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HEALEY ALS Platform Trial

Community Q&A – October 23, 2025

Massachusetts General Hospital
Founding Member, Mass General Brigham

HARVARD MEDICAL SCHOOL

Healey & AMG Center
Sean M. Healey & AMG Center for ALS
at Massachusetts General Hospital

TACKLE ALS "DON'T BE SORRY LETS BEAT THIS"

ALS ASSOCIATION

MDA Muscular Dystrophy Association

SALSA For a Cure

alsFINDINGaCURE

NEALS Northeast Amyotrophic Lateral Sclerosis Consortium

IAM ALS

TAMBOURINE

NCRI NEUROLOGICAL CLINICAL RESEARCH INSTITUTE

BARROW Neurological Institute

ALS ONE

RUN2REVIVE MIND · BODY · POTENTIAL

Berry Consultants Statistical Innovation

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BASEBALL WINTER MEETINGS SAN DIEGO 2015

SEELOS THERAPEUTICS

Calico

DENALI THERAPEUTICS

AMG The AMG Foundation

Decoding HEALEY ALS Platform Trial Publications

Lori B. Chibnik, PhD, MPH
Biostatistician

Associate Professor
Massachusetts General Hospital
Harvard TH Chan School of Public Health

What are the HEALEY Platform Papers trying to tell me?

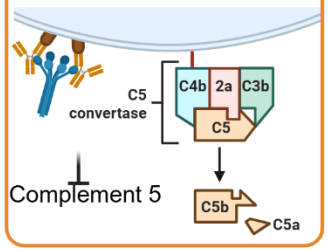
- Walk through the 5 papers with a critical eye
- What should I look for?
- A bit about how to read published papers

- Skip to the end

Published Results

Regimen A

Zilucoplan

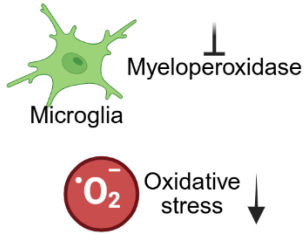


Zilucoplan in the HEALEY ALS Platform Trial

JAMA NETWORK OPEN

Regimen B

Verdiperstat

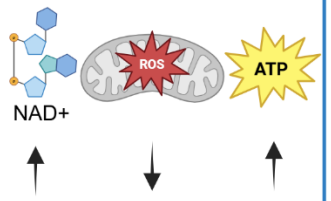


Verdiperstat in the HEALEY ALS Platform Trial

JAMA NEUROLOGY

Regimen C

CNM-Au8

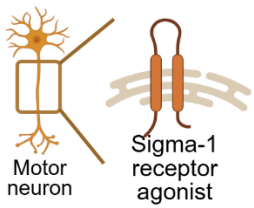


CNM-Au8 in the HEALEY ALS Platform Trial

JAMA

Regimen D

Pridopidine

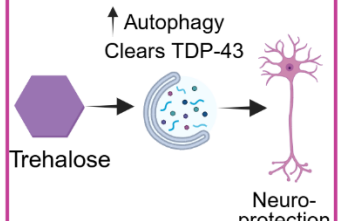


Pridopidine in the HEALEY ALS Platform Trial

JAMA

Regimen E

Trehalose



Trehalose in the HEALEY ALS Platform Trial

LANCET NEUROLOGY

A Typical Manuscript

- Abstract – short summary, always free to see

- Introduction – why they did it
- Methods – what they did
- Results – what they found
- Discussion – how they think you should interpret it

- Some Journals
  - Lay Summary
  - Infographics
  - Podcasts

A Typical Manuscript

- Abstract – short summary, always free to see

- Introduction – why they did it
- Methods – what they did
- Results – what they found
- Discussion – how they think you should interpret it

Abstract

Abstract

Importance: The etiology of amyo
unknown. However, neuroinflamma
progression.

Objective: To determine the effects
ALS.

Design, setting, and participants:
Trial, a phase 2 to 3 multicenter, ran
clinical trial with sharing of trial infr
was conducted from August 17, 20
receive zilucoplan (122 [75.3%]) or
concurrently randomized participar

Interventions: Eligible participants
placebo within strata of edaravone
(zilucoplan, 0.3 mg/kg) and placebo

Main outcomes and measures: Th
through 24 weeks as measured by
(ALSFRS-R) total score and survival,
as disease rate ratio (DRR; <1 indic
early stopping for futility. Outcome
zilucoplan group with the total shared placebo group (n = 164).

Results: Among the 162 participants who were randomized (mean [SD] age, 59.6 [11.3]; 99 [61.1%] male), 115 (71.0%) completed the trial. The estimated DRR common to ALSFRS-R and survival was 1.08 (95% credible interval, 0.87-1.31; posterior probability of superiority, 0.24). The trial was stopped early for futility. No unexpected treatment-related risks were identified.

Conclusions and relevance: In this randomized clinical trial of zilucoplan in ALS, treatment did not alter disease progression. The adaptive platform design of the HEALEY ALS Platform Trial made it possible to test a new investigational product with efficient use of time and resources.

Trial registration: ClinicalTrials.gov Identifier: NCT04297683.

Main outcomes and measures: The primary end point was change in disease severity from baseline through 24 weeks as measured by the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) total score and survival, analyzed using a bayesian shared-parameter model and reported as disease rate ratio (DRR; <1 indicating treatment benefit). The study included prespecified rules for early stopping for futility. Outcome analyses were performed in the full analysis set comparing the zilucoplan group with the total shared placebo group (n = 164).

Results: Among the 162 participants who were randomized (mean [SD] age, 59.6 [11.3]; 99 [61.1%] male), 115 (71.0%) completed the trial. The estimated DRR common to ALSFRS-R and survival was 1.08 (95% credible interval, 0.87-1.31; posterior probability of superiority, 0.24). The trial was stopped early for futility. No unexpected treatment-related risks were identified.

Abstract

Abstract

Importance: The etiology of amyotrophic lateral sclerosis (ALS), a fatal neurodegenerative disease, is unknown. However, neuroinflammation and complement activation may play a role in disease progression.

Objective: To determine the effects of zilucoplan, an inhibitor of complement C5, in individuals with ALS.

