ASX: PAA

Phase 1 MEND Study Top-Line Results

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Phase 1
Executive Summary

Positive Phase 1 study results showing monepantel has an excellent safety profile and the ability to slow the progression of MND/ALS

Highlights

Primary Objectives	Excellent safety and tolerability profile
Preliminary efficacy data	Slows the rate of progression by 58% (Cohort 2 High Dose)
Blood Brain Barrier	Monepantel and its active metabolite, MPL Sulphone, and is detectable in cerebrospinal fluid
Competitive Advantage	Superior safety, tolerability and preliminary efficacy profile to leading FDA approved drug Relyvrio®
Survival	May prolong a patient's life expectancy by 13.5-56.5 months
Phase 2/3 Dose	Optimal dose selected for pivotal Phase 2/3 clinical study

Phase 1
Study Design

PATIENT POPULATION:
11 Men, 1 Woman

- Adults with Familial or Sporadic ALS/MND
- 1st 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**

STUDY OBJECTIVES:

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

LOCATIONS:

Two Centres in Australia

- Calvary Hospital Bethlehem, Melbourne
- Macquarie University, Sydney

PRIMARY & EXPOLORATORY OUTCOMES:

- Safety and tolerability
- Pharmacokinetic (MPL and its metabolite MPL 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)

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				
	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

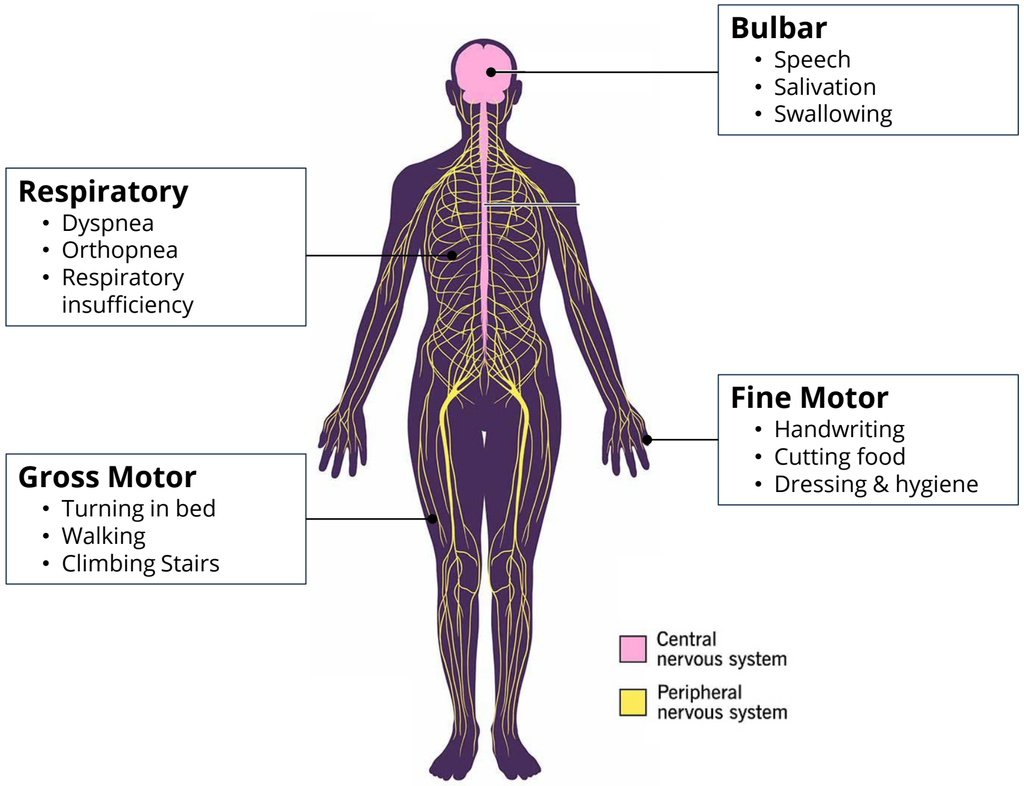
- **No deaths**
- **No patients withdrew or were discontinued from the study**
- **One Serious Adverse Event (SAE) reported that was unrelated to treatment**
  - 1 patient (Dose Level 3 – 6 mg/kg) - hospitalised for Intestinal dilatation and Pneumonia

Phase 1

Preliminary Efficacy Amyotrophic Lateral Sclerosis Function Rating Scale – Revised (ALSFRS-R)

