

## Neurizon to Present at 4<sup>th</sup> Annual ALS Drug Development Summit

**14 May 2025 – Melbourne, Australia:** Neurizon® Therapeutics Limited (ASX: NUZ & NUZOA) (“Neurizon” or “the Company”), a clinical-stage biotech company advancing treatments for neurodegenerative diseases, is pleased to announce that the Company’s Managing Director and Chief Executive Officer, Dr. Michael Thurn, will present at the **4<sup>th</sup> Annual ALS Drug Development Summit 2025** on Day 2, 14 May, in Boston, USA.

The ALS Drug Development Summit is a leading global forum that brings together pharmaceutical and biotech leaders, academic researchers, clinicians, and patient advocates to accelerate the development of effective treatments for amyotrophic lateral sclerosis (ALS). Neurizon’s participation underscores its commitment to advancing NUZ-001 as a potential disease-modifying therapy for ALS and related TDP-43 proteinopathies.

The presentation, titled "**Preclinical & Early Clinical Development of NUZ-001: A Novel mTOR Inhibitor Demonstrating Potential as a Therapeutic Agent for Amyotrophic Lateral Sclerosis.**" Will highlight key findings from both preclinical and early clinical studies, including:

- The global need for therapies that can simultaneously target TDP-43 pathology and restore STMN2, addressing two critical drivers of ALS progression.
- The latest research on NUZ-001, a novel small-molecule mTOR inhibitor, being investigated for its multi-targeted mechanism of action, including the reduction of TDP-43 aggregation, restoration of STMN2 expression, and enhancement of autophagy, a key protein clearance pathway.
- Positive preclinical results in human iPSC-derived motor neuron models of ALS, demonstrating that NUZ-001:
  - Significantly decreased cytoplasmic TDP-43 aggregation
  - Increased STMN2 protein levels
  - Activated autophagy (indicated by p62 accumulation and LC3 vesicle formation)
  - Delivered functional neuroprotective effects, including enhanced neurite outgrowth and preserved motor neuron function
- Preliminary results from Neurizon’s Phase 1 clinical trial in patients with ALS, confirming that NUZ-001 is well tolerated, with a favourable safety profile and pharmacokinetics, alongside early indications of efficacy and biomarker modulation, supporting continued clinical development as a potential disease-modifying therapy.

Presentation slides are available as an attachment to this announcement.

-ENDS-

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.

### 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.

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## 4th Annual ALS Drug Development Summit

**Preclinical and Early Clinical Development of NUZ-001:  
A Novel mTOR Inhibitor Demonstrating Potential as a  
Therapeutic Agent for Amyotrophic Lateral Sclerosis**

**Dr Michael Thurn  
Managing Director and Chief Executive Officer**

**14 MAY 2025  
ASX: NUZ**



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Our mission is to lead the development of neurodegenerative treatments towards a promising new horizon for patients



# Amyotrophic Lateral Sclerosis

## Urgent need for life-changing therapies

Neurodegenerative disorder that primarily affects motor neurons, typically fatal within 2-5 years of symptom onset, with currently no disease modifying therapeutics on the market.

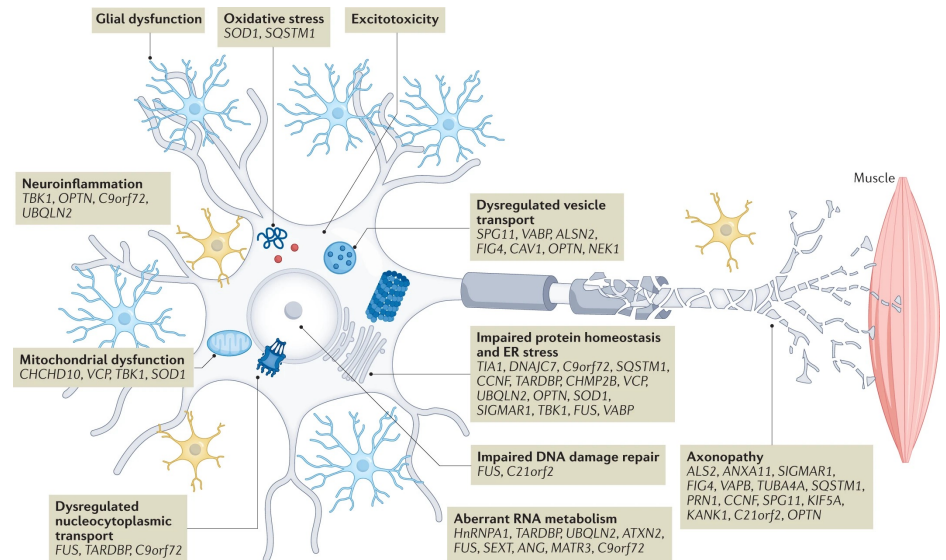
This is in part due to the complexity of the disorder, both on a clinical and molecular level.

### Disease Biology

Various cell types contribute to ALS pathogenesis and progression, such as:

- Motor neurons (MNs)
- Astrocytes
- Oligodendrocytes
- Microglia

At a molecular level in ~97% of ALS cases TDP-43 protein aggregates are identified, indicating its relevance to ALS disease



**From:** Mead, R.J., Shan, N., Reiser, H.J. *et al.* Amyotrophic lateral sclerosis: a neurodegenerative disorder poised for successful therapeutic translation. *Nat Rev Drug Discov* **22**, 185–212 (2023). <https://doi.org/10.1038/s41573-022-00612-2>

# Product candidates for neurodegenerative diseases



## Rediscovering Monepantel

Monepantel an approved veterinary product – NUZ-001 – anthelmintic for sheep



## Strong IP Position

Strong intellectual property with 6 patent families and protection beyond 2039



## Neurodegenerative Diseases

Current evidence points to exploiting autophagy as a hunter for toxic aggregates, a common pathology in neurodegenerative diseases



## Pipeline Synergies

Pipeline synergies to leverage commercial infrastructure across development programs



## Motor Neurone Disease

Lead clinical program for the treatment of motor neurone disease/ Amyotrophic Lateral Sclerosis (MND/ALS)