Design, setting, and participants: Zilucoplan was tested as regimen A of the HEALEY ALS Platform Trial, a phase 2 to 3 multicenter, randomized, double-blind, placebo-controlled perpetual platform clinical trial with sharing of trial infrastructure and placebo data across multiple regimens. Regimen A was conducted from August 17, 2020, to May 4, 2022. A total of 162 participants were randomized to receive zilucoplan (122 [75.3%]) or regimen-specific placebo (40 [24.7%]). An additional 124 concurrently randomized participants were randomized to receive placebo in other regimens.

Interventions: Eligible participants were randomized in a 3:1 ratio to receive zilucoplan or matching placebo within strata of edaravone and/or riluzole use for a planned duration of 24 weeks. Active drug (zilucoplan, 0.3 mg/kg) and placebo were provided for daily subcutaneous dosing.

Main outcomes and measures: Th
through 24 weeks as measured by
(ALSFRS-R) total score and survival,
as disease rate ratio (DRR; <1 indic
early stopping for futility. Outcome
zilucoplan group with the total sha

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Published Manuscripts are peer-reviewed
These are NOT press releases
These are not 3rd party websites

Conclusions and relevance: In this randomized clinical trial of zilucoplan in ALS, treatment did not alter disease progression. The adaptive platform design of the HEALEY ALS Platform Trial made it possible to test a new investigational product with efficient use of time and resources.

Abstract

Abstract

Background: Trehalose is a disaccharide that activates autophagy pathways in animal models of neurodegenerative diseases, with the potential to catalyse clearance of toxic, misfolded proteins in motor neurons and slow disease progression in amyotrophic lateral sclerosis (ALS). We aimed to evaluate the safety and efficacy of trehalose in individuals with ALS.

Methods: The HEALEY ALS Platform Trial is a perpetual, adaptive, phase 2/3, randomised, double-blind, multi-regimen trial conducted at 60 geographically diverse sites in the USA. In the current regimen, adults with clinically possible, probable, laboratory-supported probable, or definite ALS, defined by the revised El Escorial criteria, were randomly allocated (3:1), stratified by use of edaravone and riluzole, to receive trehalose 0·75 g per kg intravenously weekly over 24 weeks, or matching placebo. The primary outcome was a composite of the relative rate of disease progression, as measured by the Revised ALS Functional Rating Scale (ALSFRS-R), and survival over 24 weeks, estimated in a Bayesian shared-parameter model. The study included prespecified stopping rules for futility; interim analyses occurred every 12 weeks. The primary outcome was analysed according to the intention-to-treat principle in all participants in the trehalose group, the placebo group within the regimen, and placebo groups from other contributing regimens; the safety analysis population was comprised of all participants who initiated treatment. This study is registered with ClinicalTrials.gov, NCT05136885.

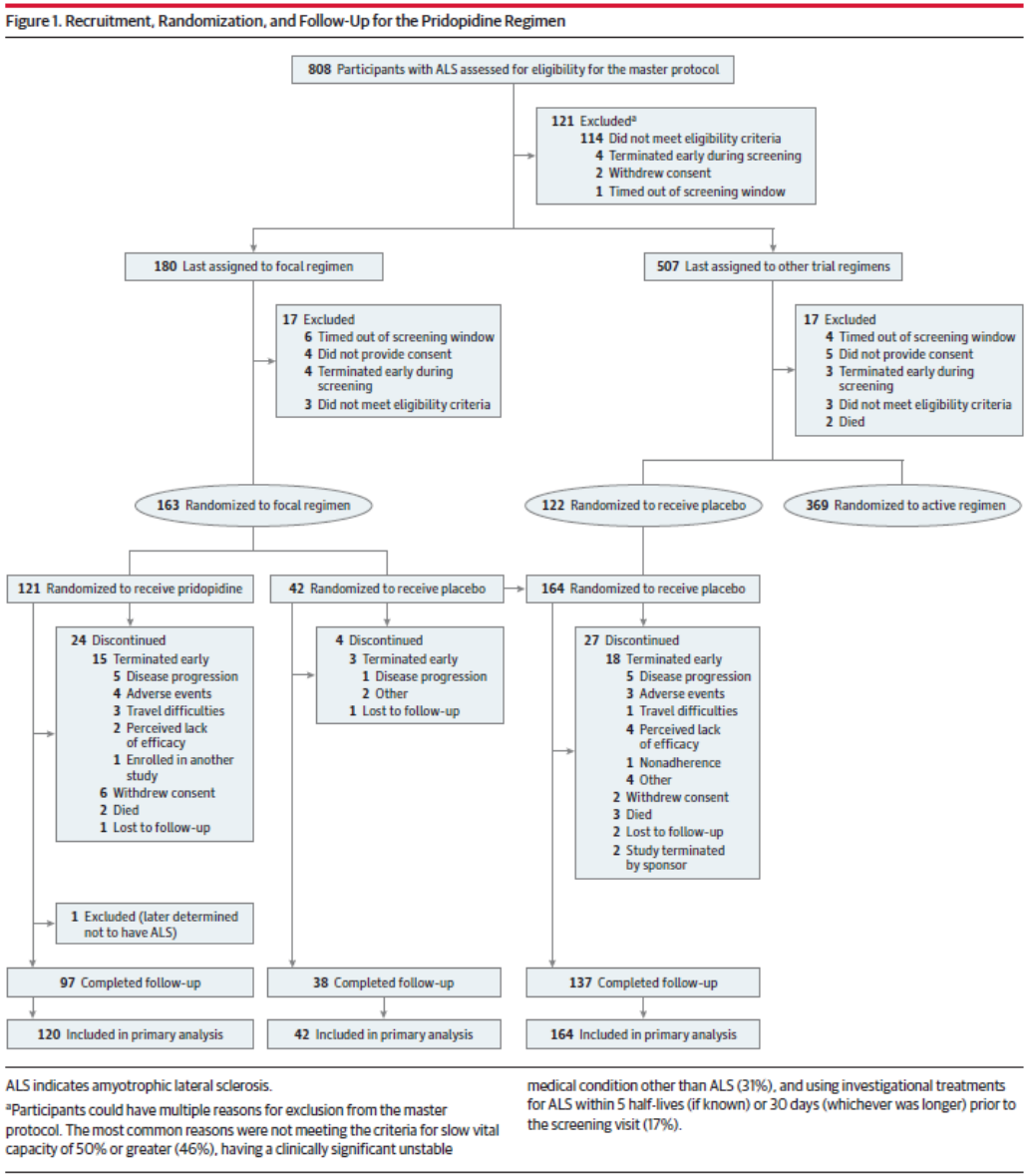
Findings: Between Feb 21, 2022, and Feb 1[illegible], 20[illegible] trial and 171 were assigned to the trehalose reg[illegible] with 120 randomly allocated to trehalose and 4[illegible] randomly allocated to placebo in other regimen[illegible] recipients). The disease rate ratio for change in [illegible] 0·665-1·102, posterior probability of superiority [illegible] participants in the trehalose group and three (7[illegible] leading to premature discontinuations in 14 (12[illegible] emergent adverse events occurred in seven par[illegible] regimen-only placebo group. No death was cor[illegible] cause of death was respiratory failure, consistent with the natural history of ALS.

