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Neurizon Presents Phase 1 MEND Study Data at Prestigious International ALS Annual Meeting

Highlights:

- Neurizon Therapeutics' Chief Operating Officer, John Clark, presented the Phase 1 MEND study data at the 2024 Annual NEALS Meeting, October 21-24, 2024.
- Key data demonstrated that the drug is safe and well tolerated, and demonstrated a statistically significant survival benefit in ALS patients treated with monepantel (NUZ-001) compared to untreated matched controls from the PRO-ACT database.
- Neurizon continues to prepare for the Phase 2/3 HEALEY ALS Platform Trial, set to begin in Q1 2025.
- The abstract for the poster presentation has been published in the proceedings from the conference in the scientific Journal Muscle and Nerve

October 25, 2024 – Melbourne, Australia: Neurizon Therapeutics (ASX: NUZ & NUZOA) ("Neurizon" or "the Company") is excited to announce the presentation of its Phase 1 MEND study data at the prestigious 2024 Annual NEALS (Northeast Amyotrophic Lateral Sclerosis Consortium) Meeting. The event, which ran from October 21 to 24, is one of the world's most significant gatherings in the field of Amyotrophic Lateral Sclerosis (ALS) research, bringing together physicians, key opinion leaders, and industry representatives to discuss advancements in ALS and motor neurone disease (MND) treatments.

John Clark, Neurizon's Chief Operating Officer, presented the data, showcasing the following key results from the Phase 1 MEND study completed earlier this year in patients with ALS (as announced on 27th February 2024):

- Study met its primary endpoint showing long-term safety and tolerability of NUZ-001 - No deaths, no Serious Adverse Events related to treatment, and a very low incidence of Adverse Events
- A monthly 0.48-point improvement in ALSFRS-R scores for patients treated with NUZ-001 versus untreated PRO-ACT matched controls
- The effects of treatment with NUZ-001 on biomarkers demonstrated a large reduction in cerebrospinal fluid (CSF) Neurofilmant Light Chain (NfL)
- These findings demonstrate NUZ-001 shows promise as an innovative treatment for ALS.

The abstract for the poster presentation has been published in the proceedings from the conference in the scientific Journal Muscle and Nerve[1].

Looking Ahead: Phase 2/3 HEALEY ALS Platform Trial

Neurizon Therapeutics is preparing to build on this success by advancing to the next stage of clinical trials. The Phase 2/3 HEALEY ALS Platform Trial, in collaboration with Massachusetts General Hospital, is scheduled to commence in Q1 2025. This prestigious trial is designed to further explore the potential of NUZ-001 in treating ALS and accelerate patient access to this promising therapy.

Dr. Michael Thurn, CEO of Neurizon Therapeutics, commented:

"We are honored to have presented our Phase 1 MEND study data at such a leading international event. Our mission at Neurizon is to bring innovative therapies to patients suffering from neurodegenerative diseases like ALS. Being part of the NEALS Annual Meeting reinforces our commitment to advancing science and patient care, as we work tirelessly to deliver life-changing treatments to those in need."

About the PRO-ACT Database

The PRO-ACT database[2] is the largest public repository of ALS clinical trial data, with information pooled from more than 10,000 patients. It provides valuable insights that have supported Neurizon's groundbreaking research and development.

-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.

[1] S Mathers, D Rowe, P White, M Quintana, J Clark, M Thurn Phase 1. Study of a mTOR Inhibitor in Patients with Amyotrophic Lateral Sclerosis. Proceedings of the 23rd Annual NEALS Meeting. Muscle Nerve. 2024 Oct;70 Suppl 1:S1-S92. doi: 10.1002/mus.28259. PMID: 39417631.

[2] 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. doi: 10.1212/WNL.0000000000000951.Epub 2014 Oct 8. PMID: 25298304; PMCID: PMC4239834.

Appendix A: Poster Abstract

Phase 1 Study of a mTOR Inhibitor in Patients with Amyotrophic Lateral Sclerosis

Susan Mathers[1, 2], Dominic Rowe[3], Philip White[4], Melanie Quintana[4], John Clark[5] and Michael Thurn[5].