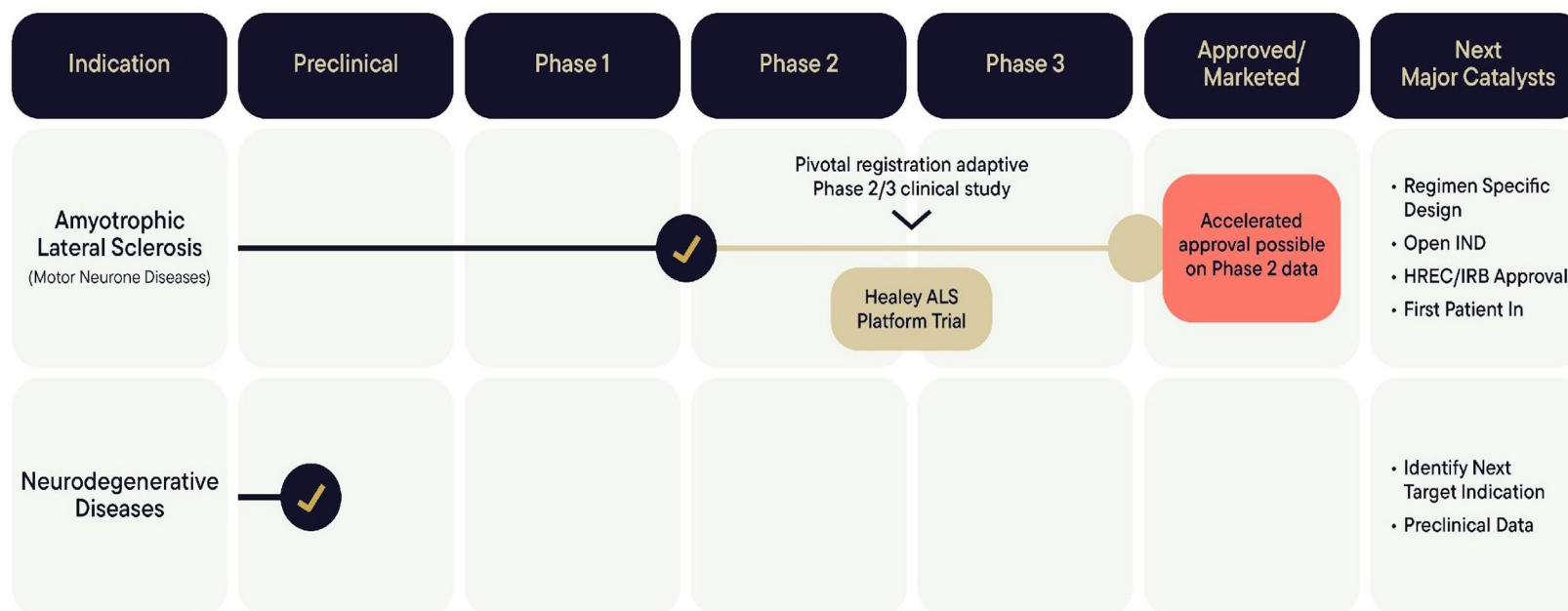


## Experienced Management

Experienced world-class Board and management team

# Pipeline

## Multiple synergistic product opportunities in neurodegenerative disease for NUZ-001



- Single pivotal registration clinical study for ALS
- Targeting accelerated approval from Phase 2 data
- Selected into the HEALEY ALS Platform Trial reduces study cost and time, and increases patient participation rate

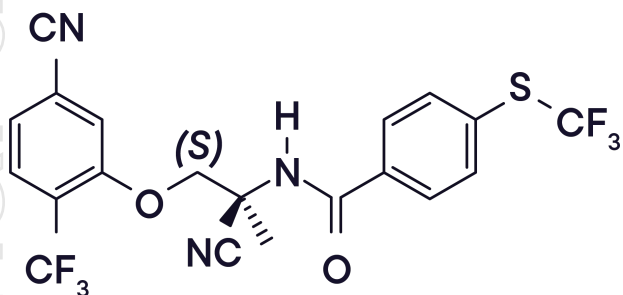
# NUZ-001 ((S)-monepantel)

## Active Substance, Pharmacological Class, History

**Name:** | NUZ-001 ((S)-monepantel)  
**CAS No.:** | 887148-69-8

**Pharmacological Class:**  
mTOR inhibitor

NUZ-001 (S)-enantiomer



### Chemical Name

N-((1S)-1-Cyano-2-(5-cyano-2-trifluoromethyl-phenoxy)-1-methyl-ethyl)-4-trifluoromethylsulfanyl-benzamide

### Structural Formula

(S)-monepantel enantiomer is used in the Drug Product for treatment of ALS

### History

NUZ-001 was previously developed as the veterinary drug (Zolvix®), and has been approved since 2009 in Australia, New Zealand, and 36 other countries as an oral broad spectrum anthelmintic for the treatment of gastrointestinal roundworms in sheep. Nematode-specific positive allosteric modulator of DEG-3/DES-2 type nicotinic acetylcholine receptors (nAChRs).

# Preclinical Data

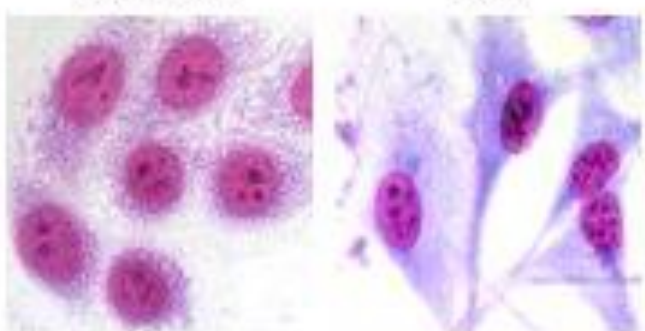
## NUZ-001 Induces Autophagy

NUZ-001 causes a clear development of intracytoplasmic cavities

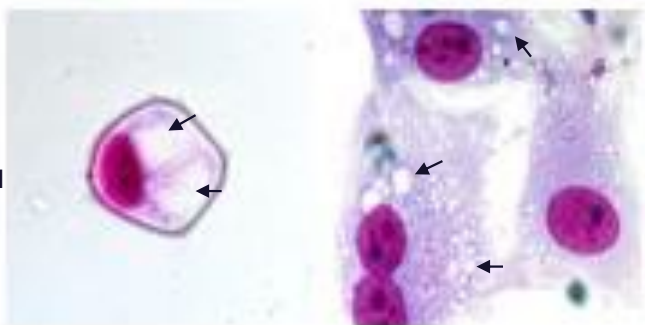
### Methods

- A2780 ovarian tumor cells, U87-MG glioma cells, and HOSE (ovarian surface epithelial) cells were examined after 72 hours of NUZ-001 treatment.
- Cavities were identified as lysosomal autophagic vacuoles using acridine orange staining.