Interpretation: Trehalose was well tolerated but there was no evidence to suggest a difference in ALS disease progression compared with placebo in this study. No statistical benefit was seen in secondary clinical or biomarker measures, suggesting that trehalose at this dosage is unlikely to be efficacious for treatment of ALS.

Funding: AMG Charitable Foundation, Tackle ALS, the ALS Association, ALS Finding a Cure, the Muscular Dystrophy Association, ALS ONE, the Arthur M Blank Family Foundation, I AM ALS, Tambourine ALS Collaborative, and other community fundraising initiatives and donors. Study drug and partial regimen-related funding was provided by Seelos.

Interpretation: Trehalose was well tolerated but there was no evidence to suggest a difference in ALS disease progression compared with placebo in this study. No statistical benefit was seen in secondary clinical or biomarker measures, suggesting that trehalose at this dosage is unlikely to be efficacious for treatment of ALS.

Consort Diagram (Figure 1)



Participant Flow

Standardized format for all CONSORT Diagrams

Screening

Randomized to

Completed

Analysed

Table 1: Baseline Characteristics

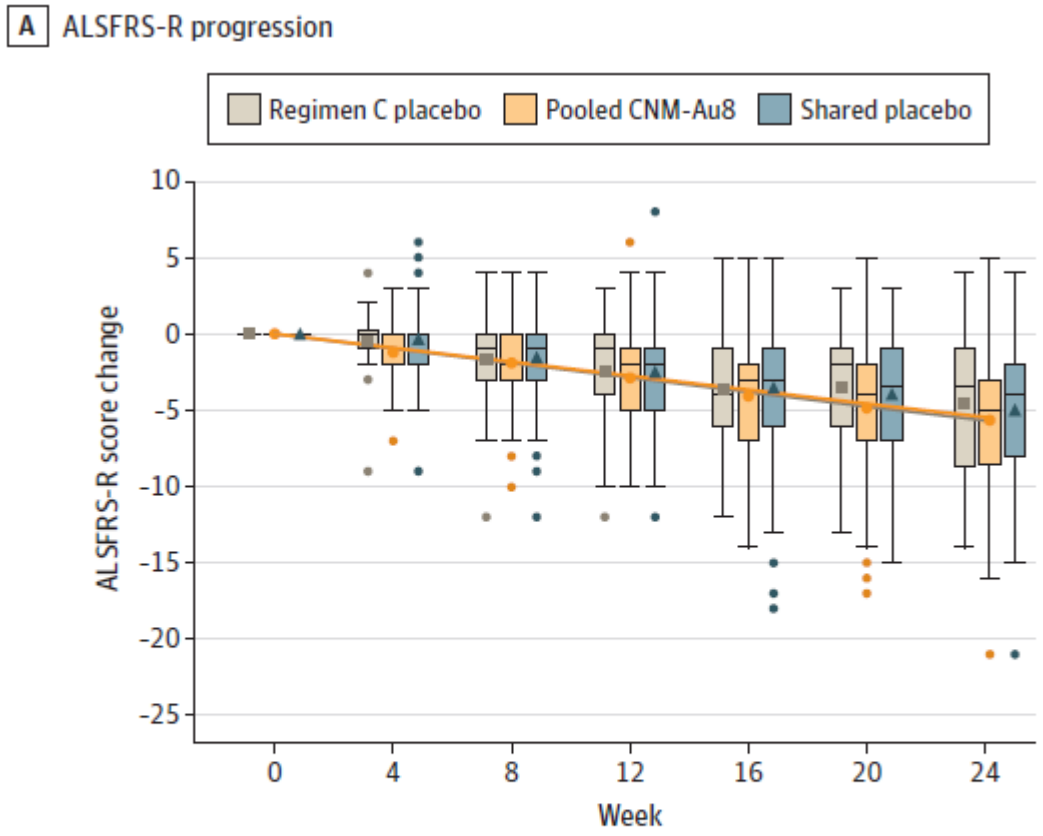
Table 1. Demographic and Baseline Characteristics of Participants in the HEALEY ALS Platform Trial Regimen C (CNM-Au8)

Characteristic	No. (%)			
	CNM-Au8		Placebo	
	30 mg (n = 59)	60 mg (n = 61)	Shared (n = 164)[a]	Regimen-specific (n = 41)
Sex				
Female	26 (44.1)	23 (37.7)	49 (29.9)	12 (29.3)
Male	33 (55.9)	38 (62.3)	115 (70.1)	29 (70.7)
Race				
Asian			2/160 (1.2)[b]	
Black or African American			6/160 (3.8)[b]	2 (4.9)
White	59 (100.0)	61 (100.0)	151/160 (94.4)[b]	38 (92.7)
Multiple races			1/160 (0.6)[b]	1 (2.4)
Ethnicity				
Not Hispanic or Latino	56 (94.9)	60/60 (100.0)	157/163 (96.3)	38 (92.7)
Age, mean (SD), y	57.7 (10.2)	58.6 (9.9)	57.2 (11.3)	57.0 (11.7)
BMI, mean (SD)	27.4 (5.3)	26.6 (4.8)	27.3 (5.0)	28.4 (5.5)
Bulbar onset	10 (16.9)	8 (13.1)	29 (17.7)	6 (14.6)
El Escorial criteria[c]				
Clinically definite ALS	28 (47.5)	30 (49.2)	66 (40.2)	14 (34.1)
Clinically probable ALS	22 (37.3)	21 (34.4)	40 (24.4)	10 (24.4)
Clinically probable ALS - laboratory-supported	8 (13.6)	8 (13.1)	42 (25.6)	16 (39.0)
Clinically possible ALS	1 (1.7)	2 (3.3)	16 (9.8)	1 (2.4)
King's stage[d]				
1 (1 clinical region involved)	3 (5.1)	10 (16.4)	34 (20.7)	9 (22.0)
2 (2 clinical regions involved)	18 (30.5)	18 (29.5)	39 (23.8)	11 (26.8)
3 (3 clinical regions involved)	22 (37.3)	19 (31.1)	45 (27.4)	7 (17.1)
4a/4b (nutritional failure)	1 (1.7)		1 (0.6)	
4b (respiratory failure)	15 (25.4)	14 (23.0)	45 (27.4)	14 (34.1)