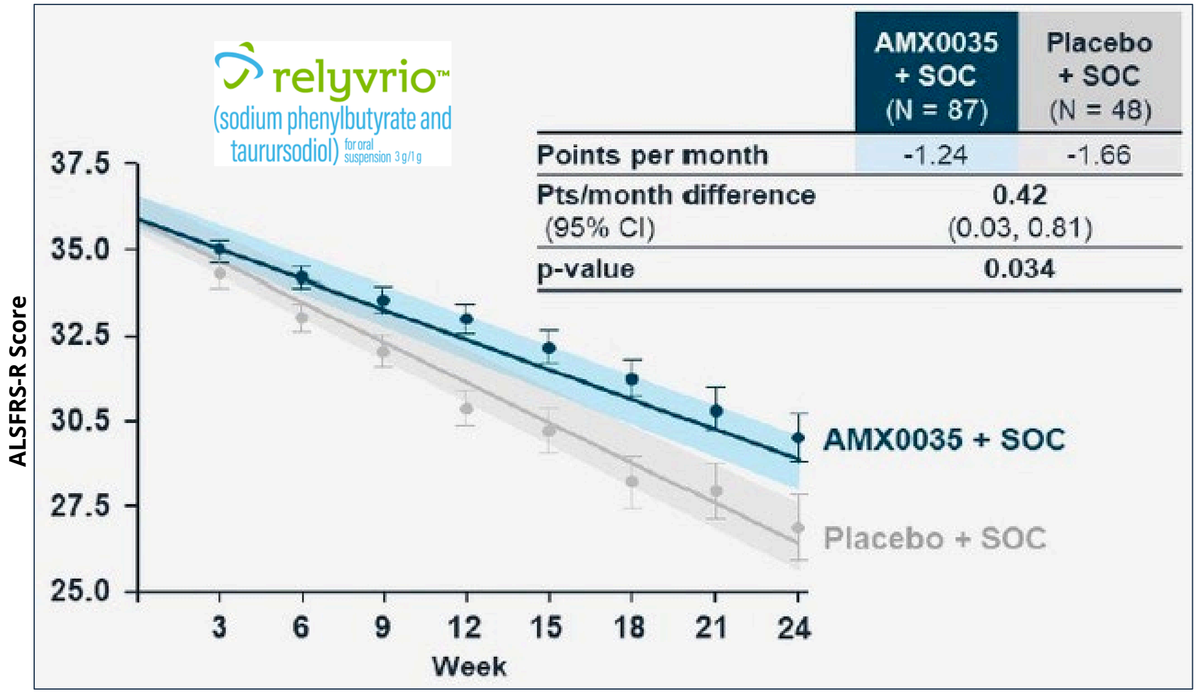
ALSFRS-R is a predictor of survival time in ALS patients.[1] The speed at which ALS progresses, measured by the rate of decline in a patient's ALSFRS-R score over time, can be used to confidently predict disease prognosis.

ALSFRS-R Domains Assessed



Each task is rated on a five-point scale from 0 = can't do, to 4 = normal ability. Individual item scores are summed to produce a reported score of between 0=worst and 48=best.

AMX0035[2] – 25% Slower Decline in ALSFRS-R



Slowing the decline in ALSFRS-R by 16.5% = 4-5 months median survival[3]

[1]Beghi E, Mennini T, Bendotti C, et al. The heterogeneity of amyotrophic lateral sclerosis: a possible explanation of treatment failure. *Curr Med Chem*. 2007;14(30):3185-3200
[2]FDA Briefing Document 2022 NDA# 216660 Drug Name: AMX0035/ sodium phenylbutyrate (PB) and taurursodiol (TURSO) Applicant: Amylyx Pharmaceuticals, Inc.
[3]Leigh PN, Swash M, Iwasaki Y, et al. Amyotrophic lateral sclerosis: a consensus viewpoint on designing and implementing a clinical trial. Amyotroph Lateral Scler Other Motor Neuron Disord. 2004;5(2):84-98