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Background: A key pathological feature of amyotrophic lateral sclerosis (ALS) is the formation of cytoplasmic protein aggregates. The induction of autophagy is viewed as a possible therapeutic approach to clear the toxic build-up of protein aggregates. Inhibition of mTOR (mammalian target of rapamycin) pathway has been shown to induce autophagy, clear protein aggregates and provide benefits in mouse models of ALS. Monepantel (MPL) is a potent oral small molecule inhibitor of mTOR being developed for a range of neurodegenerative conditions. Here, we investigate the safety, tolerability, pharmacokinetics (PK) and preliminary efficacy of orally administered MPL, in 12 subjects with ALS.

Material/methods: The Phase 1 study was a multicenter, open label study comprised of a 24-hour escalating single-dose PK study and 4-week escalating multiple dose study of MPL administered orally to subjects with ALS. During the study, the following were assessed: safety and tolerability, PK (plasma and CSF) and pharmacodynamic parameters, preliminary efficacy (ALS Functional Rating Scale – Revised, ALSSQOL-R Quality of Life Questionnaire, Edinburgh Cognitive and Behavioural ALS Screen [ECAS], and seated Slow Vital Capacity [SVC]), and biomarker measures (plasma and CSF neurofilament/light chain [NfL] and urinary p75ECD levels).

Discussion: Once daily oral administration of MPL at doses of up to 10 mg/kg body weight to 12 subjects with ALS over a 7- to 12-month period was well-tolerated and did not result in any dose-limiting toxicities. Preliminary assessments of MPL's therapeutic effect on survival and ALSFRS-R scores indicate promise when compared to historical control subjects from the PRO-ACT database with similar baseline characteristics. Functional and biomarker data will also be presented supporting progression of MPL into larger Phase 2 clinical study.

Phase 1 Study of a mTOR Inhibitor in Patients with Amyotrophic Lateral Sclerosis

Susan Mathers 1, 2 , Dominic Rowe3 , Philip White4 , Melanie Quintana4 , John Clark5 , and Michael Thurn6

INTRODUCTION

- Monepantel is an mTOR (mechanistic target of rapamycin) inhibitor being investigated for efficacy in slowing disease progression of amyotrophic lateral sclerosis (ALS).
- Study treats N = 12 patients and is not placebo controlled.
- Exploratory efficacy is based on ALS Functional Rating Scale – Revised (ALSFRS-R) and survival.

mTOR Pathway

- mTOR pathway regulates gene transcription and protein production to control cellular mitosis proliferation and immune cell differentiation.
- mTOR inhibition stimulates autophagy, a self-degradative process that recycles organelles, proteins, and macromolecules, playing a crucial role in cell survival and homeostasis.

PRO-ACT Database and Matching

- Clinical data for more than 10,000 patients from previous clinical trials. Contains ALSFRS-R and survival data.
- Matched many historical controls with baseline characteristics similar to each patient in the Monepantel treatment group. Matched controls to estimate the relative effect of the treatment.

PRO-ACT DATABASE

- Used historical PRO-ACT control subjects with baseline characteristics similar to Monepantel treatment subjects.
- Restrictions to PRO-ACT Database to match to Monepantel study:
  1) Recorded time of onset
  2) Onset within three years of the start of the trial
  3) At least three follow-up visits
  4) Observed disease onset location (bulbar or other)
- Used treatment and control subjects in PRO-ACT database to estimate a propensity score (i.e., probability of treatment) used in our matching procedure.

MATCHING

Propensity score (PS) used for matching PRO-ACT controls to Monepantel treatment subjects. PS is computed using time since onset, baseline ALSFRS-R, pre-baseline slope, and onset location.

