Neurizon Therapeutics Limited
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NUZ-001 Shows Promise in Zebrafish Model of Huntington's Disease

Highlights:

- **NUZ-001 and its active metabolite NUZ-001 Sulfone demonstrated significant neuroprotective effects in a zebrafish model of Huntington's disease**
- **Treatment prevented hallmark developmental and morphological abnormalities, protected against neuronal cell death, restored delayed haemoglobin production, and rescued BDNF expression following Htt protein knockdown**
- **Neurizon plans to initiate additional validation studies in mammalian models of Huntington's disease**
- **These findings reinforce NUZ-001's potential as a platform therapy targeting core neurodegenerative mechanisms**

16 June 2025 – Melbourne, Australia: Neurizon® Therapeutics Limited (ASX: NUZ & NUZOA) ("Neurizon" or "the Company"), a clinical-stage biotech company dedicated to advancing innovative treatments for neurodegenerative diseases, is pleased to announce new preclinical data demonstrating significant neuroprotective effects of NUZ-001 and its active metabolite, NUZ-001 Sulfone, in a zebrafish model of Huntington's disease (HD). HD is a rare, inherited neurodegenerative disorder that causes progressive degeneration of motor function, cognition, and mental health.

In this disease model of HD, the targeted knockdown of the Htt (huntingtin) protein mRNA knockdown approach, triggers characteristic HD-related deficits, including increased cell death (acridine orange staining), morphological malformations, impaired haemoglobin production (Benzidine staining), and reduced expression of brain-derived neurotrophic factor (BDNF), a critical biomarker of neuronal function and survival. Treatment with NUZ-001 or NUZ-001 Sulfone following Htt knockdown prevented developmental and morphological abnormalities, attenuated neuronal cell death, restored the delayed production of haemoglobin, and rescued BDNF expression, providing evidence of their potential to counteract early neurodegenerative damage.

Dr. Michael Thurn, **Managing Director and Chief Executive Officer, commented:** "These results mark another important milestone in the realisation of the potential for NUZ-001 to treat a range of neurodegenerative diseases. HD is a devastating, rare genetic disorder that causes the progressive breakdown of nerve cells in the brain, leading to a range of symptoms including uncontrolled movements, cognitive decline, and emotional disturbances. HD affects between 2.7 and 4.8 per 100,000 people globally. There is no cure and no disease-modifying treatments, only treatments that manage symptoms. These exciting results demonstrate NUZ-001 has consistent neuroprotective effects beyond amyotrophic lateral sclerosis (ALS), strengthening our conviction in NUZ-001's potential as a disease-modifying platform therapy across a range of neurodegenerative conditions."

About the Zebrafish Disease Model

Wild-type zebrafish embryos were raised in standard conditions. Morpholino antisense oligonucleotides (MOs) targeting Htt were injected into one-cell stage embryos to decrease Htt expression. NUZ-001 or NUZ-001 Sulfone at 1 and 10 µM concentrations were added to the embryonic media 6 hours post-fertilisation to evaluate the protective effects of NUZ-001 and NUZ-001 Sulfone on Htt knockdown-induced deficits. Changes in morphology (eye size and hindbrain swelling), neuronal cell death (apoptosis), and the levels of BDNF expression were analysed 2 days post-fertilisation (See Figure 1).