Phase 1

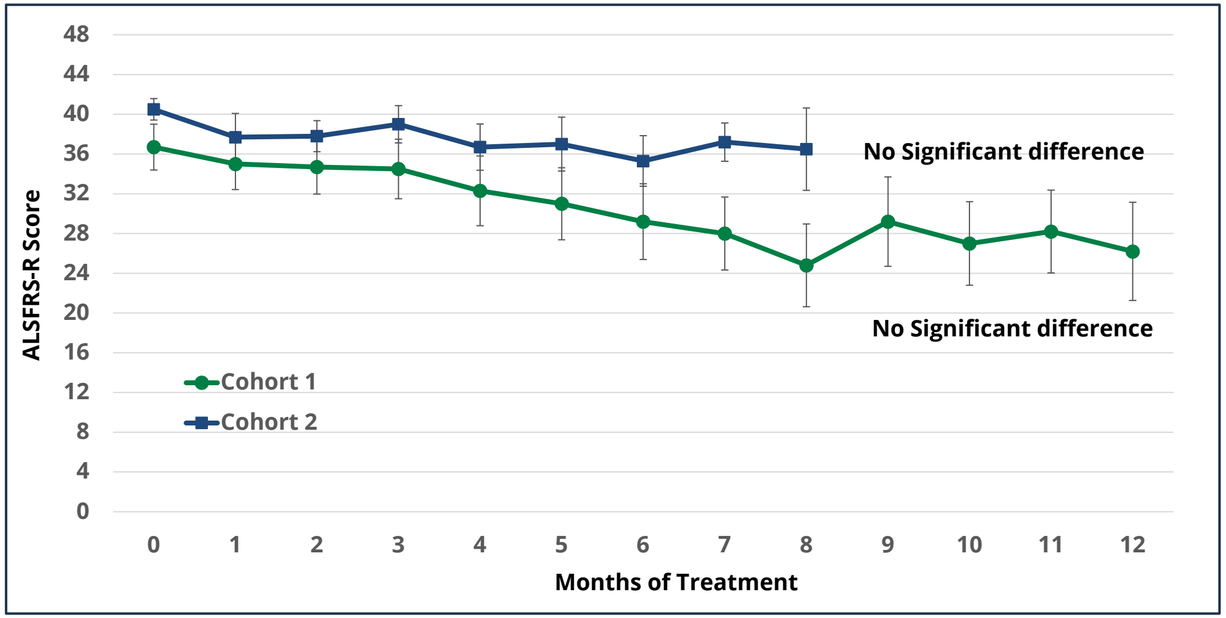
Preliminary Efficacy Amyotrophic Lateral Sclerosis Function Rating Scale – Revised (ALSFRS-R)

There were no significant differences in ALSFRS-R scores between predose and end of treatment for all 12 patients Cohort 1, and Cohort 2 suggesting that treatment with monepantel over 8 – 12 months slowed the rate of disease progression

Rate of Decline of ALSFRS-R From Predose

Visit	Statistic	Cohort 1	Cohort 2	Total
Predose	n	7	6	12
	Mean +/- SD	36.7 +/- 6.10	40.5 +/- 2.43	38.5 +/- 4.99
	Median	35.0	41.5	41.0
	Min, Max	28, 44	37, 43	28, 44
End of Treatment	n	6	6	12
	Mean +/- SD	23.7 +/- 12.18	34.7 +/- 10.05	29.2 +/- 12.10
	Median	26	37.5	34.5
	Min, Max	7, 37	15, 43	7, 43
	p-value	0.4065	0.8794	0.7789

Rate of Decline of ALSFRS-R



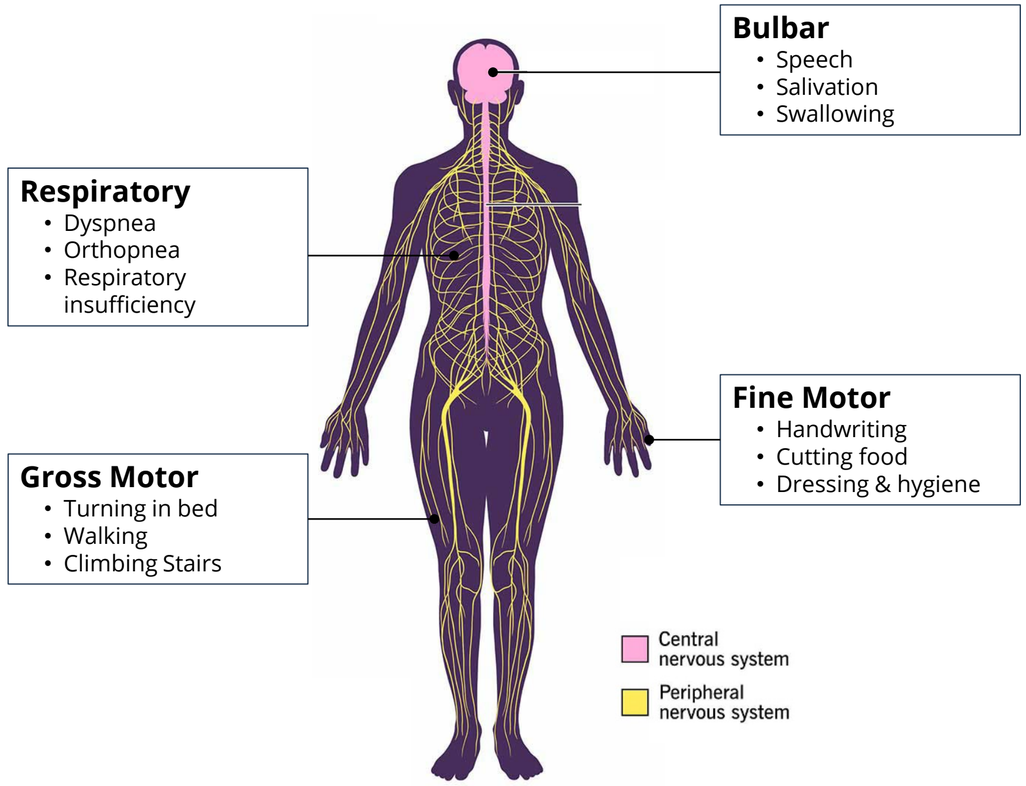
No significant difference between Predose and End of Treatment

