Preclinical Success with Targeted Combination Therapies: Diclofenac + NTI164

- **Significant development with NTI164 combination therapy program – NTI164 is a proprietary cannabis strain, with full-spectrum composition, exclusively licensed from Dolce Cann Global Ltd. NTI164 contains high levels of unique minor cannabinoids and less than 0.3% THC (patent pending).**

- **Preclinical studies conducted in human neuronal cells have demonstrated that NTI164, when combined with Diclofenac (the pharmaceutical active found in Voltaren™) significantly reduced and normalised the levels of key inflammatory biomarkers – specifically, Tumour Necrosis Factor (TNF)-alpha, COX-2 expression, Interleukin-6 (IL-6) and Interleukin-1A (IL-1a). Diclofenac alone had a significantly lesser effect on these markers.**

- **These key biomarkers/cytokines are associated with the onset and development of multiple neuro-inflammatory disorders including multiple sclerosis (MS) and Alzheimer's disease as well as inflammatory auto-immune diseases such as rheumatoid arthritis.**

- **When combined with NTI164, Diclofenac's effect was significantly enhanced, showing a 93% reduction in the expression of TNF-alpha, 80% reduction in the expression of IL-6 as well as 38% - 66% reduction in other key biomarkers (see Table 1 below).**

- **The Diclofenac market size is expected to reach $6.1 billion by 2027[i]. Diclofenac belongs to a class of drugs known as non-steroidal anti-inflammatory drugs (NSAIDs) and is used to treat the pain and inflammation associated with a large variety of conditions including osteoarthritis, rheumatoid arthritis, musculoskeletal pain, migraine and more. Whilst extremely effective, there are many adverse side effects that limit the use of NSAIDs, particularly with long-term use.**

- **Reducing the Diclofenac dose whilst achieving increased effect (with NTI164 compared to Diclofenac alone) could overcome many of the unwanted adverse side effects that are directly related to the dosage of Diclofenac. These results provide NTI with an ideal platform to progress strategic partnerships and further expand its clinical trial portfolio in the combination product category.**

- **NTI has previously released preclinical results regarding combination of NTI164 and the corticosteroid, Prednisone, with similar significantly positive results (ASX release: 1 December 2021).**

- **Given the impending results of the Phase I/II Autism Spectrum Disorder (ASD) clinical trial in June 2022, the Company is particularly pleased with the Diclofenac study results and looks forward to achieving a number of key milestones in the second half of 2022.**

Neurotech International Limited (ASX: NTI) ("Neurotech" or "the Company") is pleased to report positive preclinical research demonstrating that NTI164 can improve Diclofenac efficacy at low doses (i.e. 5uM). When NTI164 was coupled with Diclofenac, significant anti-inflammatory synergistic action was seen (at low doses). As previously stated, lowering the Diclofenac dose while increasing efficacy could alleviate many of the negative side effects that are directly tied to Diclofenac dosage. These findings could have far-reaching implications for the use of Diclofenac across a variety of applications.

Importantly, NTI's provisional patents include the combination treatment and formulation (ASX Release: 14 October 2021). The findings give NTI an excellent foundation on which to build strategic alliances and extend its clinical portfolio. The Diclofenac + NTI164 combination therapy trial adds to NTI's preclinical portfolio, allowing the company to build a strong pipeline of combination pharmaceuticals based on significant off-patent generic actives that have demonstrated efficacy and tolerability.

In order to further develop and commercialise combination therapies, the Company will seek to accelerate commercial negotiations with potential strategic partners.

Table 1: A Summary of Results

Cytokine	Control	Inflammation only	Diclofenac	Diclofenac + NTI164	Significance Diclofenac vs Diclofenac+NTI 164	% Reduction in Inflammation Diclofenac + NTI versus Diclofenac
Cox 2 PROTEIN	**0.755**	1	**0.565**	**0.350**	**P=0.05**	**38%**
+/- SEM	**0.046**	0	**0.184**	**0.058**		
TNF-a	**12.55**	**258.05**	**228.8**	**15.55**	**P<0.001**	**93%**
+/- SEM	**2.65**	**1.83**	**5.307**	**5.51**		
IL-6	4.75	262.05	200.3	40.3	P<0.001	**80%**
+/- SEM	9.40	42.25	30.21	8.64		
IL-1a	**31.25**	**79.5**	**70.50**	**34**	**P<0.001**	**52%**
+/- SEM	**1.02**	**6.95**	**3.674**	**1.62**		
GM-CSF	46	356.5	477.75	164.50	**P=0.001**	**66%**
+/- SEM	2.44	57.56	43.88	36.55		

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 Diclofenac concentration 5uM
Combination therapy: Diclofenac 5uM + NTI164 concentration 7.5ug/ml

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

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

Chairman of Neurotech International, Brian Leedman commented:

"These preclinical results are incredibly exciting from a Company development perspective. We now have both Prednisone and Diclofenac, two very commonly used off patent pharmaceutical drugs for inflammatory disorders, demonstrating significant improvement in effect using up to 90% less active dosage when used in combination with NTI164. The potential to create combination treatments with NTI164 plus Diclofenac and/or Prednisone that increases efficacy and significantly reduces side effects is now a major driver for the company. Given the impending release of our final ASD study results, the Company is well and truly positioned for an extremely busy second half to the year as we move to secure strategic partners and undertake further clinical trials given our results to date."

