July 2, 2025

VIA ELECTRONIC SUBMISSION
Docket No. FDA-2013-S-0610

Division of Dockets Management
Department of Health & Human Services
Food & Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Honorable Secretary Robert F. Kennedy Jr.
Dep't of Health & Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

CommissionersOffice@fda.hhs.gov
Marty Makary, MD MPH
Commissioner of the FDA
10903 New Hampshire Avenue
Silver Spring, MD 20993

Vinay Prasad, MD MPH
Chief Medical & Scientific Officer
Director of the Center for
Biologics Evaluation & Research
Food & Drug Administration

Re: Citizens' Petition Requesting FDA Approve Debamestrocel based on New Evidence and Totality of the Evidence

Secretary Kennedy, Commissioner Makary and Director Prasad:

The undersigned Petitioners Klingenberg, Stevens, Smith, Muggli, Simons, Krummel, Rogers, Saenz, Collazo, Manhardt, Berry, Saxena, Minokadeh, Warack, et al., submit this petition under 21 U.S.C. section 301 et seq., in accord with 21 C.F.R. sections 10.25(a) and 10.30. Petitioners request the following ACTIONS by the Commissioner of the Food and Drug Administration to:

A. ACTIONS REQUESTED:

1. Invite the drug sponsor, Brainstorm Cell Therapeutics, to re-file its Biologics License Application (BLA) for debamestrocel (aka "NurOwn"), a first-in-class, autologous, mesenchymal stem cell therapy enhanced with neurotrophic factors.
2. Approve debamestrocel for ALS, with a Phase 4 study mandating participation in a biorepository with a natural history and exposome database.
3. Expedite the review of this evidence using the Commissioner's new Priority Voucher system.

B. STATEMENT OF GROUNDS:

Petitioners submit that the FDA's *de novo* review should include the new survival, respiratory, functional and biomarker data; the real-world evidence; expert opinions; and the existing "totality of the evidence" -- all of which demonstrate that NurOwn improves how people "feel, function and survive."

First, Petitioners are submitting herein new long-term data from the Expanded Access Program and those data are evidence of efficacy that are unprecedented in the history of ALS clinical trials:

- 100% Five-year Survival versus 20% ALS natural history
- Tracheostomy-free survival - as much as 5 years longer than median ALS natural history
- Overall Survival improved by 5.5 months over matched controls as of 2022
- Extended periods of Progression-free survival (PFS)
- Long-term slowing of ALS progression by as much as 85%
- Significant impact on respiratory function as measured by 5 - 8 year delay in time-to-event for non-invasive ventilation; and favorable changes in forced vital capacity
- Decreases of in CSF neurofilament light, a biomarker of harmful neurodegeneration

Survival data are the gold standard for drug approvals and NurOwn's survival data are unprecedented in ALS. NurOwn's survival data also meet or exceed the survival data supporting the Accelerated Approval of various cancer therapies.

The 2019 ALS Guidance Document provides that "the demonstration of a treatment benefit on respiratory endpoints may also provide evidence of effectiveness." Respiratory outcomes can include progression to mechanically assisted ventilation as well as measures of respiratory function, such as forced vital capacity. NurOwn caused unprecedented, large magnitude improvements in time to tracheostomy, time to non-invasive ventilation and FVC.

NurOwn's CSF biomarker data is objective data demonstrating target engagement across biological pathways of neuroinflammation, neurodegeneration and neuroprotection. And all of this new data -- coupled with the totality of the evidence -- prove that people with ALS "live longer and live better" when receiving NurOwn.

Thus, NurOwn meets the statutory threshold of "substantial evidence" of efficacy. Both the quality and quantity of evidence meet the threshold for traditional approval with one trial plus supporting evidence. And the NurOwn Phase 3 and EAP data meet the "reasonable likelihood" threshold for accelerated approval. Those survival, respiratory and biomarker data, both individually and collectively, are data that are reasonably likely to predict a clinically meaningful impact and/or to predict an impact on mortality.