Control



Monepantel  
(25  $\mu$ M)



A2780 ovarian  
cancer cells

U87-MG glioma  
cells

Arrows depict autophagolysosomes (small lysosomal sacs or vacuoles that breaks down the cellular debris in cells during the process of autophagy)

### Results

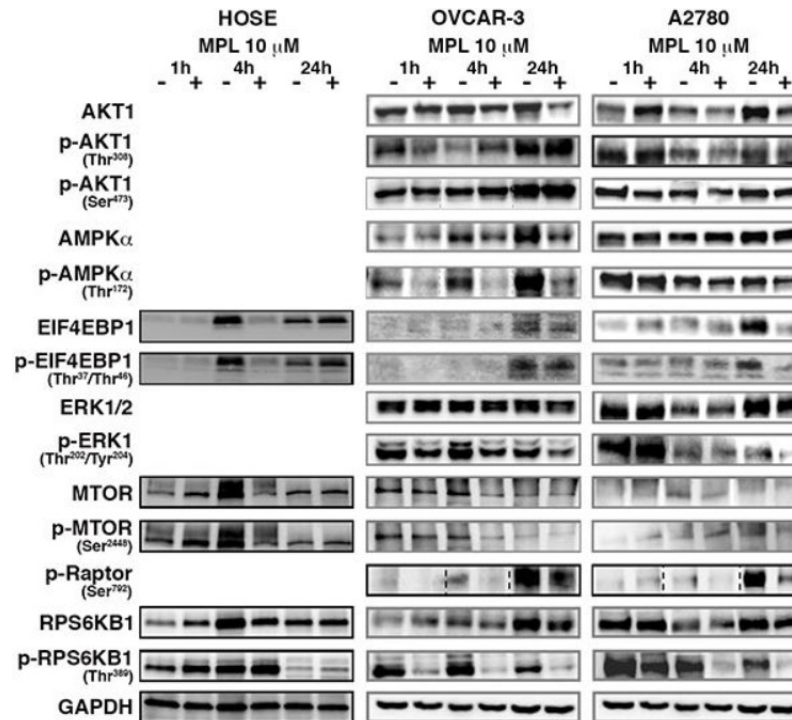
- **U87-MG cells: 20-fold increase at 72 hours**
- **A2780 cells: 100-fold increase at 72 hours**
- HOSE control cells: earlier increase (20-fold at 48 hours) that was no longer seen at 72 hours (conclusion: adaptation to culture conditions).

# Preclinical Data:

## NUZ-001 Impacts Phosphorylation Status of Autophagy-Associated Proteins

### Methods

- Components of the PI3K/AKT/MTOR and (RAF)-MEK-ERK signaling pathways were investigated to determine changes in protein levels or phosphorylation status following NUZ-001 treatment.
- HOSE cells were controls as well as GAPDH protein.

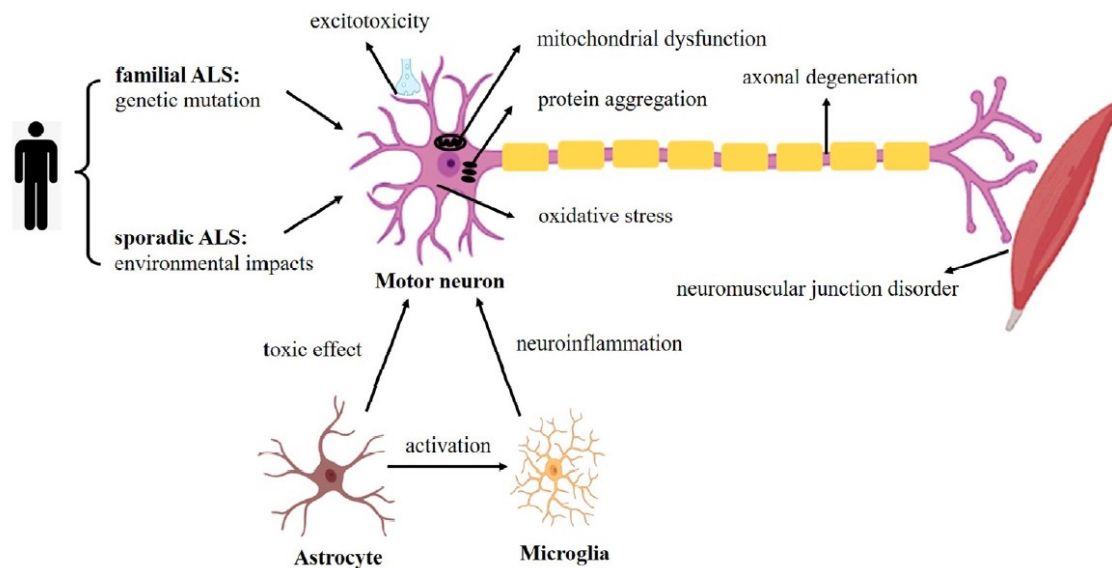


### Results

- NUZ-001 reduces RPS6KB1 and ERK1/2 protein phosphorylation, which are associated with increased autophagy
- Decreases RAPTOR phosphorylation, which is associated with inhibition of MTOR Complex I signalling and induction of autophagy

# ALS Preclinical Model

## Induced Pluripotent Stem Cells




- Induced pluripotent stem cells (iPSCs) have advanced the modelling of amyotrophic lateral sclerosis (ALS).
- iPSCs generate disease-related cell types with the **same genetic background** as ALS patients in nearly **unlimited quantities**.
- This allows effective in vitro **study of disease mechanisms**.

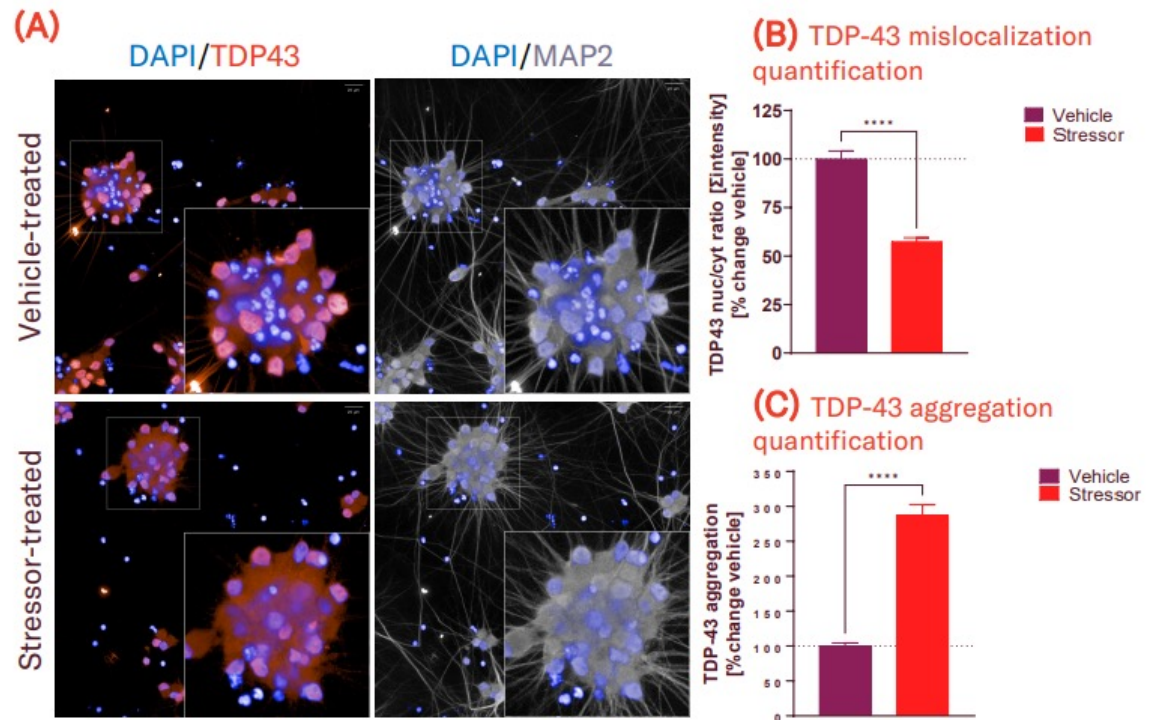
Du, H.; Huo, Z.; Chen, Y.; Zhao, Z.; Meng, F.; Wang, X.; Liu, S.; Zhang, H.; Zhou, F.; Liu, J.; et al. Induced Pluripotent Stem Cells and Their Applications in Amyotrophic Lateral Sclerosis. *Cells* **2023**, *12*, 971. <https://doi.org/10.3390/cells12060971>