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

"These preclinical findings are very encouraging as they are in line with the results we previously reported with Prednisone. What a reduction in these key biomarkers means is promising since these cytokines all play vital roles in the onset, development and progression of multiple neuro-inflammatory diseases and autoimmune disorders. We look forward to translating the in vitro results with our upcoming human studies; better clinical outcomes with less side effects would be welcomed for the treatment of diseases associated with immune inflammation."

Background Information

The Diclofenac Market size is set to reach $6.1 billion by 2027 and is poised to grow at a CAGR of 3.9% over the forecast period of 2022-2027[ii]. Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) used to treat a variety of pain and inflammatory conditions such as osteo and rheumatoid arthritis, muscle and ligament sprains/strains, back pain, migraine, gout, and ankylosing spondylitis.

Diclofenac Use and Side Effects

Despite its high efficacy, Diclofenac's usage is limited due to its numerous side effects which appear to be proportional to both dosage and cumulative duration. While rare, prolonged, high-doses of NSAIDs may increase risk of cardiovascular events and stroke and may induce stomach ulcers, bleeding, and perforations in the intestine[iii].

Results

Preclinical studies conducted in human neuronal cells demonstrated:

- Diclofenac alone had a modest effect in suppressing / lowering these important biomarkers and cytokines across all preclinical investigations.
- When combined, Diclofenac + NTI164 proprietary combination formulation was able to reduce and normalise the levels of Tumour Necrosis Factor (TNF)-alpha, Interleukin-6 (IL-6), Interleukin-1a (IL-1a), granulocyte-macrophage colony-stimulating factor (GM-CSF) levels and COX-2 protein expression. Diclofenac alone had a modest effect on these markers.
- These findings show that NTI164 and Diclofenac have a substantial combination/synergistic effect.

Summary

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

Reducing the Diclofenac dose whilst achieving increased efficacy (with NTI164 compared to Diclofenac alone) could overcome many of the undesirable/negative side effects that are proportionately related to the NSAID dosage.

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

Over the last five years, there has been an increase in the development and use of combination therapies. The idea of combination therapy is to combine medications that function through different mechanisms of action. When medications with various effects are combined, each drug can be given at its optimal dose without causing severe side effects, giving patients the best results. For example, TNF-alpha inhibitors (e.g., Infliximab) in combination with anti-seizure medications (e.g., Lamotrigine) have shown to be particularly successful in the treatment of seizures and related inflammatory diseases[iv],[v].

The ability to lower the dose while maintaining the same high level of efficacy would be an important advance forward in the application of Diclofenac.

Corporate Advisory Mandate

Neurotech has also entered into a corporate advisory mandate with Winx Capital Pty Ltd ("Winx") for the provision of services, being the introduction of the Company to local and overseas retail and institutional investors through traditional and digital mediums, as well as general corporate advice ("Mandate").

Winx Capital Pty Ltd is a boutique Sydney based corporate advisory firm with particular expertise in emerging Australian biotech opportunities.

Under its Listing Rule 7.1 capacity, the Company agreed to issue 35,000,000 options to Winx Capital Pty Ltd (or its nominees) as consideration and equity incentives for this engagement. Subject to a vesting condition, the Options will be exercisable at $0.065 and expire on 30 June 2023. The Options will vest subject to the Company achieving a 10 day VWAP share price of $0.09 at any time on or before 30 September 2022. The initial term of the agreement is six months and may be extended by mutual consent ("Term"). The Company may terminate this Mandate at any time, with or without cause, on written notice to Winx on the basis that the equity incentives remain in place irrespective of termination. Winx may terminate the Mandate before the end of Term if the Company is in material breach of the Mandate.

Next Steps

Given the impending final results of the Phase I/II ASD clinical trial in June 2022, the Company is particularly pleased with the Diclofenac study results and looks forward to hitting a number of key milestones in the second half of 2022.

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 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 has submitted key provisional patents relating to the composition and use of NTI164 for the treatment of a range of neurological disorders including ASD. 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

[i] https://www.industryarc.com/Research/Diclofenac-Market-Research-502786

[ii] https://www.industryarc.com/Research/Diclofenac-Market-Research-502786

[iii] https://www.drugs.com/sfx/diclofenac-side-effects.html

[iv] https://pubmed.ncbi.nlm.nih.gov/21052764/

[v] https://www.ncbi.nlm.nih.gov/books/NBK482425/