Neurizon Therapeutics Limited
ABN 35 094 006 023
www.neurizon.com

Verification of Significant Blood-Brain Barrier Penetration of NUZ-001

Highlights:

- **High levels of NUZ-001 and its major active metabolite NUZ-001 Sulfone cross the blood-brain barrier in a rodent PK study**
- **In a repeat of the TDP-43 aggregation assay designed to extend the dose-response curve, both compounds significantly prevented the aggregation of TDP-43 in a patient-derived iPSC neuronal model of ALS at all concentrations tested**
- **CNS concentrations achieved overlapped with the concentrations shown to reverse TDP-43 aggregation**
- **The new results emphasise the capacity to reach target-relevant CNS exposure, supporting the therapeutic potential for ALS and other TDP-43 proteinopathies.**

20 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 rodent preclinical pharmacokinetic (PK) data demonstrating that NUZ-001 and its major active metabolite, NUZ-001 Sulfone, effectively cross the blood-brain barrier (BBB) and achieve brain concentrations consistent with those shown to reverse pathological TAR DNA-binding protein 43 (TDP-43) aggregation in patient-derived induced pluripotent stem cells (iPSC).

The ability of therapeutics to access the central nervous system (CNS) remains a major barrier in the treatment of neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS). This crucial aspect, in addition to delivering therapeutically relevant amounts to the CNS, is vital for their success. These new results highlight the ability to achieve target-relevant CNS exposure and mark a pivotal moment in validating the potential of NUZ-001 to act directly on disease-driving mechanisms within the brain. This not only reinforces the encouraging efficacy results seen in Neurizon's Phase 1 MEND study in ALS with NUZ-001, but also supports broader applications across TDP-43-proteinopathies, including frontotemporal dementia (FTD), Alzheimer's disease (AD), and limbic predominant age-related TDP-43 encephalopathy (LATE).

Dr Michael Thurn, Managing Director and Chief Executive Officer, commented: "These excellent results provide compelling evidence that NUZ-001 and its Sulfone metabolite not only effectively penetrate the BBB but do so at concentrations that are proven to reverse pathological TDP-43 aggregation in vitro. This new data provides strong translational validation for our mechanism and reinforces the potential of NUZ-001 as a transformative disease-modifying therapy for ALS. With these findings, we are more determined than ever to deliver a therapy that precisely targets the underlying pathology driving this devastating disease, supporting the accelerated advancement of NUZ-001."

Blood-Brain Barrier Penetration

In a rodent PK study, a single administration of NUZ-001 resulted in brain concentrations ranging from 285 to 1,300 nM across dose groups (Maximum brain levels for NUZ-001: 135 ng/g @ 3 mg/kg (285 nM), 335 ng/g @ 10 mg/kg (708 nM) and 616 ng/g @ 50 mg/kg (1,300 nM) with an average brain to plasma ratio of 0.47 across dose levels. NUZ-001 Sulfone reached brain levels of 177 to 1,231 nM (Maximum brain levels for NUZ-001 Sulfone: 89 ng/g @ 3 mg/kg (177 nM), 312 ng/g @ 10 mg/kg (617 nM) and 622 ng/g @ 50 mg/kg (1,231 nM) with an average brain to plasma ratio of 0.13 across dose groups (Figures 1 and 2).

TDP-43 Aggregation Assay

The ability of NUZ-001 and NUZ-001 Sulfone to reduce TDP-43 aggregation in M337V Motor Neurons co-cultured with astrocytes was evaluated in response to a proteasomal stressor (MG-132). TDP-43 is a known driver of ALS pathology. The results (Figure 3) show that NUZ-001 and NUZ-001 Sulfone significantly prevented ($p = <0.05$) the aggregation of TDP-43 in M337V Motor Neurons treated simultaneously with the proteasomal stressor at all concentrations tested (270–4,400 nM).

These findings represent results from a repeat assay designed to extend the dose-response curve from our initial results reported for TDP-43 aggregation late last year (See ASX announcement dated November 15, 2024). The

effective concentration (270 nM) for both compounds to significantly reverse TDP-43 aggregation in the patient-derived iPSC neuronal model of ALS overlaps with the concentrations achieved in the rodent PK study.

Notably, these levels were achieved through peripheral administration of NUZ-001, with brain exposure confirmed for both NUZ-001 and NUZ-001 Sulfone. This supports their potential to exert disease-modifying effects directly within the CNS.