Phase 1

Preliminary Efficacy Amyotrophic Lateral Sclerosis Function Rating Scale – Revised (ALSFRS-R)

Treatment with monepantel for up to 12 months slowed the progression of MND/ALS in all 12 patients by 39% when compared to matched controls from the PRO-ACT database[1]

ALSFRS-R Domains Assessed



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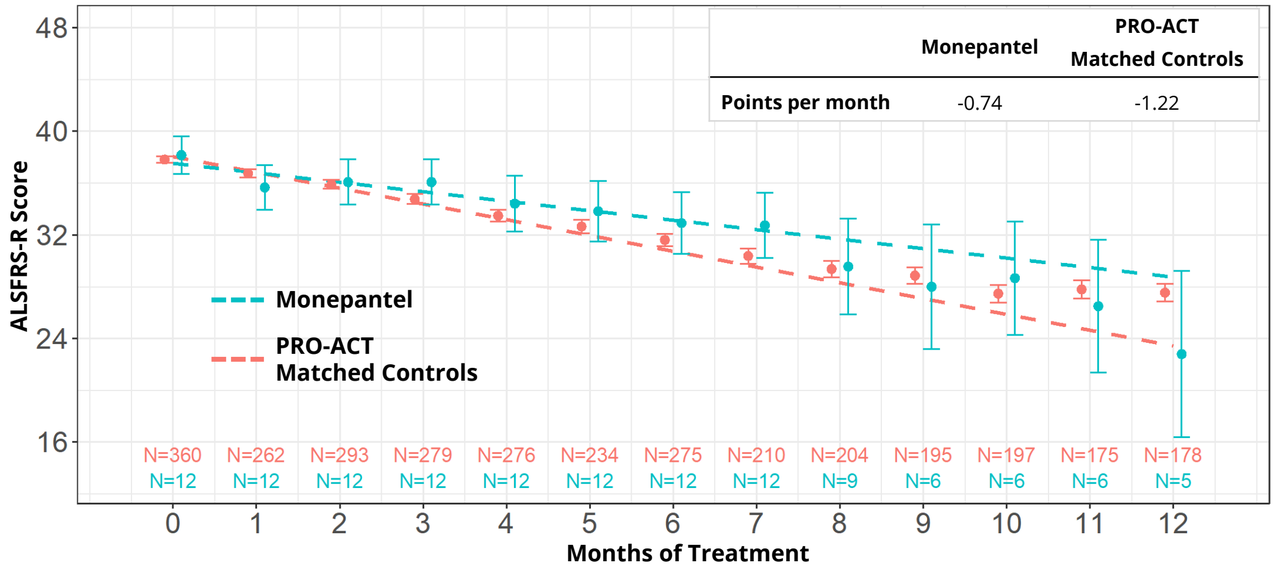
MPL – 39% Slower Decline in ALSFRS-R