# ALS Preclinical Model

## Induced Pluripotent Stem Cells

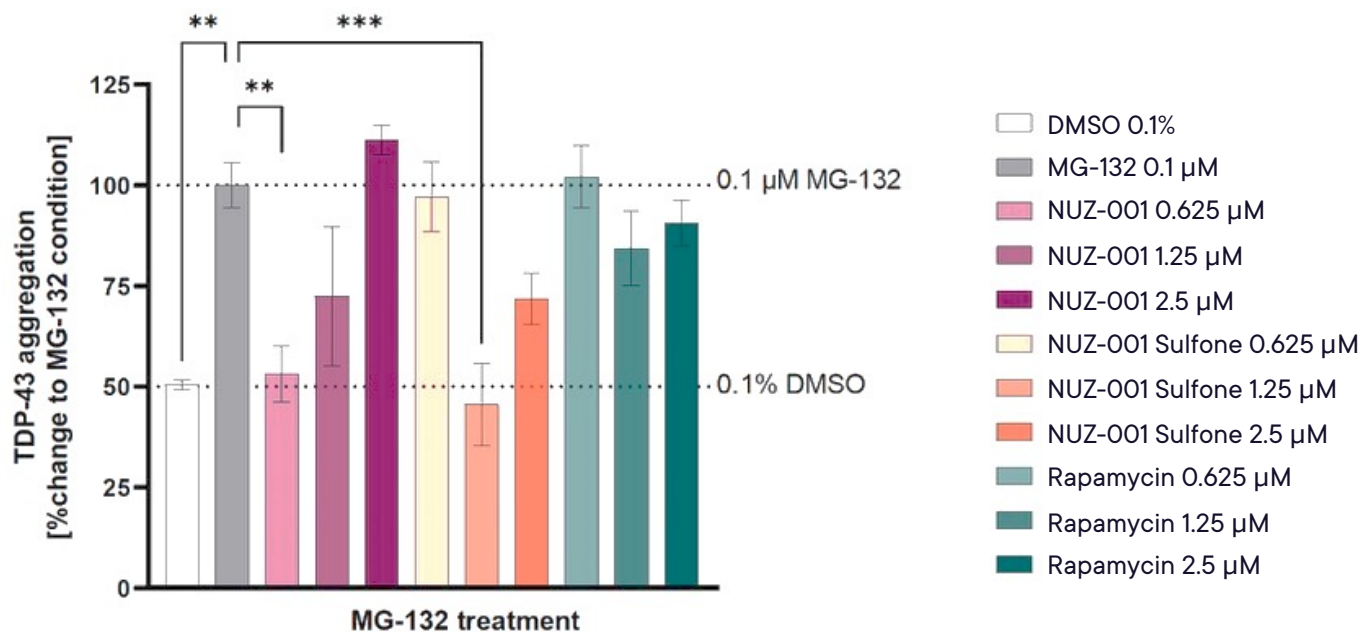
READOUT	TECHNOLOGY
TDP-43 mislocalization	High Content Imaging
<b>TDP-43 aggregation</b>	<b>HTRF</b>
STMN2 mis-splicing	qPCR
Neurite growth	High Content Imaging
Proteasomal activity	
NF-L release	MSD
Cytokine Release	
<b>Electrophysiology</b>	<b>MEA</b>

 Ncardia \* iCell® Motor Neurons 01279 from FUJIFILM Cellular Dynamics, Inc



(A) HCI images (40x) of vehicle-treated compared to stressor-treated TDP-43 M337V Motor Neurons. Immunoreactivity to DAPI in blue, TDP-43 in red and MAP2 in grey. Zoom-in of relevant structures in bottom-right.

# ALS Preclinical Model: HTRF TDP-43 Aggregation Assay



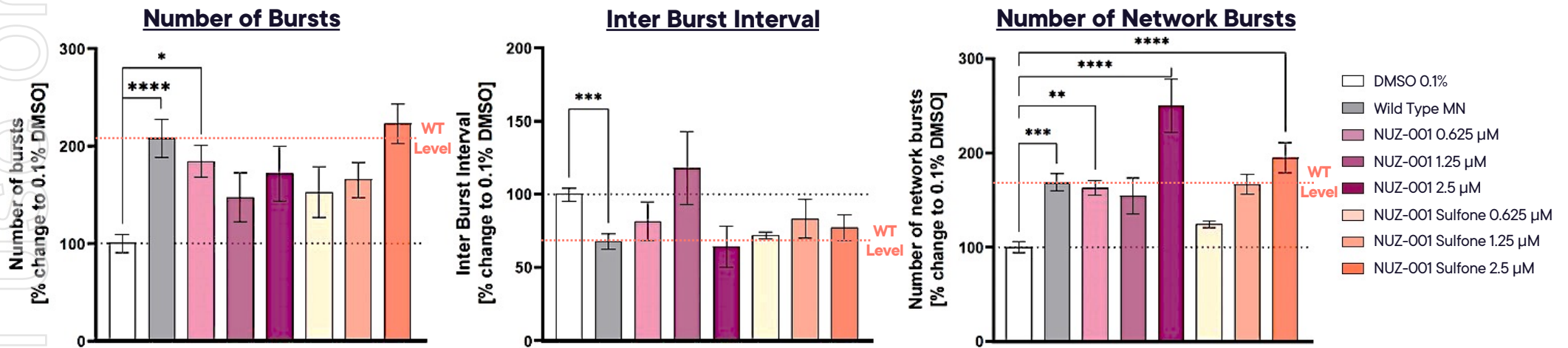
## Methods

- Co-cultures of TDP-43 M337V Motor Neurons with astrocytes were treated with aggregation stressor (MG-132) and compounds for 7 days (from day 14 to day 21) at every medium change.
- At day 21 lysates were prepared from cultures and TDP-43 aggregation kit supplier's (Revity) recommendations were followed to perform the assay.