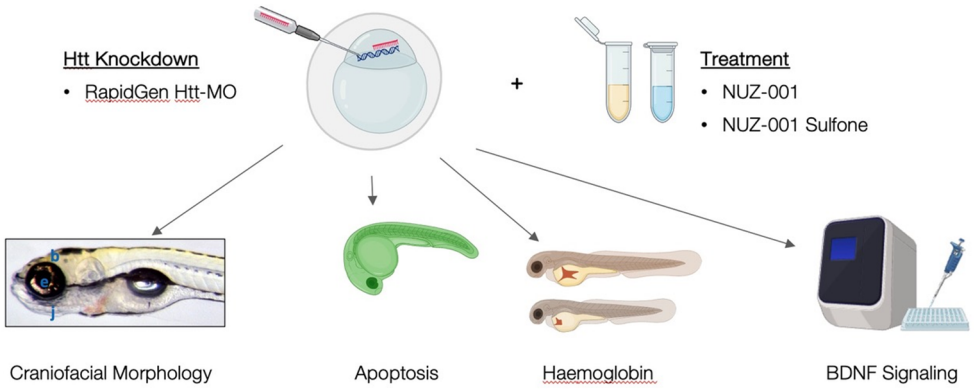

Figure 1: Htt knockdown and treatment procedure

Knockdown of Htt (Htt MO) resulted in zebrafish embryos with smaller eyes and swollen hindbrain ventricles (See Figure 2a; arrows indicate hindbrain and eye regions) compared to the control group (Control MO). Partial rescue of eye size was observed following treatment with 1 µM and 10 µM NUZ-001 and NUZ-001 Sulfone, with full reversal of hind brain swelling at 10 µM NUZ-001 and NUZ-001 Sulfone. (Figure 2b). At 2 dpf, neuronal cell death (Apoptosis; See Figure 3) was significantly higher in the Htt knockdown zebrafish embryos compared to the control group. Treatment with 1 µM and 10 µM NUZ-001, and 10 µM NUZ-001 Sulfone significantly reduced neuronal cell death. Haemoglobin levels (Benzidine staining; See Figure 4) were significantly decreased in the Htt knockdown group compared to controls, whereas treatment with 1 µM and 10 µM NUZ-001, and with 1 µM and 10 µM NUZ-001 Sulfone provided partial rescue. Expression of BDNF transcripts (See Figure 5) was significantly rescued following treatment with 10 µM NUZ-001 and 10 µM NUZ-001 Sulfone.