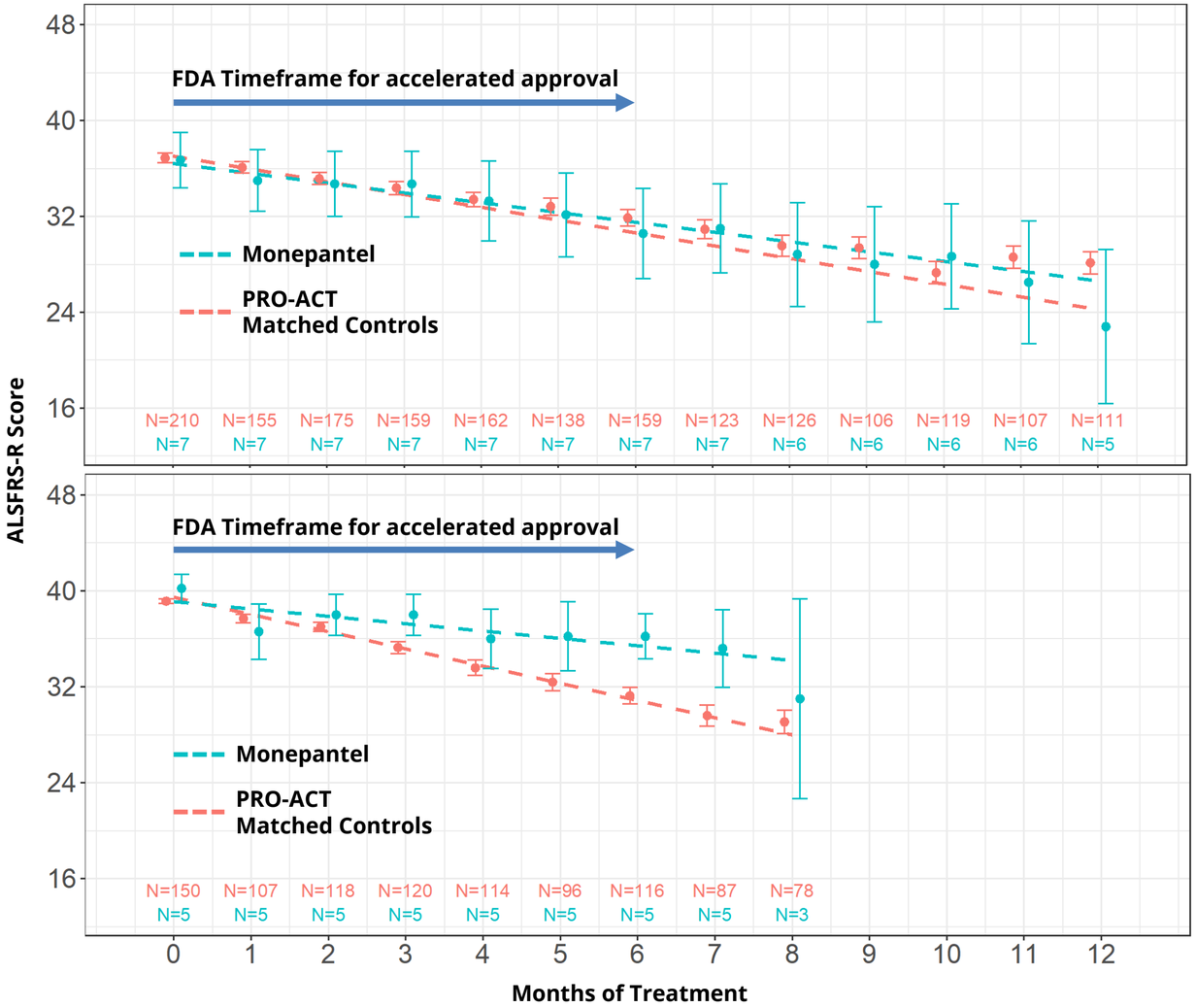
The PRO-ACT database is the largest publicly available repository of merged ALS clinical study data. Data were pooled from 16 completed Phase 2/3 ALS clinical studies and one observational study. Over 8 million de-identified longitudinally collected data points from more than 8,600 persons with ALS, including demographics, family histories, and longitudinal clinical and laboratory data.

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

Phase 1

Preliminary Efficacy Amyotrophic Lateral Sclerosis Function Rating Scale – Revised (ALSFRS-R)

Dose response observed between Cohort 1 and 2. Rate of disease progression in Cohort 2 was slowed by an impressive 58% compared to the PRO-ACT database matched controls



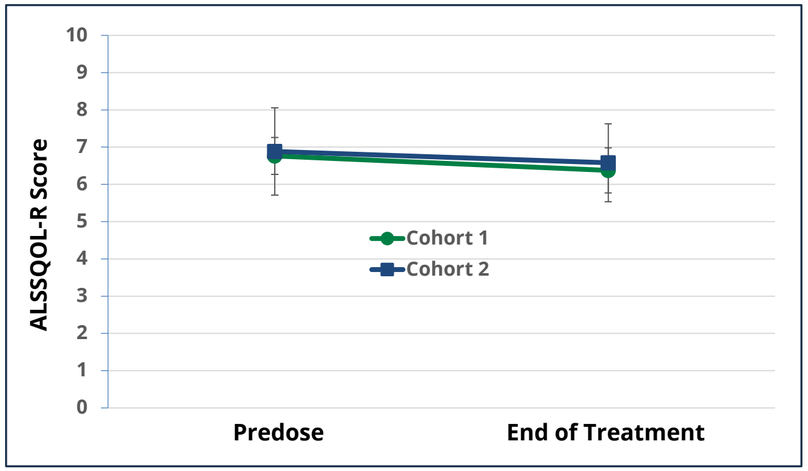
Cohort 1
-0.83 points per month
23% Slower Decline in ALSFRS-R