**Dose-dependent effect of treatment was observed on TDP-43 aggregate reduction for:**

- NUZ-001 at 0.625 μM (50% reduction) and 1.25 μM (25% reduction)
- NUZ-001 Sulfone at 1.25 μM (statistically significant; 65% reduction) and 2.5 μM (25% reduction)
- Rapamycin at 3 μM (20% reduction)

# ALS Preclinical Model: Multi-electrode Assay Activity



NUZ-001 and NUZ-001 Sulfone significantly improved the ALS TDP-43 M337V associated phenotype/MEA

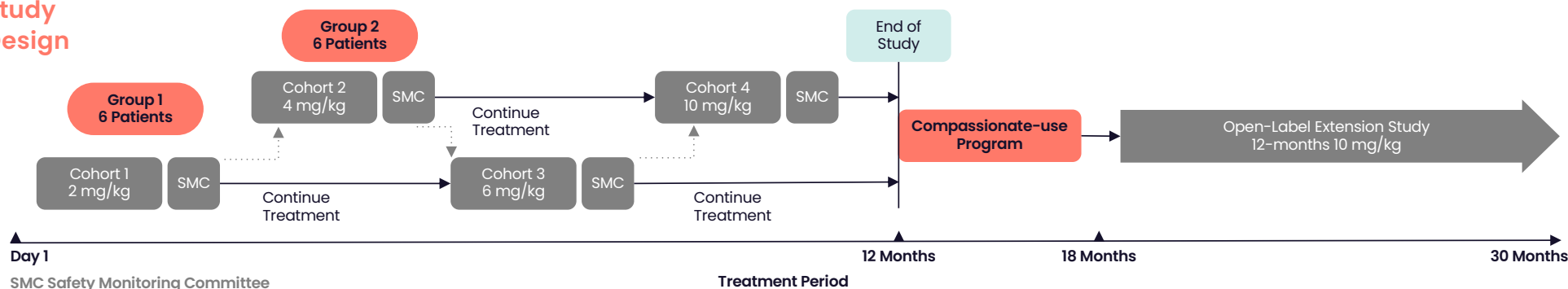
- increasing bursting (NUZ-001 0.625 μM  $p < 0.05$ )
- Increasing network burst activity (NUZ-001 0.625 μM  $p < 0.0005$ ; NUZ-001 2.5 μM  $p < 0.0005$  and NUZ-001 Sulfone 2.5 μM  $p < 0.00005$ )
- decreasing inter-burst interval at day 18 (corresponding to 4 days of treatment with NUZ-001)

# Phase 1

## ALS MEND Study

The Phase 1 MEND Study was an open label, multicentre study involving 12 patients with ALS with the goal of determining the recommended Phase 2/3 dose based on safety and preliminary efficacy

### Study Design



### Study Update



- Positive top-line data released in Q1 CY24
- 12 patients continued treatment with NUZ-001 under a compassionate-use program
- 10 patients have rolled-over into 12-month Open-Label Extension (OLE) Study
- Treatment continues to be very well-tolerated
- First group of patients are entering their 32nd month of continuous treatment with NUZ-001
- OLE Top-line results due Q3 CY25
- Phase 1 and baseline OLE data used to design pivotal registration adaptive Phase 2/3 Study, to commence in 2H CY25

# Phase 1

## ALS MEND Study Design



### Patient Population: 11 Men, 1 Woman

- Adults with Familial or Sporadic ALS/MND
- 1<sup>st</sup> symptoms occurred < 3 years prior to screening
- Adequate bone marrow reserve, renal & liver function
- Seated Slow Vital Capacity ≥ 50% of predicted value
- **Median Age: 63.5 (42–78) years**



### Intervention: 12 patients randomised

- Open label, 24 hour escalating single dose PK study, followed by 4-week repeated escalating dose study  
Treatment continued until dose escalation or End of Dosing
- **Cohort 1: 2 and 6 mg/kg/day dose levels**
  - **Cohort 2: 4 and 10 mg/kg/day dose levels**



### Primary & Exploratory Outcomes:

- Safety and tolerability
- Pharmacokinetic (NUZ-001 and its metabolite NUZ-001 sulfone in plasma and CSF) and pharmacodynamic (p-RPS6KB1 and p-EIF4EBP1 peripheral blood mononuclear cells)
- ALS Functional Rating Scale–Revised, ALS Quality of Life Questionnaire, Edinburgh Cognitive and Behavioural ALS Screen, slow vital capacity and biomarkers (serum neurofilament /light chain, CSF neurofilament/light chain and urinary p75 levels)



### Study Objectives:

- Tolerability and safety of NUZ-001 with a goal of defining a maximally tolerated dose (MTD)
- Pharmacokinetics of NUZ-001 and its metabolite NUZ-001 sulfone in plasma and cerebrospinal fluid (CSF)
- Preliminary efficacy (ALSFRS-R)



### Locations:

#### Two Centres in Australia

- Calvary Hospital Bethlehem, Melbourne
- Macquarie University, Sydney

# Phase 1

## ALS MEND: Demographics, Baseline Characteristics, ALS History, and Treatment Duration

- Most patients were male (91.7%)
- Median age was 63.5 years
- The most common site for the 1st disease onset was the Upper Limb region (58%)
- ALS diagnosis was considered Probable (58.3%) in most cases
- Median ALS duration (Time Since Symptom Onset) was 14.3 months
- Median Baseline ALSFRS-R was 39.5
- Median Pre-Baseline ALSFRS-R Slope was 0.74 p/mth
- Median Treatment Duration was:
  - Dose Level 1: 32.4 weeks
  - Dose Level 2: 22.6 weeks
  - Dose Level 3: 16.7 weeks
  - Dose Level 4: 8.1 weeks

Gender, n (%)	
Female	1 (8.3)
Male	11 (91.7)
Age (years)	
Mean (SD)	61.9 (10.90)
Median (Min, Max)	63.5 (42,78)
Site of First Disease Onset, n (%)	
Lower Limb	2 (16.7)
Upper Limb	7 (58.3)
Limb Onset	1 (8.3)
Bulbar	2 (16.7)
ALS Diagnosis, n (%)	
Definite	5 (41.7)
Probable	7 (58.3)
Time since Onset (Months)	
Mean (SD)	14.7 (8.38)
Median (Min, Max)	14.3 (3.65, 34.0)