Figure 1

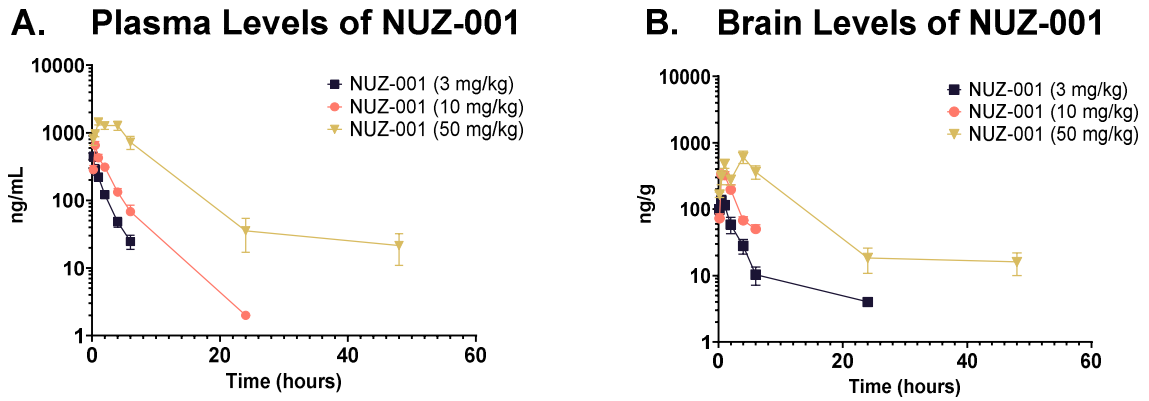


Figure 2

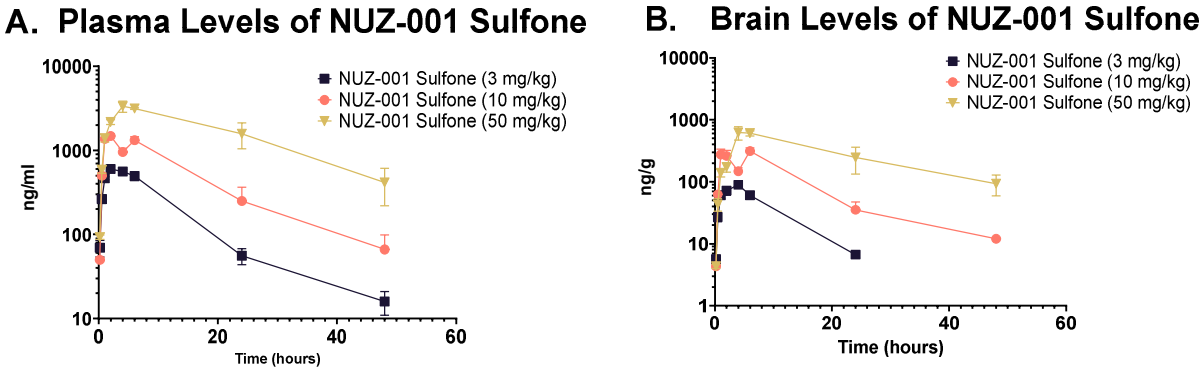
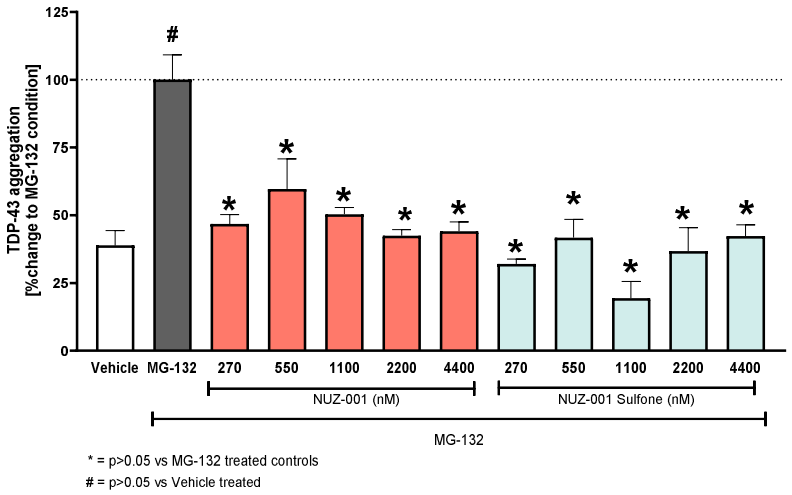


Figure 3



About TDP-43

TDP-43 protein aggregation is common in several neurodegenerative diseases, including ALS, frontotemporal dementia (FTD), Alzheimer's disease (AD), and limbic predominant age-related TDP-43 encephalopathy (LATE). In ALS, cytoplasmic accumulation of TDP-43 disrupts cellular processes, leading to motor neuron dysfunction and degeneration. By targeting TDP-43 pathology, NUZ-001 offers a new approach to mitigating ALS progression and highlights the potential for expanded applications in other neurodegenerative diseases.

-ENDS-

This announcement has been authorized for release by the Board of Neurizon Therapeutics Limited.
For further information, please contact:

Dr. Michael Thurn
Managing Director and Chief Executive Officer
Neurizon Therapeutics Limited
enquiries@neurizon.com
+61 (3) 9692 7222

Lidija Damjanovic
Head of Marketing and Corporate Affairs
Neurizon Therapeutics Limited
lidija@neurizon.com
+61 (0) 425 700 504

Released through: Henry Jordan, Six Degrees Investor Relations, +61 (0) 431 271 538

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 the potential of NUZ-001 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.

Neurizon Investor Hub

We encourage you to utilise our Investor Hub for any enquiries regarding this announcement or other aspects concerning Neurizon.
This platform offers an opportunity to submit questions, share comments, and view video summaries of key announcements.

To access Neurizon Investor Hub please scan the QR code or visit
https://investorhub.neurizon.com