Cohort 2
-0.60 points per month
58% Slower Decline in ALSFRS-R

Phase 1
Exploratory Endpoints

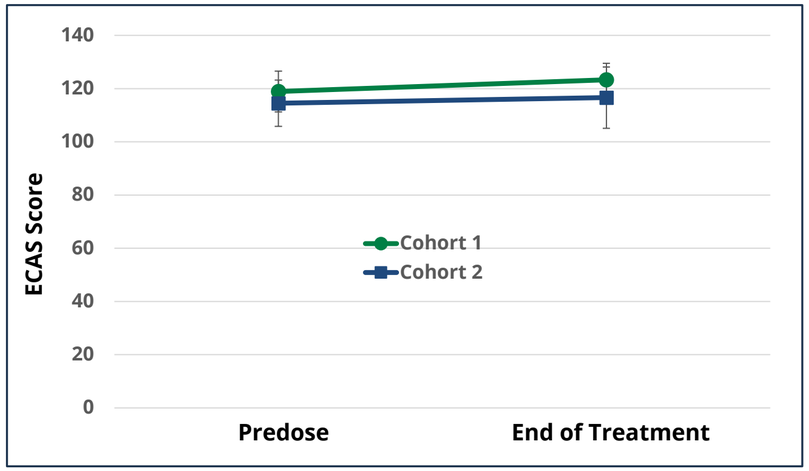
No significant difference in ALS Quality of Life Questionnaire, Edinburgh Cognitive and Behavioural ALS Screen, and Slow Vital Capacity between predose and end of treatment

ALSSQOL-R Quality of Life Questionnaire



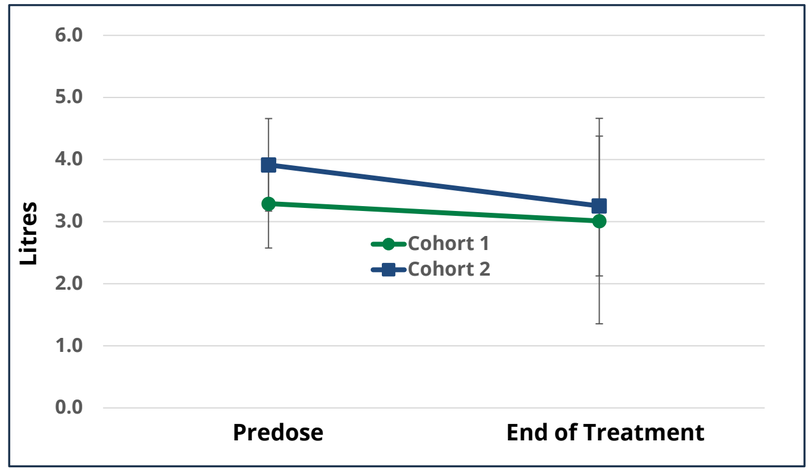
50-item disease-specific questionnaire that is completed by the individual with ALS. Each item is rated on a 10-point Likert scale, with 0 being the least desirable situation and 10 being the most desirable. The instrument produces a single-item QoL score and six domain scores (negative emotion, interaction with people and environment, intimacy, religiosity, physical symptoms, and bulbar function).

Edinburgh Cognitive and Behavioural ALS Screen



A clinical cognitive screening tool for cognitive and behavioural abnormalities in ALS. Includes assessment of fluency, executive functions, language, memory, and visuospatial functions. The total score is 136 points.

Slow Vital Capacity

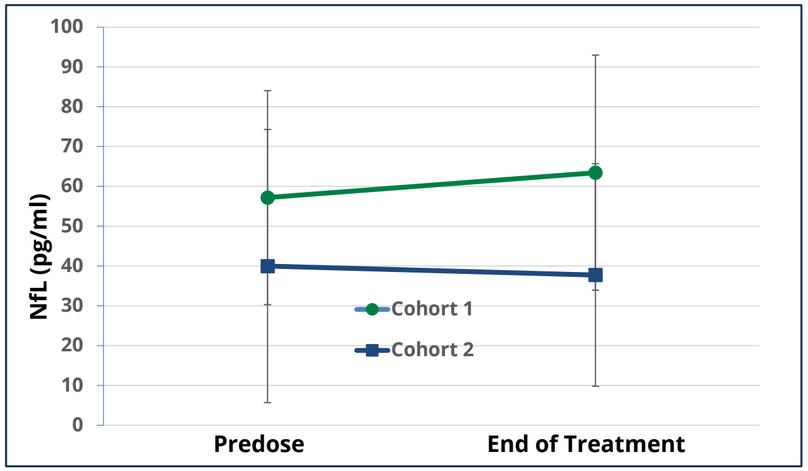


A lung function test that measures how much air can be exhaled out in a relaxed manner, similar to a gentle sigh, until your lungs are completely empty.

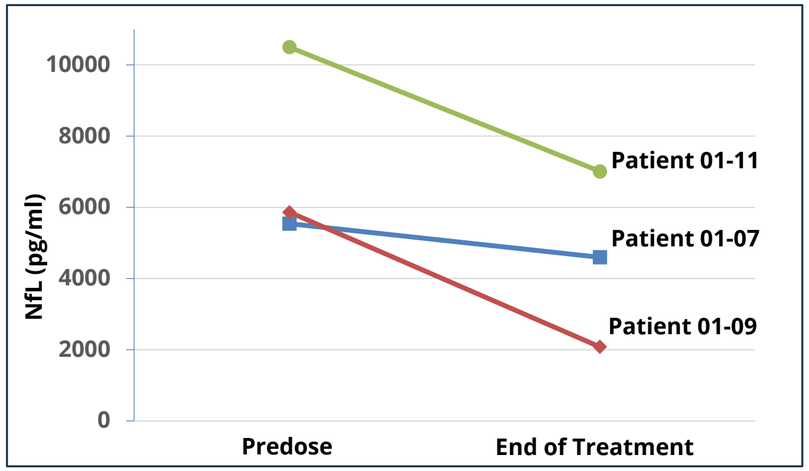
Phase 1
Exploratory Biomarkers

No significant difference in biomarkers serum neurofilament /light chain (NfL) and urinary $p75^{ECD}$ levels between pre-dose and end of treatment