Baseline ALSFRS-R	
Mean (SD)	38.2 (5.10)
Median (Min, Max)	39.5 (28, 44)
Pre-Baseline Slope	
Mean (SD)	0.826 (0.461)
Median (Min, Max)	0.739 (0.210, 1.48)
Treatment Duration (weeks)	
Dose Level 1, Mean (SD)	28.1 (9.41)
Dose Level 1, Median (Min, Max)	32.40 (8.1, 34.1)
Dose Level 2, Mean (SD)	22.8 (2.86)
Dose Level 2, Median (Min, Max)	22.60 (20.1, 26.3)
Dose Level 3, Mean (SD)	17.0 (1.70)
Dose Level 3, Median (Min, Max)	16.70 (15.1, 20.1)
Dose Level 4, Mean (SD)	8.2 (0.13)
Dose Level 4, Median (Min, Max)	8.10 (8.1, 8.4)

# Phase 1

## Safety and Tolerability Summary

No deaths, no Serious Adverse Events related to treatment and a very low incidence of Adverse Events

	Incidence of Adverse Event (n)				Total
	Dose 1 (2 mg/kg)	Dose 2 (4 mg/kg)	Dose 3 (6 mg/kg)	Dose 4 (10 mg/kg)	
Adverse Events	29	6	12	9	56
Related to Treatment	2	1	-	-	3

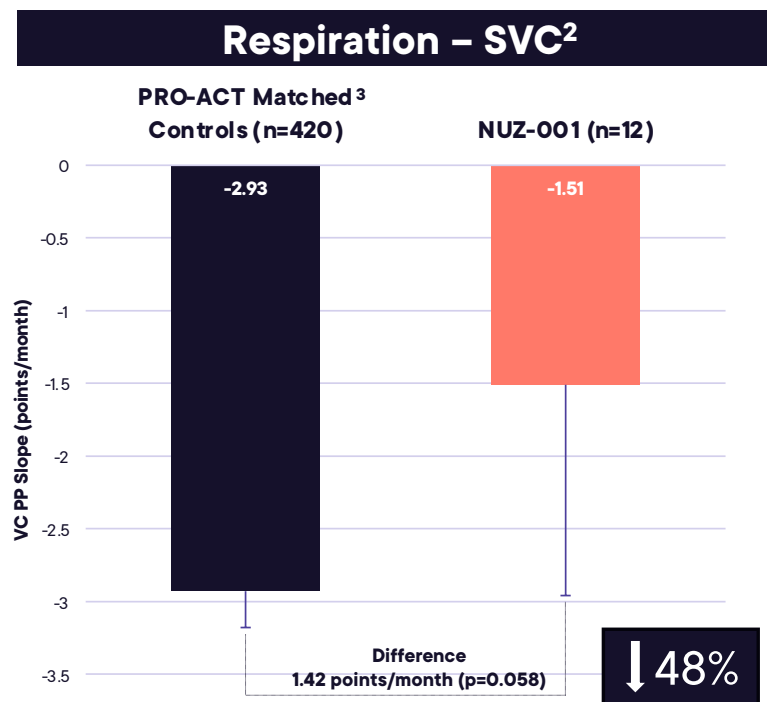
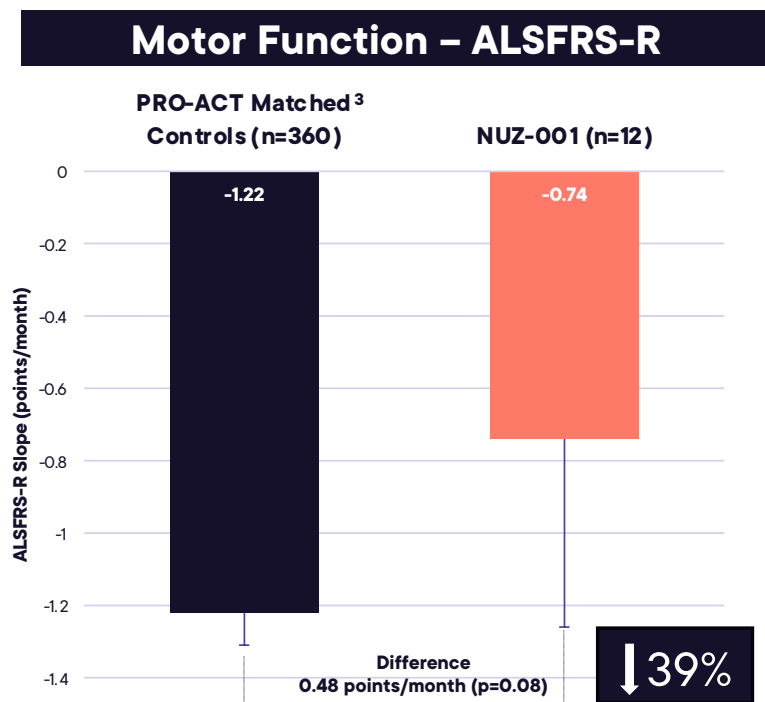
- **Only 3 Adverse Events (mild in severity) possibly related to treatment**
  - Raised liver enzymes
  - Increased hair growth
  - Constipation
- **No deaths**
- **No patients withdrew or were discontinued from the study**
- **One Serious Adverse Events (SAEs) reported that was unrelated to treatment**
  - 1 patient (Dose Level 3-6 mg/kg)
  - Hospitalised for Intestinal dilatation and Pneumonia



# Phase 1

## Preliminary Efficacy ALSFRS-R and SVC

Treatment with NUZ-001 for up to 12 months slowed the progression of ALS in all 12 patients by 39% for ALSFRS-R and 48% for SVC when compared to matched controls from the PRO-ACT historical database<sup>1</sup>



1. Atassi N, Berry J, Shui A, Zach N, Sherman A, Sinani E, Walker J, Katsovskiy I, Schoenfeld D, Cudkovicz M, Leitner M. The PRO-ACT database: design, initial analyses, and predictive features. *Neurology*. 2014 Nov 4;83(19):1719-25. doi: 10.1212/WNL.0000000000000951.Epub 2014 Oct 8. PMID: 25298304; PMCID: PMC4239834