Participant Characteristics

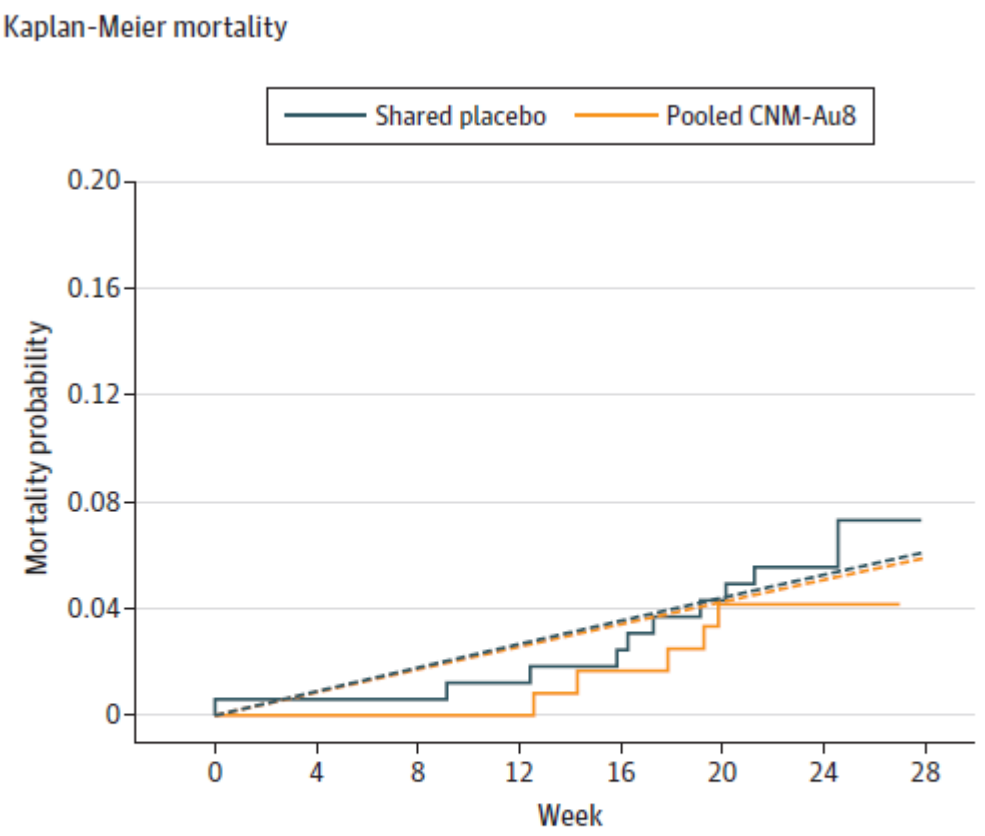
- Columns for Active and Placebo separate
- For HEALEY we also separate out “shared placebo” and “regimen-placebo”
- Eyeball to see if groups look similar

Results figures – HEALEY papers



No. of participants at risk

Shared placebo	154	151	148	147	145	140	140
Pooled CNM-Au8	115	115	111	112	109	110	111
Regimen C placebo	37	36	36	37	35	35	34



No. of participants exposed (No. of events)

Shared placebo	164	162	162	160	158	155	115	0
	(1)	(0)	(0)	(1)	(2)	(3)	(2)	(1)
Pooled CNM-Au8	120	120	120	120	118	115	91	1
	(0)	(0)	(0)	(0)	(2)	(3)	(0)	(0)

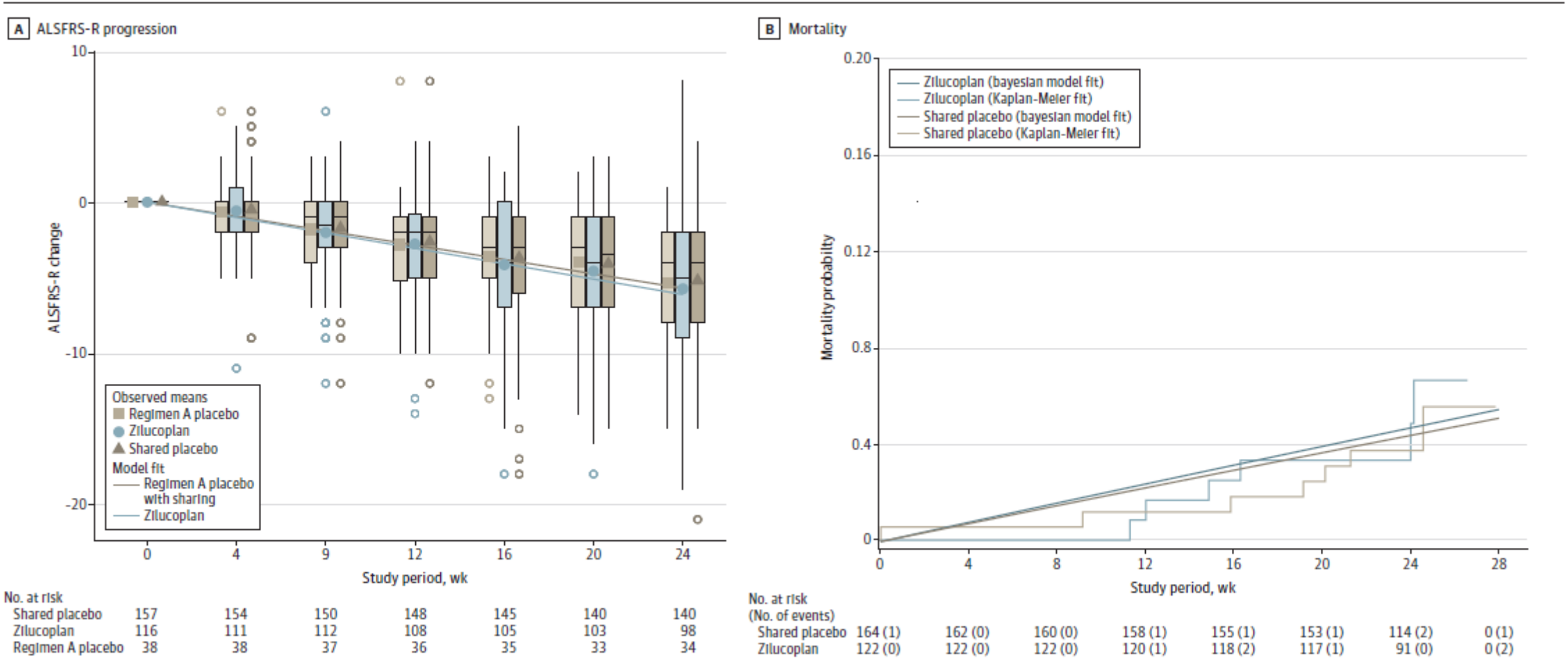
Disease Rate Ratio (DRR): 0.97; 95% credible interval 0.78 to 1.18; posterior probability of superiority = 0.65