Petitioners also reassert Brainstorm's position that those biomarker data demonstrate a plausible mechanism of action and target engagement across disease pathways of neuroinflammation, neurodegeneration and neuroprotection. As such, NurOwn meets the Commissioner's new "plausible mechanism of action" threshold. And finally, the FDA can exercise its promised regulatory flexibility to approve NurOwn for this 100% terminal, heterogenous rare disease with a critical unmet need.

Second, the expedited review of this evidence is appropriate under the Commissioner's new Priority Voucher system. Since NurOwn first showed efficacy on some in the Phase 2 trial in 2015, approximately 60,000 Americans have died waiting when this stem cell therapy could have helped them live. The ALS community cannot wait four years for the completion of yet another Phase 3 trial.

Likewise, people cannot wait 180 days for the response to this Petition then another 10+ months for review of the data from the trial and EAP.

C. Environmental Impact – None

D. Economic Impact – None.

E. Certification:

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

Petitioners are aware of many other people who believe NurOwn helped them. If they have confirmation that they received NurOwn, we invite them or their family members to reach out to share that evidence with Petitioners Nick Warack or Mitze Klingenberg, mother of the lead Petitioner.

Electronically submitted this 2nd day of July 2025,

_____

Nicholas Warack, Esq.
Veterans4Nurown@gmail.com

Other Petitioners:
Matt Klingenberg - NurownWorks@gmail.com
Eric Stevens
Joshua Smith
Lesley Krummel
Estate of Kade Simons
Estate of Roberto Muggli
Estate of Justin Rogers
Terri Pickering Saenz
Tara Collazo
Mayuri Saxena
Estate of Jamie Rose Berry
Estate of Patricia Manhardt
Shahriar Minokadeh, MD

TABLE OF CONTENTS

GRAPHICS

Table of Contents

35. Totality Of Evidence in Floor Effect Subgroup Consistent Across Endpoints
36. Totality Of Evidence in Floor Effect Subgroup Consistent Across Domain Subscales
37. Totality Of Evidence in Floor Effect Subgroup Consistent Across Endpoints
38. Secondary Endpoints by Cut-point ≥ 26 to ≥35
39. Primary Endpoint: No Floor Effect Subgroup and ≥ 27 Subgroup
40. Secondary Endpoint: No Floor Effect Subgroup and ≥ 27 Subgroup
41. Tofersen Change from Baseline at 28 weeks
42. Tofersen vs. NurOwn: Change from Baseline at 28 weeks
43. NurOwn Primary & Secondary Endpoint ≥35 Demonstrating Stabilization
44. NurOwn's Phase 2 Trial Results
45. NurOwn's Phase 2 Trial Results ≥100% Improvement in Slope in Rapid Progressors
46. Tofersen's Phase 3 Survival Data in A5V Rapid Progressors
47. Eric Stevens' ALSFRS-R Phase 3 and EAP
48. Josh Smith's ALSFRS-R scores in Phase 3 and EAP
49. Kade Simons' ALSFRS-R scores in Phase 3 and EAP
50. Lesley Krummel's ALSFRS-R scores in Phase 3 and EAP
51. Justin Rogers' Bulbar Survival versus Median Survival from Diagnosis
52. Right to Try Bill Signing with Matt Bellina and Nicole Cimbura
53. Tara Collazo's ALSFRS-R scores by Domain
54. Military Medicine Study regarding Post 9/11 Veterans and ALS
55. Matt Bellina's Real-World Data
56. WLWT Broadcast: Fighting for Their Lives
57. Time-to-Event Data in ALS
58. Time-to-NIV
59. Josh Smith's FVC Tests 2020 Pre-EAP vs. 2021 Post-EAP
60. FVC Tests 2021 vs. 2022 Post-EAP for Eric Stevens and Phil Green
61. NurOwn CSF Biomarkers across 3 Primary Pathways
62. NurOwn CSF Biomarkers PCA across 3 Primary Pathways
63. NurOwn Biomarker Changes (Table S3 in Muscle & Nerve)
64. Totality of CSF Biomarker Evidence Supports Mechanism of Action
65. FDA Slides about Neurofilament Light from Tofersen AdComm
66. NurOwn's Neurofilament Light Results from Phase 3
67. NurOwn's Neurofilament Light Results from Phase 3 and EAP
68. NurOwn's Neurofilament Light Results from Early Start vs Delayed Start in EAP
69. NurOwn's Neurofilament Light Results - Percentage of Change Bar Chart
70. NurOwn's Neurofilament Light Results - Percentage of Change - by Participant
71. Neurofilament Light Pattern Changes - NurOwn vs. Tofersen
72. UNC13A and the 66 Mis-splicing Genes in ALS
73. UNC13A in ALS GWAS