2. Forced vital capacity (FVC) was used when SVC was not collected

3. Matched on time since onset, baseline ALSFRS-R, pre-baseline slope, and disease onset location

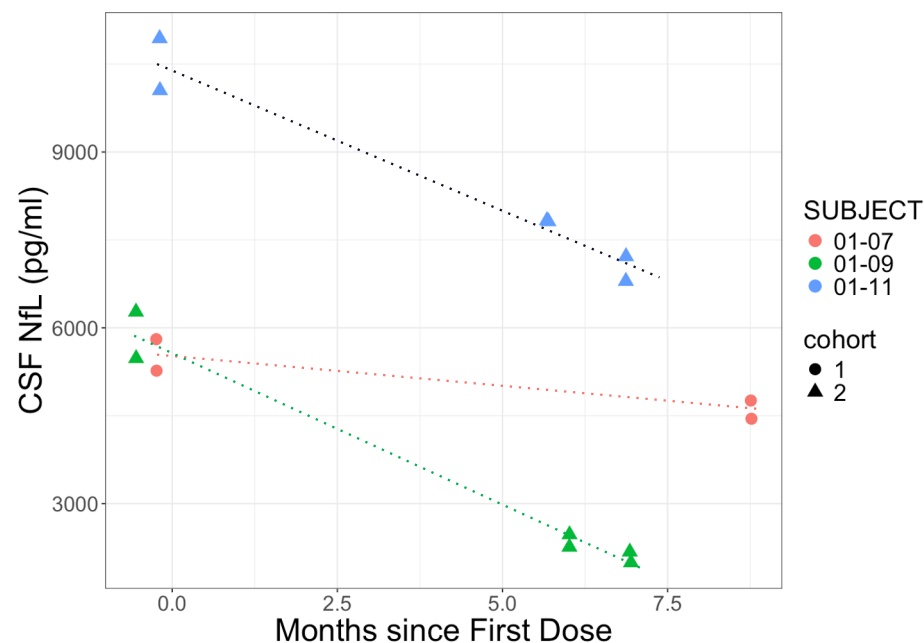
# Phase 1

## Exploratory Biomarkers Assessment

Neurofilament levels correlate with disease progression rate in ALS and higher levels of neurofilament are associated with faster/greater decline of ALSFRS-R over time<sup>1</sup>

- Marked decreased NfL cerebrospinal fluid levels in 3 patients
- Decline of 6.9% (14.0 %, 0.9%) per month in CSF NfL levels
- Predose values ranged from 5540.53 to 10500.13 pg/mL and had decreased at Day 29 of their second Dose Level for All Subjects (reduction ranged from 17.0 to 64.5%)
- Although limited data, the CSF NfL data is encouraging
- NfL samples continue to be collected in the OLE study with results due in H2 CY24

Change in CSF NfL Levels



# Phase 1

## Conclusion

Phase 1 study results showed that NUZ-001 has an excellent safety profile and the ability to slow the progression of ALS

### Highlights



#### Primary Objectives

- Excellent safety and tolerability profile



#### Preliminary efficacy data

- Favourable comparison to historical matched controls from PRO-ACT database



#### Blood Brain Barrier

- NUZ-001 and its active metabolite, NUZ-001 Sulfone, detectable in cerebrospinal fluid



#### Survival

- All patients completed the study and continued to receive NUZ-001 under compassionate use



#### Phase 2/3 Dose

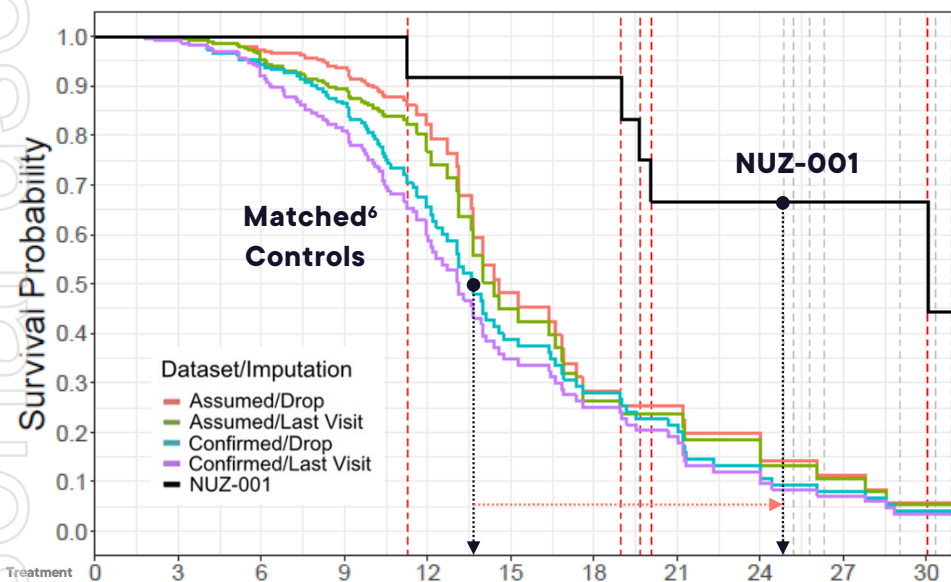
- Optimal dose selected for pivotal Phase 2/3 clinical study

# Phase 1

## ALS Open Label Extension Study

Compared to matched controls from the PRO-ACT Historical Database<sup>1</sup>, treatment with NUZ-001 results in a significantly ( $\chi^2=14.1, p=0.00017$ ) longer survival of patients with ALS reducing the risk of death by 78.5%

### Overall Survival Probability



### Survival Statistics

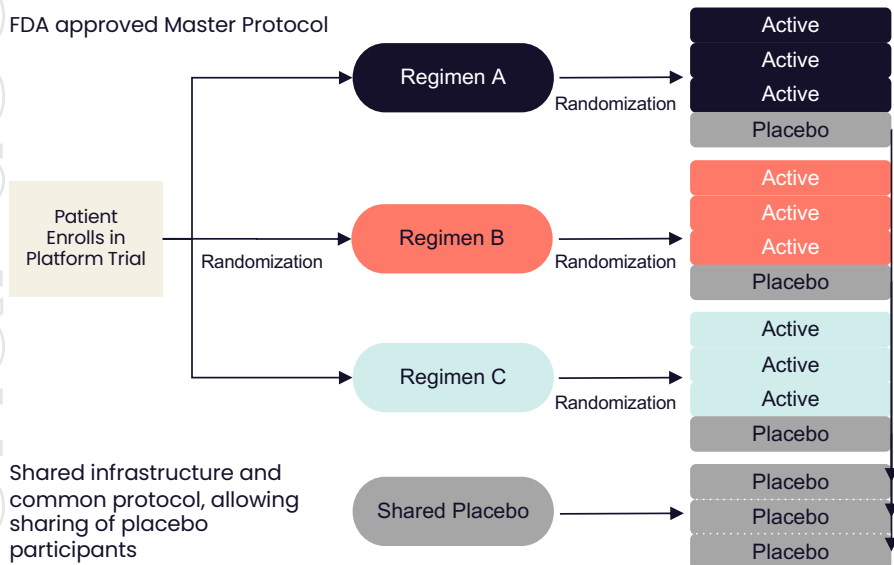
- Median survival ~2 years from diagnosis<sup>2</sup>
- 20% live 5 years or more, and up to 10% survive for more than 10 years<sup>3</sup>
- Time to diagnosis on average is 12 months in the US<sup>4</sup>
- Population-based prospective registries report 1-year mortality rates after diagnosis ranging from 22% to 34%<sup>5</sup>