DRR and complicated statistics

- Disease Rate Ratio (DRR)
  - How to interpret effect measures should be explained in methods section
- posterior probability of superiority [Pr(DRR<1)]
  - Different than a p-value
  - P-value lower is better
  - Pr(DRR<1) higher is better

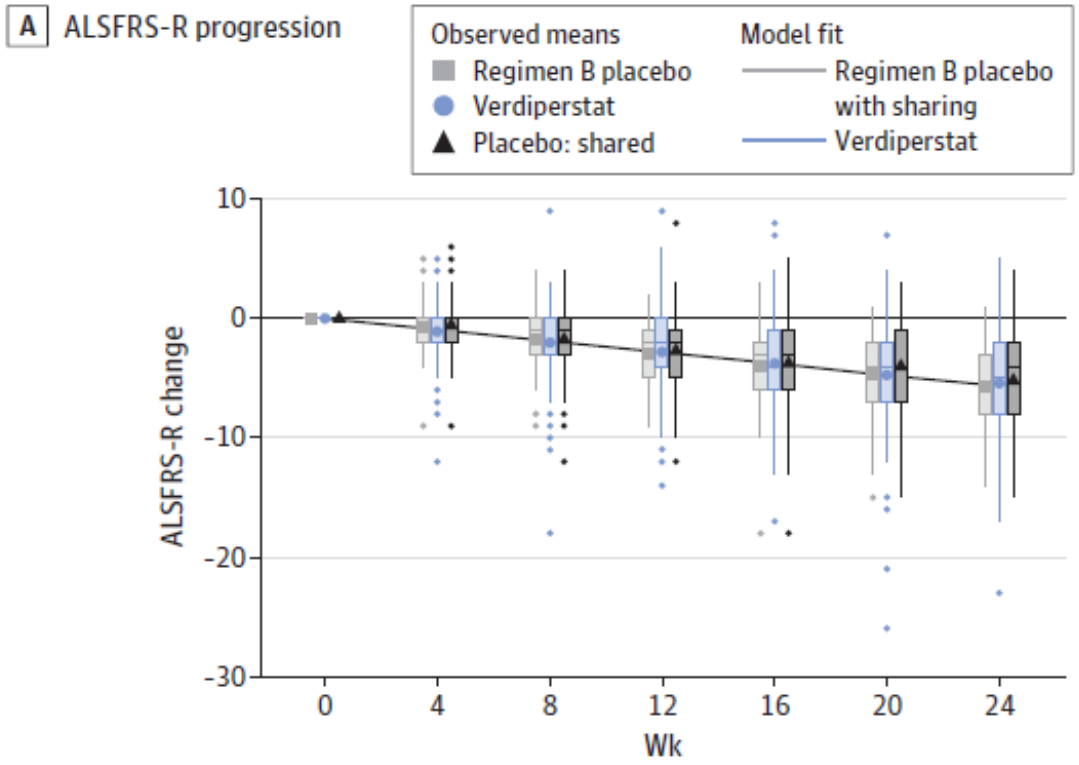
The model has components for function (measured by the ALSFRS-R) and survival that are linked through an integrated estimate of disease slowing in treatment relative to controls across the 2 end points (denoted as the disease rate ratio [DRR]). A DRR of 1 corresponds to no difference between treatments, whereas DRR values of less than 1 indicate slowing in disease progression on treatment relative to placebo. In the functional component, ALSFRS-R data are

Results figures – HEALEY papers

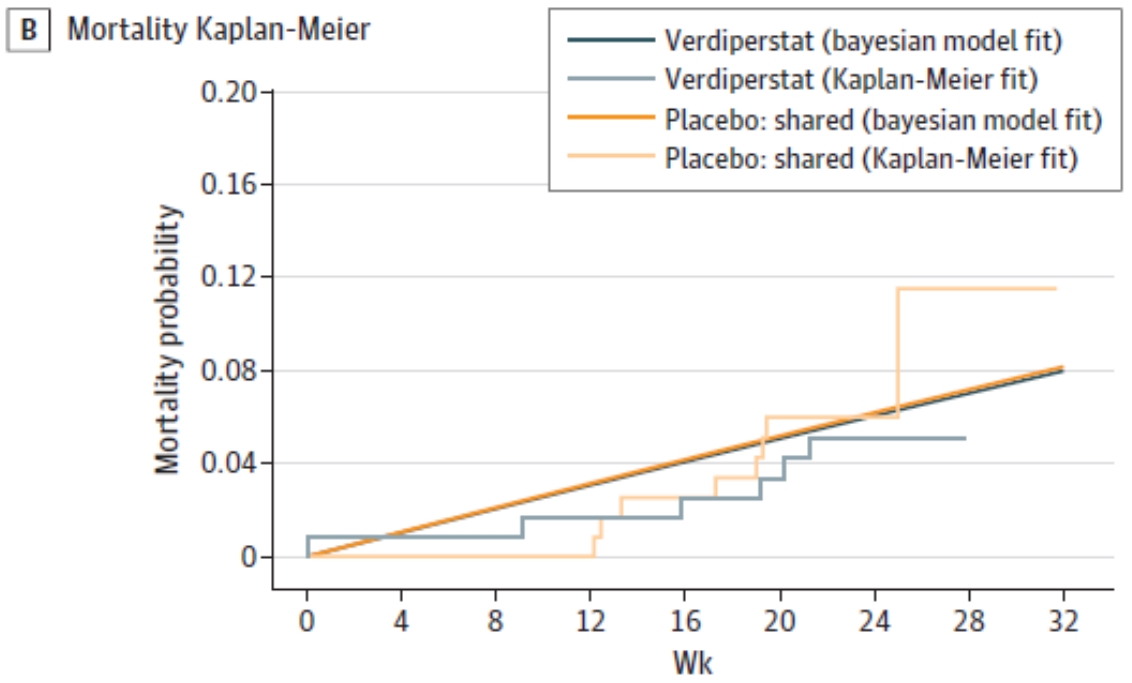


Disease Rate Ratio (DRR): 1.08; 95% credible interval 0.87 to 1.31; posterior probability of superiority = 0.24

