis strains. 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 and Mente Autism please visit http://www.neurotechinternational.com