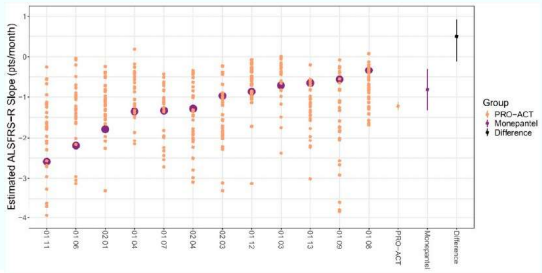
- Covariates are not well-balanced using PS only. Likely due to n = 12 in treatment group.
- To improve covariate balance, we also use baseline covariate in addition to PS.
- Match many PRO-ACT control subjects to each Monepantel treatment subject using nearest-neighbor matching based on Mahalanobis distance.

Results

- The absolute standardized mean difference is less than 0.1 for all covariates.
- Variance ratios are all between the recommended 0.5 and 2.0.

	All PRO-ACT Controls (N = 1559)	Matched PRO-ACT Controls (N = 360)	Monepantel (N = 12)
Time since Onset (Months)			
Mean (SD)	17.0 (7.42)	15.2 (7.37)	14.7 (8.38)
Median [Min,Max]	16.3 [2.56, 35.8]	14.3 [4.21, 35.8]	14.3 [3.65, 34.0]
Baseline ALSFRS-R			
Mean (SD)	38.2 (5.22)	37.8 (4.71)	38.2 (5.10)
Median [Min,Max]	39.0 [16, 48]	38.0 [25, 46]	39.5 [28, 44]
Pre-Baseline Slope			
Mean (SD)	0.679 (0.494)	0.796 (0.438)	0.826 (0.461))
Median [Min,Max]	0.559[0, 5.85]	0.745 [0.154, 2.03]	0.739 [0.210, 1.48]
Onset Location			
Bulbar	321 (20.6%)	60 (16.7%)	2 (16.7%)
Other	1238 (79.4%)	300 (83.3%)	10 (83.3%)

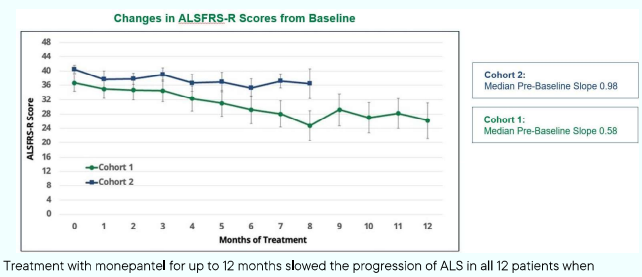
ALSFRS-R RESULTS FOR POOLED TREATMENT GROUP



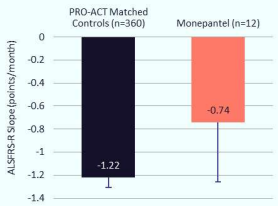
- Results correspond to an approximate disease slowing of 40%
- Estimated ALSFRS-R baselines are similar between groups, suggesting effective matching

Efficacy Endpoint	PRO-ACT Control (N=360)	Monepantel (N=12)	Between-group Differences
ALSFRS-R Slope			
Estimate	-1.22	-0.74	0.48
95% CI	(-1.31, -1.12)	(-1.26, -0.22)	(-0.06, 1.01)
p-value	——	——	0.08
ALSFRS-R Baseline			
Estimate	38.07	37.28	-0.79
95% CI	(37.84, 38.3)	(36.12, 38.45)	(-1.97, 0.40)
p-value	——	——	0.19

PRELIMINARY EFFICACY - ALSFRS-R



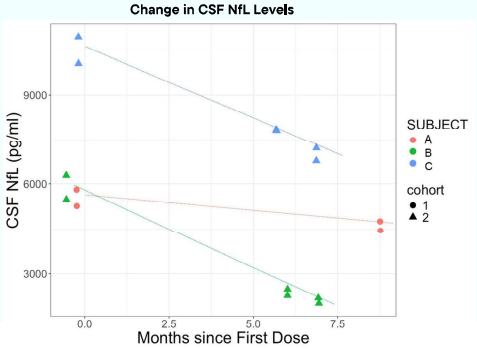
- Treatment with monepantel for up to 12 months slowed the progression of ALS in all 12 patients when compared to matched controls from the PRO-ACT database. Difference 0.48 points/month (p=0.08)