Results figures – HEALEY papers



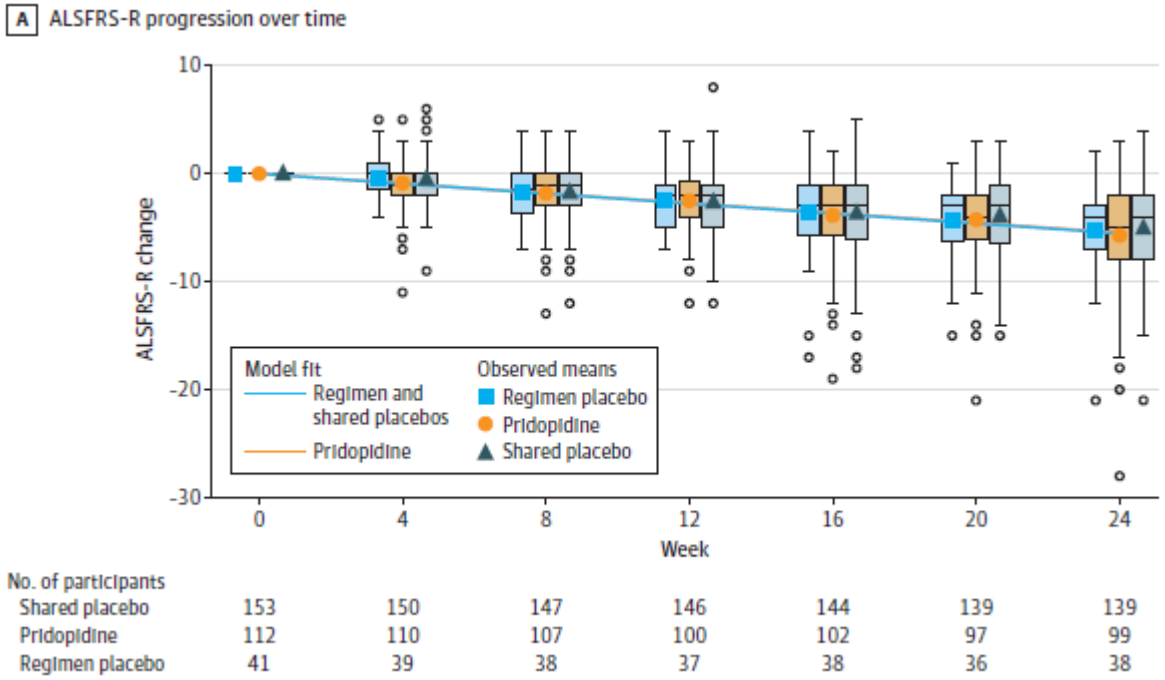
Sample size							
Placebo: shared	116	115	112	111	107	104	102
Verdiperstat	117	113	109	104	97	97	96
Regimen B placebo	39	39	38	37	37	36	34



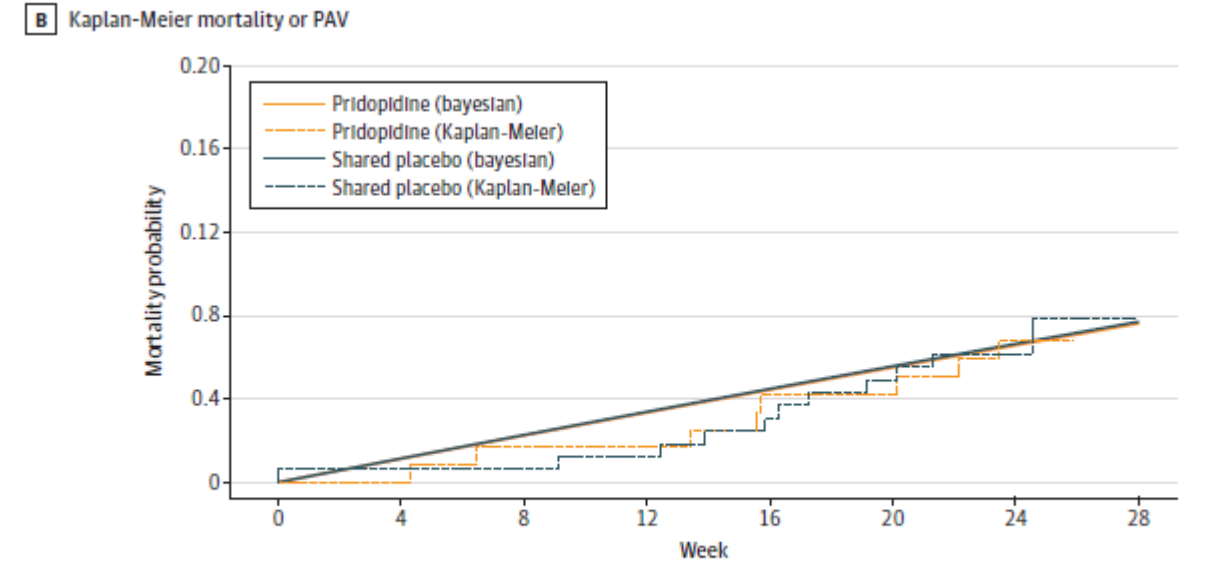
No. exposed (No. of events)									
Placebo: shared	122 (1)	121 (0)	119 (0)	117 (1)	114 (1)	112 (1)	87 (2)	0 (0)	0 (0)
Verdiperstat	126 (0)	124 (0)	122 (0)	119 (0)	114 (3)	108 (4)	83 (0)	1 (2)	0 (0)