74. UNC13A (A/C) Responder Analysis in NurOwn Phase 3 Trial
75. FDA's Presentation Slide of Neurotrophic Factors for ALS Treatments
76. Neurotrophic Factors for ALS: BDNF, GDNF, EGF and HGF
77. NurOwn's Phase 3B Trial Design
78. NurOwn Timeline
79. Tukysa Partial Response
80. Vitrakvi
81. ALS KOL, Mayo's Dr. Windebank AdComm Testimony that NurOwn Works
82. NurOwn's Totality of the Evidence: p-values by endpoint and cut-point
83. Post Hoc Data Used in all Four ALS Drug Approvals
84. Tofersen Post Hoc Data Accepted
85. PFDD – Patient Experience
86. C-Path's COAs: Patient Experience and PFDD
87. Phase 2 and 3 Data Confirms Some Patients Halted Progression
88. FDA's Regulatory Flexibility Slide from Tofersen AdComm
89. Plausible MOA: Stem Cell Trials in ALS
90. Plausible MOA: Stem Cell Trials in Other Neurodegenerative Diseases
91. Risk-Benefit: Risk of Type II Errors
92. Heterogeneity in ALS Trials and Impact on Trial Outcomes
93. Heterogeneity: SETX-VUS
94. Gene-Time-Environment Hypothesis
95. Genetic Risk and ALS Exposome
96. Genetic Risk and ALS Exposome Natural History Database
97. Prospective ALS Exposome Natural History Database
98. NurOwn Phase 3 Trial Participant Betsy McCormick on Cancelled EAP

SUMMARY OF PETITIONERS' ARGUMENT

NurOwn marries the promise of stem cell therapies with the science of neurotrophic factors. In the 2016 documentary, *"Die Trying: the Battle for ALS Treatments,"* Mayo Clinic's Dr. Tony Windebank described the innovative mechanism of action of Brainstorm's autologous mesenchymal stem cell therapy enhanced with neurotrophic factors (MSC-NTF):[1]

> *"One of the important steps in the Brainstorm trial is that the cells come out of the bone marrow and then they're treated in a way that makes them protective for nerve cells. So they're kind of **enhanced stem cells**... He'll have a spinal tap and that allows us to inject the stem cells into the fluid around the spinal cord. When you have an injury anywhere in your body, those cells will move out of the bone marrow and they go to the area that's injured and they aid the healing process. Now we're taking these healing cells and we're putting them into the nervous system, so we're putting them into a place where they don't usually go."*

(See documentary at 12:45).

Developed by world-renowned neurologist and researcher Eldad Melamed, NurOwn combines the restorative powers of stem cells with the regenerative powers of neurotrophic factors. One neurologist explained that neurotrophic factors are like "Miracle-Gro" for your neurons. But the problem in the past has been the delivery system. Neurotrophic factor trials have failed as oral or IV delivery systems couldn't overcome the obstacles presented by the blood brain barrier. Uniquely, NurOwn uses your body's own stem cells as an innovative delivery system for those neurotrophic factors. Once injected directly into the CSF, your stem cells work like a Fed Ex truck, delivering nano-packages of neurotrophic factors and immunomodulatory cytokines directly to the sites of the motor neurons damaged by ALS.