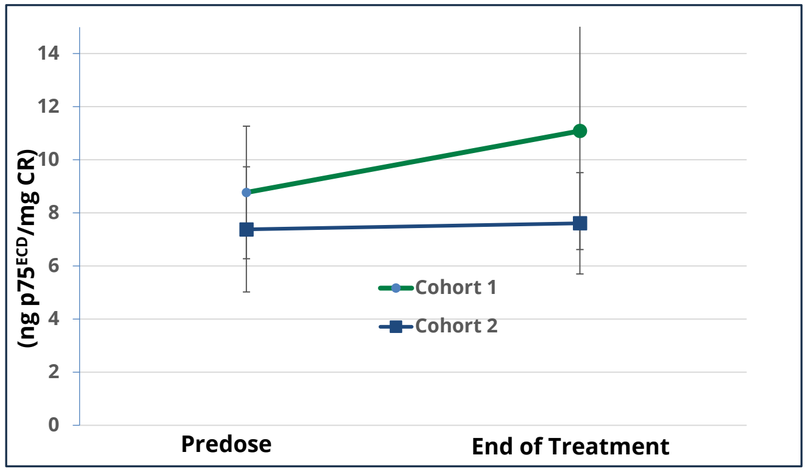
Neurofilament Light Chain Serum



Neurofilament Light Chain Cerebrospinal Fluid



Urinary $p75^{ECD}$/Creatinine

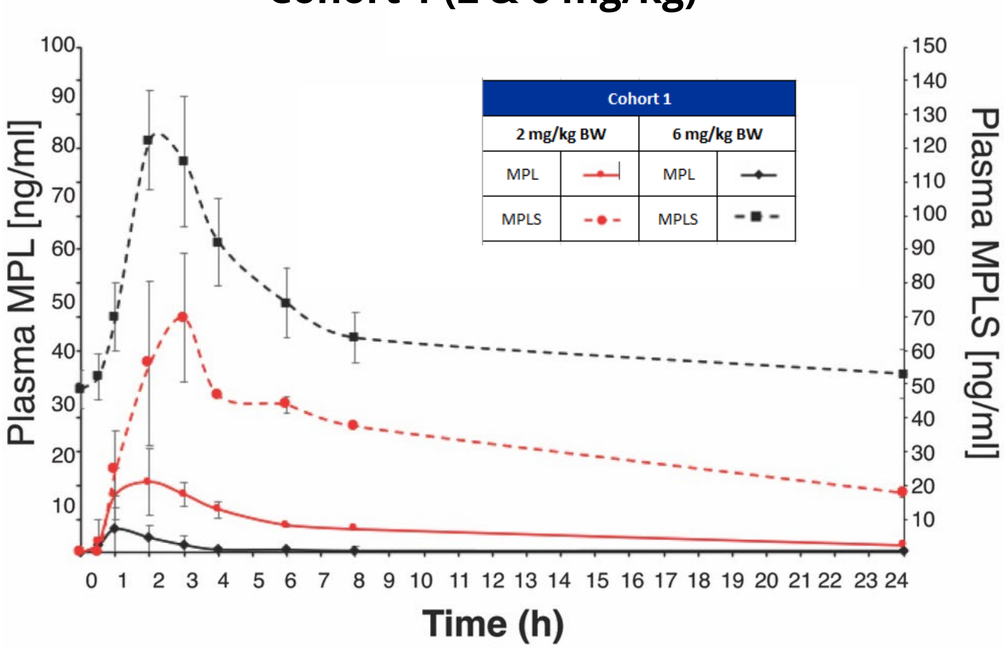


Marked decreased NfL cerebrospinal fluid (CSF) levels in all 3 patients where CSF samples were available