Disease Rate Ratio (DRR): 0.98; 95% credible interval 0.77 to 1.24; posterior probability of superiority = 0.57

Results figures – HEALEY papers



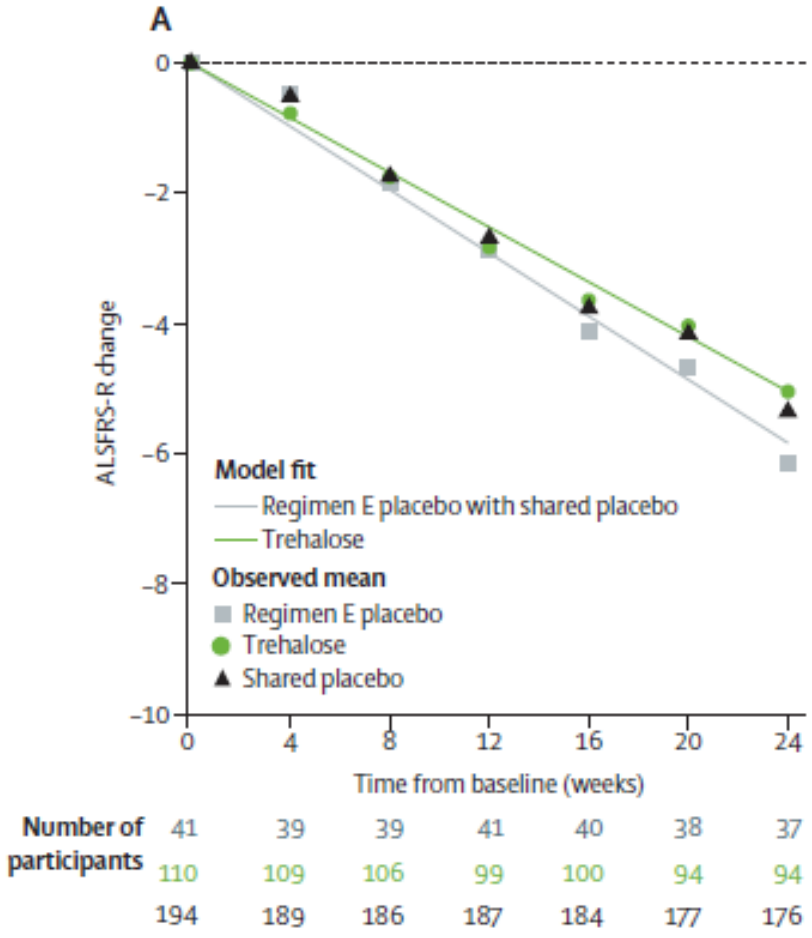
No. of participants							
Shared placebo	153	150	147	146	144	139	139
Pridopidine	112	110	107	100	102	97	99
Regimen placebo	41	39	38	37	38	36	38

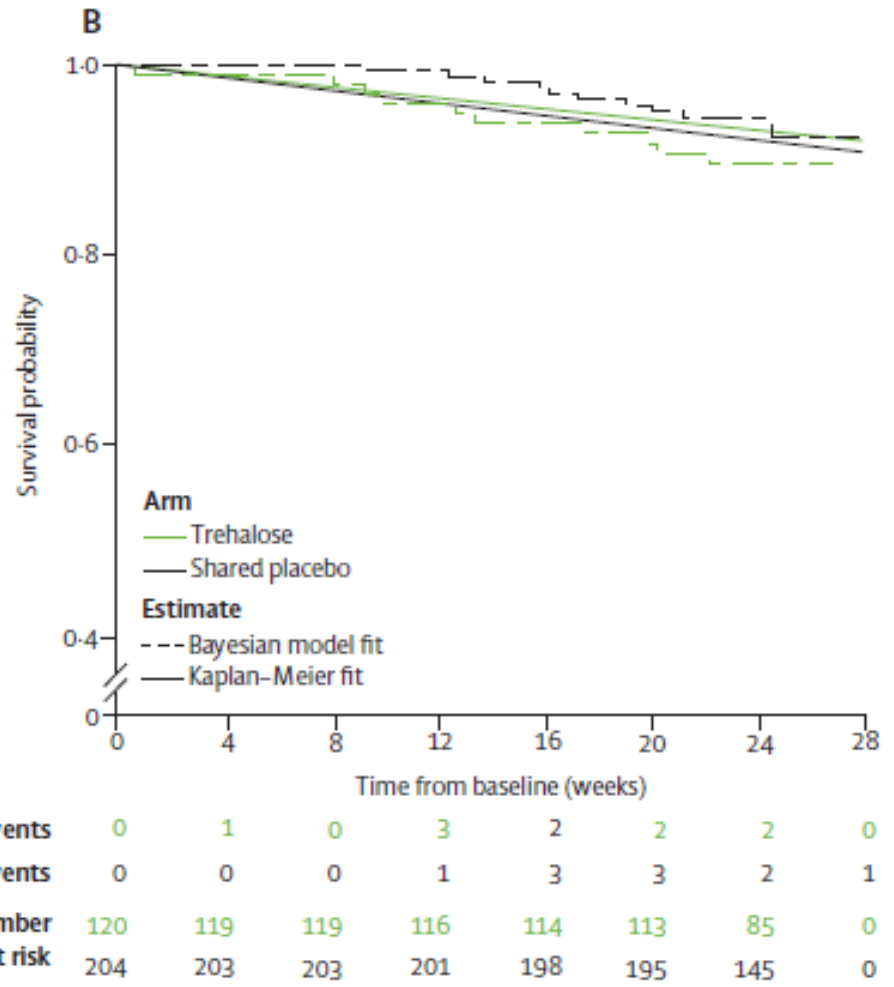


No. of participants exposed (No. of events)								
Shared placebo	164 (1)	162 (0)	162 (0)	160 (1)	157 (3)	154 (3)	115 (2)	0 (1)
Pridopidine	120 (0)	120 (0)	117 (2)	117 (0)	114 (3)	112 (0)	81 (3)	0 (0)

Disease Rate Ratio (DRR): 0.99; 95% credible interval 0.80 to 1.21; posterior probability of superiority = 0.55

Results figures – HEALEY papers





Disease Rate Ratio (DRR): 0.87; 95% credible interval 0.67 to 1.10; posterior probability of superiority = 0.88