EXPLORATORY BIOMARKERS - CSF NfL

- Marked decreased NfL cerebrospinal fluid (CSF) levels in the 3 patients sampled. 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

Change in CSF NfL Levels



EXPLORATORY BIOMARKERS – URINARY p75ECD / CREATININE AND SERUM NfL

- Compared to pre-study, daily administration of Monepantel resulted in a small (non-statistically significant) numerical increase in mean urinary p75ECD and mean urinary p75ECD creatinine levels for All Subjects.
- Compared to pre-study, daily administration of Monepantel resulted in a small (non-statistically significant) numerical increase in serum NfL for All Subjects.

SAFETY AND TOLERABILITY

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

INCIDENCE OF ADVERSE EVENTS (n)					
	Dose 1 (2 mg/kg)	Dose 2 (4 mg/kg)	Dose 3 (6 mg/kg)	Dose 4 (10 mg/kg)	Total
Adverse Events	29	6	12	9	56
Related to Treatment	2	1	–	–	3

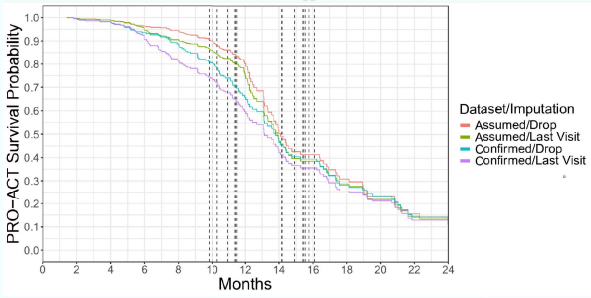
- Only 3 Adverse Events (mild in severity) possibly related to treatment: raised liver enzymes; increased hair growth, constipation
- No deaths
- No patients withdrew or were discontinued from the study
- One Serious Adverse Event (SAEs) reported that was unrelated to the treatment
  - 1 patient (Dose Level 3 – 6 mg/kg BW) – hospitalized for Intestinal dilatation and Pneumonia

SURVIVAL RESULTS

- No deaths at the end of study led to unique survival analysis.
- One-sided p-value testing for the effect of survival under the null hypothesis.
- With independence across subjects and no effect, the joint probability of all subjects surviving is

$$\Pr(\text{No Deaths}) = \Pr(\text{All Subjects Surviving}) = \prod_{i=1}^{12} p_i,$$

where p_i is the probability of surviving until time t_i. $\prod$ represents the product.



Analysis Method		Monepantel Joint Group Survival		Individual Patient 12-Month Survival	
Dataset	Death Time Imputation	Probability All Survive	95% CI	12-Month Probability One Patient Survives	95% CI
Assumed	Leave out	0.275%	(0.006%, 2.903%)	80.4%	(75.9%, 85.1%)
Survival	Last visit	0.139%	(0.003%, 1.604%)	75.0%	(69.9%, 80.4%)
Confirmed	Leave out	0.085%	(0.003%, 0.741%)	65.9%	(59.3%, 73.2%)
Survival	Last visit	0.028%	(0.001%, 0.266%)	59.8%	(53.4%, 67%)

STUDY SUMMARY AND NEXT STEPS

- Positive Phase 1 study results showed that monepantel has an excellent safety profile and the potential to slow the progression of ALS
- Doses of up to 10 mg/kg body weight to 12 subjects over a 7- to 12-month period was well-tolerated and did not result in any dose-limiting toxicities
- Monepantel and its active metabolite, monepantel sulfone, detectable in cerebrospinal fluid
- Favourable comparison to historical control subjects from PRO-ACT database
- Promising biomarker findings, especially at higher dose
- Encouraging results observed in small study population, suggesting that Monepantel may slow the rate of disease progression over the treatment period (range 28 to 53 weeks).
- More definitive evidence of the efficacy of Monepantel is needed in larger, placebo-controlled studies.
- 10 mg/kg BW dose selected for pivotal Phase 2/3 HEALEY ALS Platform Trial, scheduled to commence in Q1 2025