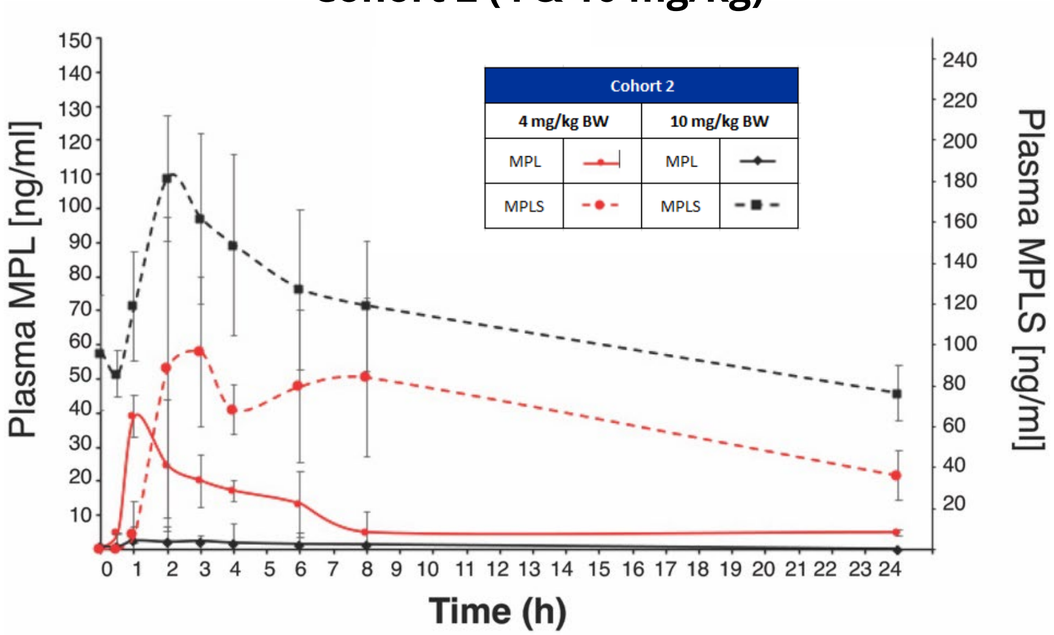
Urinary $p75^{ECD}$ levels remained stable in Cohort 2 patients. Urinary $p75^{ECD}$ levels increase on average 0.19 ng/mg of creatinine per month as the disease progresses

Phase 1
Pharmacokinetics and Target Engagement (mTOR Pathway)

Cohort 1 (2 & 6 mg/kg)



Cohort 2 (4 & 10 mg/kg)



Pharmacokinetics

Concentrations of MPL Sulphone, the active metabolite of MPL, increased somewhat proportionally with higher doses of MPL. MPL and MPLS was found in the cerebrospinal fluid.

Target Engagement (mTOR Pathway)

Target engagement of the mTOR pathway (p-EIF4EBP1 and p-RPS6KB1) in peripheral mononuclear blood cells was confirmed at all dose levels

Phase 1
Comparison to Leading FDA-Approved Product

Monepantel displays a superior safety, tolerability and preliminary efficacy profile to the leading FDA approved drug Relyvrio®

Estimated Additional Life Expectancy for MPL

	Estimated rate of ALSFRS-R Decline (points per month)	Slowing in ALSFRS-R Decline (%)	Slope Change from PRO-ACT matched controls	Additional Life Expectancy (months)
Combined Cohort 1 & 2	-0.74	39%	0.48	13.5 – 56.5
Cohort 1 (Low Dose)	-0.83	23%	0.24	
Cohort 2 (High Dose)	-0.60	58%	0.83	
Relyvrio®	-1.24	25%		8 – 9

Treatment with monepantel may prolong a patient's life expectancy by 13.5-56.5 months

Median Survival Table[1]

ALSFRS-R Slope (points per month)	Median Survival (Months)	Increase in Life Expectancy (Months)
<-0.25	78.5	56.5
-0.25-0.45	44.0	22.0
-0.50-0.99	35.5	13.5
>-1.0	22.0	

[1]Elamin M, Bede P, Montuschi A, Pender N, Chio A, Hardiman O. Predicting prognosis in amyotrophic lateral sclerosis: a simple algorithm. J Neurol. 2015 Jun;262(6):1447-54. doi: 10.1007/s00415-015-7731-6. Epub 2015 Apr 11. PMID: 25860344; PMCID: PMC4469087.

Phase 1
Conclusion

Positive Phase 1 study results showing monepantel has an excellent safety profile and the ability to slow the progression of MND/ALS

Primary Objectives	Excellent safety and tolerability profile
Preliminary efficacy data	Elows the rate of progression by 58% (Cohort 2 High Dose)
Blood Brain Barrier	Monepantel and its active metabolite, MPLS, and is detectable in cerebrospinal fluid
Competitive Advantage	superior safety, tolerability and preliminary efficacy profile to leading FDA approved drug Relyvrio®
Survival	May prolong a patient's life expectancy by 13.5-56.5 months
Next Steps	Moving forward with pivotal Phase 2/3 clinical study

Thank you

FIGHT MND.
IT TAKES PEOPLE

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Health Care Bethlehem

MACQUARIE University
SYDNEY·AUSTRALIA
MOTOR NEURON DISEASE RESEARCH CENTRE

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