Results

Table 2. Results for Secondary Outcomes Using Repeated-Measures Analysis[a]

	Treatment group, 24-wk change estimate (SE)		Difference from shared placebo	
End point	Zilucoplan	Placebo[b]	Difference (SE) [95% CI]	*P* value
FAS population				
ALSFRS-R total score	−6.48 (0.49)	−5.61 (0.41)	−0.87 (0.63) [−2.11 to 0.36]	.17
HHD upper extremity, % change	−33.60 (3.21)	−30.84 (2.68)	−2.77 (4.08) [−10.78 to 5.25]	.50
SVC, % predicted	−9.66 (1.42)	−8.57 (1.16)	−1.09 (1.82) [−4.66 to 2.48]	.55
HHD lower extremity, % change	−17.38 (3.53)	−19.34 (2.93)	1.96 (4.49) [−6.86 to 10.77]	.66
Serum NfL chain protein, % change[c]	−3.19 (NA)	1.90 (NA)	−5.00 (NA) [−15.09 to 6.29]	.37
ERO population				
ALSFRS-R total score	−6.52 (0.52)	−5.85 (0.88)	−0.67 (1.01) [−2.66 to 1.33]	.51
HHD upper extremity, % change	−34.82 (3.55)	−28.33 (5.91)	−6.49 (6.81) [−19.94 to 6.96]	.34
SVC, % predicted	−9.76 (1.55)	−6.66 (2.58)	−3.10 (2.97) [−8.96 to 2.76]	.30
HHD lower extremity, % change	−18.12 (3.78)	−23.56 (6.22)	5.44 (7.18) [−8.76 to 19.64]	.45
Serum NfL chain protein, % change[c]	−1.74 (NA)	5.72 (NA)	−7.06 (NA) [−24.49 to 14.40]	.49

Results

Table 3. Key Primary and Secondary Outcome Results Using the Repeated-Measures Model for Functional End Points and Cox Proportional Hazards Model for Survival Analyses

End point	24-wk Change estimate		Difference from shared placebo	
	Verdiperstat, mean (SE)	Shared placebo, mean (SD)	Difference (SE) [95% CI]	*P* value
Repeated-measures model				
Full-analysis set population[a]				
No.	126	122	NA	NA
ALSFRS-R total score	−6.26 (0.55)	−5.95 (0.52)	−0.31 (0.74) [−1.76 to 1.15]	.68
HHD-upper (% change)	−29.29 (3.37)	−31.34 (3.12)	2.05 (4.47) [−6.73 to 10.83]	.65
SVC (% predicted)	−7.76 (1.52)	−8.05 (1.42)	0.29 (2.05) [−3.74 to 4.32]	.89
HHD-lower (% change)	−19.49 (3.75)	−21.78 (3.54)	2.30 (5.1) [−7.71 to 12.31]	.65
End point	**24-wk Change estimate**		**Difference from shared placebo**	
	Verdiperstat	Regimen-only placebo	Difference (SE) [95% CI]	*P* value
Efficacy regimen only population[b]				
No.	126	41		
ALSFRS-R total score	−6.58 (0.6)	−6.69 (0.96)	0.11 (1.11) [−2.08 to 2.30]	.92
HHD-upper (% change)	−31.67 (3.35)	−39.91 (5.27)	8.24 (6.13) [−3.88 to 20.36]	.18
SVC (% predicted)	−8.34 (1.454)	−10.64 (2.28)	2.30 (2.69) [−3.01 to 7.61]	.39
HHD-lower (% change)	−19.77 (3.98)	−21.57 (6.28)	1.80 (7.31) [−12.65 to 16.25]	.81
End point	**24-wk Events**		**Comparison with shared placebo**	
	Verdiperstat	Shared placebo	Hazard ratio (95% CI)	*P* value
Cox proportional hazards model				
Full-analysis set population				
No.	126	122	NA	NA
Survival, unadjusted, No./total No.	7/126	5/121	1.75 (0.60 to 5.69)	.32
Survival, adjusted[c]	NA	NA	1.54 (0.52 to 5.10)	.45
End point	**24-wk Events**		**Comparison with RGB placebo**	
	Verdiperstat	Regimen-only placebo	Hazard ratio (95% CI)	*P* value
Efficacy regimen-only population				
No.	126	41	NA	NA
Survival, unadjusted, No./total No.	7/126	2/41	1.50 (0.39 to 9.88)	.60
Survival, adjusted[d]	NA	NA	1.53 (0.39 to 10.1)	.59

What else?

- Post-hoc analyses
- Supplemental Materials
  - Additional information on methods
  - Additional results that didn’t fit in the paper (e.g. sub-group analyses)
  - More post-hoc analyses
  - Some things a reviewer really wanted to see
  - The official Statistical Analysis Plan (SAP) and Protocol

When overwhelmed look to the conclusions

B

Conclusions

In this randomized clinical trial, despite the negative results of this particular regimen, it is worth mentioning that the adaptive platform trial design efficiently answered the important question about clinical efficacy of verdiperstat in ALS. In this respect, the overall platform trial achieved its main objective of rapidly screening experimental drugs for clinical efficacy signal in an adequately powered phase 2 randomized clinical trial and excluding drugs and/or targets if not relevant in ALS. This and other scientific, statistical, and operational efficiencies that the platform trial paradigm brings to ALS therapeutic development is detailed in the review by Paganoni et al.[24]

E

In conclusion, this study showed that trehalose, although safe and well tolerated, was not an effective treatment at the selected dose to slow disease progression in ALS in the selected study population. Although this result is disappointing, it highlights the efficiency of the HEALEY ALS Platform Trial and its goal of rapidly determining the potential of new candidate therapeutics for ALS.

Patient Navigation

Central resource for people living with ALS

Two webinars per month

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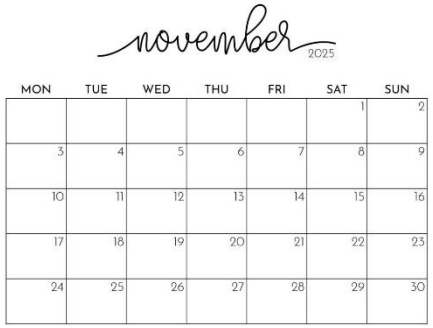

Upcoming Webinars (Thurs, 5:00- 5:30pm EST):

November 13 – Expanded Access Discussion

November 20 – Platform Trial Discussion