Figure 2a & b: Rescue of morphological abnormalities induced by *htt* knockdown

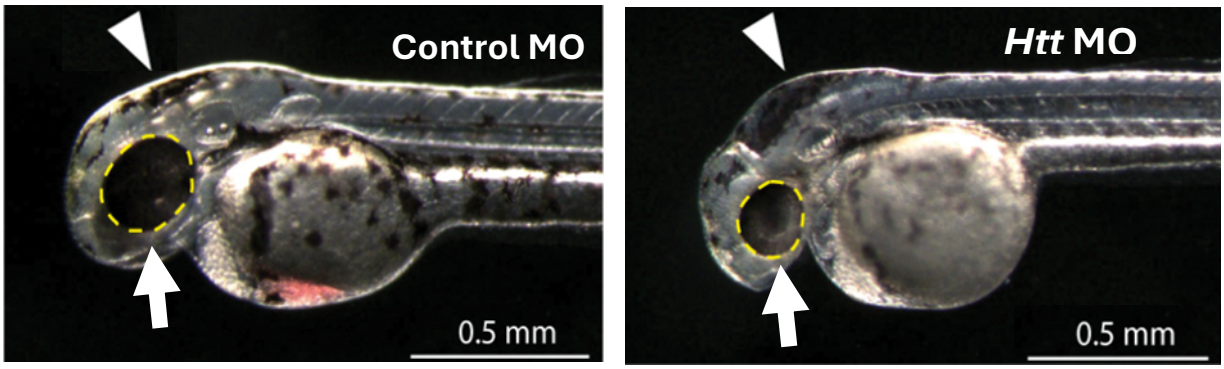

Figure 2a

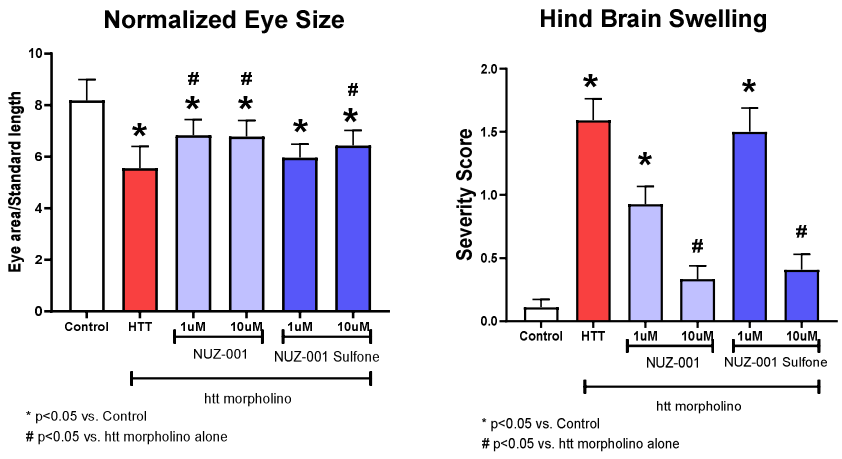

Figure 2b

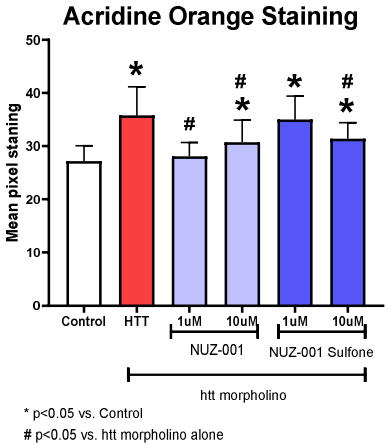

Figure 3: Reduction in neuronal cell death

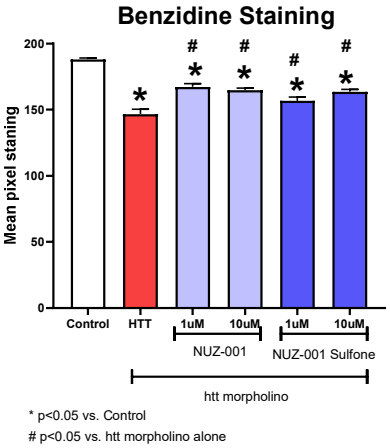

Figure 4: Partial rescue of haemoglobin levels

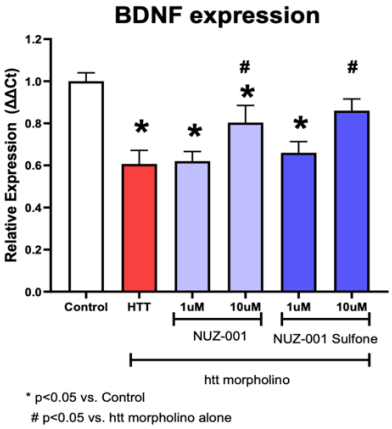

Figure 5: Rescue of BDNF levels

NUZ-001 is currently in clinical development for amyotrophic lateral sclerosis (ALS), where it has shown preclinical efficacy in enhancing proteostasis, reducing pathological protein aggregation, and preserving neuronal function. The new findings in the HD model further underscore NUZ-001's potential as a platform therapy that targets fundamental cellular stress and clearance mechanisms common to multiple neurodegenerative diseases.

Neurizon plans to advance additional preclinical studies in mammalian models of Huntington's disease as part of its broader strategy to expand the therapeutic applications of NUZ-001 into other progressive neurological disorders with high unmet need.

About Huntington's Disease

Huntington's disease (HD) is a rare, inherited (genetic) neurodegenerative disorder that causes progressive degeneration of motor function, cognition, and mental health. It is caused by a CAG trinucleotide repeat expansion in the Htt gene, leading to the production of a mutant huntingtin protein (mHtt) with an abnormally long polyglutamine (polyQ) tract. This mutant protein misfolds and forms toxic aggregates in neurons, particularly in the striatum and cortex, disrupting cellular functions such as gene transcription, protein degradation, and mitochondrial activity. Over time, these aggregates contribute to neuronal dysfunction and death, resulting in the hallmark symptoms of chorea (involuntary movements), cognitive decline, and behavioural disturbances.

HD is most often diagnosed between the ages of 30 and 50, but it can also occur earlier, including in children and adolescents (a form known as juvenile-onset Huntington's disease (JHD)). The condition typically progresses over 15 to 20 years, during which individuals experience a gradual decline in their ability to work, communicate, manage daily activities, and maintain independence.

At present, there are no approved therapies that modify the underlying progression of HD. Current treatment approaches focus on symptom management. Chorea may be treated with dopamine-depleting agents, while psychiatric symptoms are typically managed with antidepressants or antipsychotics. However, these treatments do not alter the course of the disease.

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This announcement has been authorized for release by the Board of Neurizon Therapeutics Limited.

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About Neurizon Therapeutics Limited

Neurizon Therapeutics Limited (ASX: NUZ) is a clinical-stage biotechnology company dedicated to advancing treatments for neurodegenerative diseases. Neurizon is developing its lead drug candidate, NUZ-001, for the treatment of ALS, which is the most common form of motor neurone disease. Neurizon's strategy is to accelerate access to effective ALS treatments for patients while exploring NUZ-001's potential for broader neurodegenerative applications. Through international collaborations and rigorous clinical programs, Neurizon is dedicated to creating new horizons for patients and families impacted by complex neural disorders.

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