1. Atassi N, Berry J, Shui A, Zach N, Sherman A, Sinani E, Walker J, Katsovskiy I, Schoenfeld D, Cudkowicz M, Leitner M. The PRO-ACT database: design, initial analyses, and predictive features. *Neurology*. 2014 Nov 4;83(19):1719-25.
2. Cruz MP, Edaravone (Radicava): A Novel Neuroprotective Agent for the Treatment of Amyotrophic Lateral Sclerosis. *P T*. 2018 Jan;43(1):25-28. PMID: 29290672; PMCID: PMC5737249
3. Karanevich, A.G., Statland, J.M., Gajewski, B.J. et al. Using an onset-anchored Bayesian hierarchical model to improve predictions for amyotrophic lateral sclerosis disease progression. *BMC Med Res Methodol* 18, 19 (2018).
4. Paganoni S, Cudkowicz M, Berry JD. Outcome measures in amyotrophic lateral sclerosis clinical trials. *Clin Investig (Lond)*. 2014;4(7):605-618. doi: 10.4155/cli.14.52. PMID: 28203356; PMCID: PMC5305182.
5. Wolf, J., Safer, A., Wöhrle, J.G. et al. Factors predicting one-year mortality in amyotrophic lateral sclerosis patients - data from a population-based registry. *BMC Neurol* 14, 197 (2014).
6. Matched on time since onset, baseline ALSFRS-R, pre-baseline slope, and disease onset location

# NUZ-001 selected for entry into the HEALEY ALS Platform Trial

The HEALEY ALS Platform Trial is a competitive process led by a group of expert ALS scientists and members of the Healey & AMG Center Science Advisory Committee

## HEALEY ALS Platform Trial Design<sup>1</sup>



## Innovative Trial Structure

### Design

- Shared master protocol
- >70 clinical sites across the US
- 3:1 active drug to placebo ratio
- 160–240 participants per regimen
- 7 regimens completed
- 2 regimens progressing to Phase 3



### Next Steps

- Address FDA's clinical hold concerns
- Finalise regimen-specific protocol amendment (Regimen H)
- File protocol amendment under MGH's Investigator-initiated IND
- Commence recruitment Q4 CY25

# Summary

✓ **TDP-43 aggregation** is a core pathological feature in **~97% of all ALS cases**, making it one of the most unifying **molecular hallmarks** of the disease, regardless of genetic background



✓ **Disruption in RNA processing** leads to **proteostasis collapse**, stress granule formation, impaired mitochondrial function, and subsequent microglial activation and inflammation



✓ **NUZ-001 and NUZ-001 Sulfone** can **reduce** the aggregation of **TDP-43** and help restore functional activity of motor neurons in response to a stressor



✓ **Completed Phase 1** study in patients with ALS demonstrated **excellent long-term tolerability** and promising efficacy, indicating a potential **survival benefit** over time



Q4  
CY 2025



✓ **NUZ-001, selected in the prestigious HEALEY ALS Platform Trial** run out of **Mass General Hospital**, is set to **start in Q4 CY2025**

- ✓ **Substantial animal safety data package available from ELANCO**
- ✓ **GMP material to support clinical development and potential drug launch sourced from ELANCO**
- ✓ **Potential to receive accelerated approval following completion of the HEALEY ALS Platform Trial in 2027**

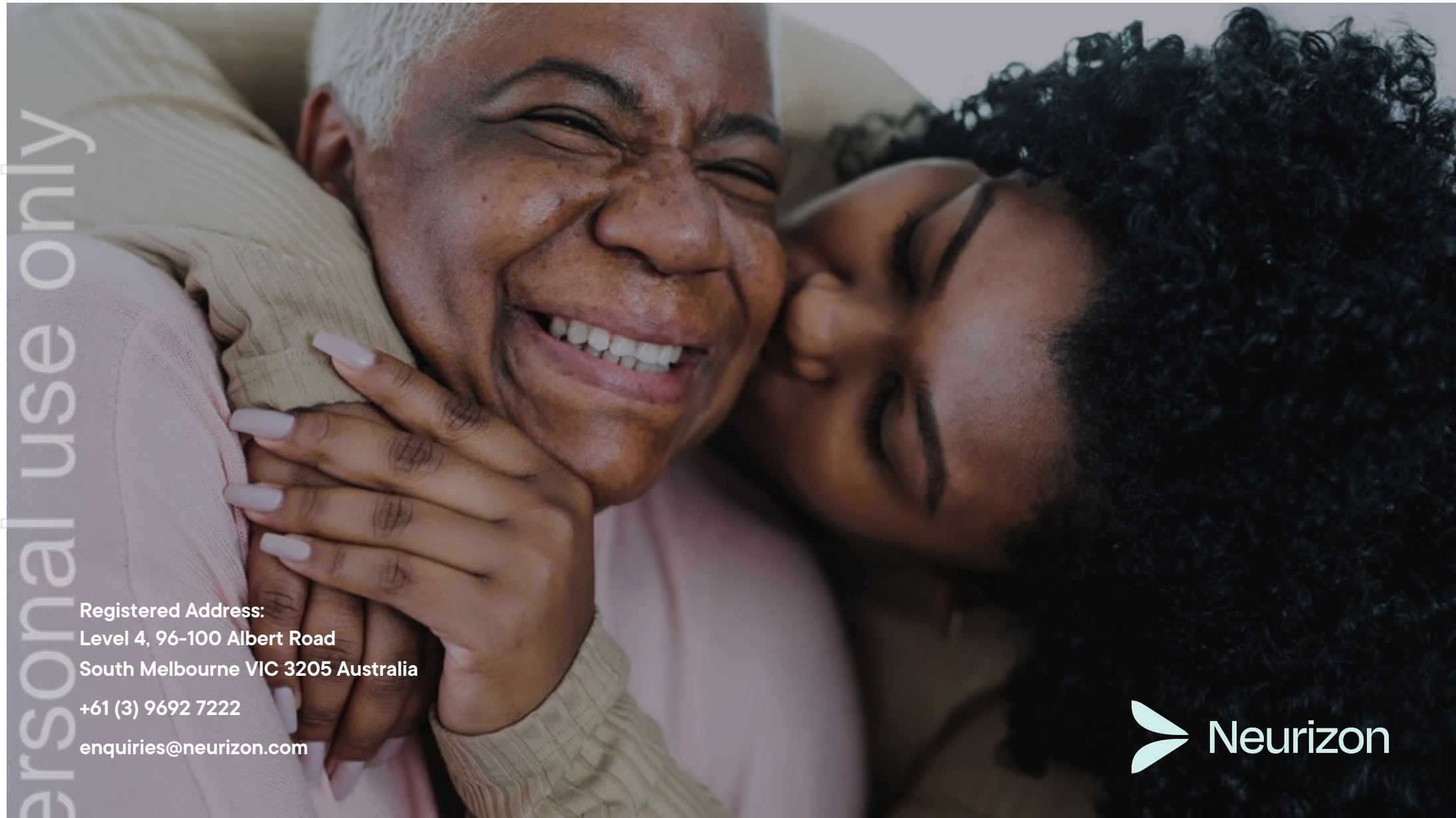
Thank You



Health Care Bethlehem



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