Almost immediately those "healing cells" go to work. Within a few days, people reported that NurOwn improved how they felt and functioned. And with more doses, we now have proof that NurOwn improves how long they survive. (See details of that survival data starting on page 18 of this Petition).

When people are dying, they know when a drug helps them live. When people are becoming paralyzed, they know when a drug helps them move again. And when people can't breathe without a non-invasive ventilator, they know when a drug helps them breathe again. That's what NurOwn did. Patient experiences and real-world evidence should matter.

When world-renowned neurologists like Anthony Windebank of Mayo and Robert Brown of UMass tell the FDA that they saw some patients regain function for the first time in their 40+ year careers of treating people with ALS -- their clinical observations should matter.

[1] Fanous, A. (Producer: HBO VICE News) (2016). *Die trying - The battle for ALS treatment*. [Video]. YouTube.

At the Advisory Committee meeting for NurOwn, Dr. Windebank presented the NurOwn clinical trial data and then shared his expert opinion about the clinically meaningful impact and "progression-free survival" that he observed when people received NurOwn:

> *"I would now like to provide my clinical perspective on NurOwn …. I think this data is compelling & it should be approved…. While not everyone responds to the treatment, there are clearly a SIGNIFICANT number who do. I have clearly seen some people STABILIZE in a way that I have never seen in any other trial.*
>
> *In fact, in the small number of people who participated in EAP & received 6-9 treatments, there were people who STABILIZED while on NurOwn in the trial. In the interval before they were in the EAP -- which was over a year or more in some cases – these participants deteriorated, then again STABILIZED in the additional treatment period. There were some who IMPROVED their score! Other investigators who have been working 'hands on' with the participants in the trial have seen similar responses...."*

When the data demonstrate a clinically meaningful and statistically significant change on those earlier in ALS progression and one of the world's top biostatisticians opines that the totality of the evidence methodology is most appropriate for rare disease trials – his expert opinion should matter.

When an innovative, small pharmaceutical company identifies two dozen first-in-class CSF biomarkers showing target engagement across biological pathways of neuroinflammation, neurodegeneration and neuroprotection – and no one on placebo had these changes – these plausible mechanisms of action and common sense should matter.

But most importantly, when all 10 people in the Expanded Access program significantly outlived or are outliving the ALS natural history, and the trach-free survival data meets or exceeds the survival data supporting Accelerated Approval in rare cancers, this survival data should matter.

Graphic- Survival Data - NurOwn Phase 3 Trial and EAP Data thru June 2025

NurOwn EAP - Trach-free Survival Data*

		Total EAP Population				EAP - Early vs Delayed Start			
SURVIVAL from	ALS Natural History	Survival Range	EAP Survival		△ months	6/10 Early Start (P3 NurOwn)	△ months	4/10 Delayed Start (P3 Placebo)	△ months
Symptom Onset	30.0	60-103 months	Median	85.0	55.0	85.0	55.0	73.5	43.5
			Mean	80.9		85		74.8	
Diagnosis	18.0	51-87 months	Median	78.0	60.0	78.0	60.0	68.5	50.5
			Mean	73.3		76.3		68.7	

1. Traxinger / Glass (2013). Prognosis and epidemiology of ALS: analysis of a clinic population
2. Chio / Traynor (NIH) (2009). Prognostic Factors in ALS: a critical review
3. Knibb / Al Chalabi (2016). A clinical tool for predicting survival in ALS

* No one in NurOwn EAP received a tracheosotomy
10/10 people in EAP survived / are survivng trach-free ≥ 5 years
6/10 still alive as of June 2025 - without tracheostomy

All of these events are unprecedented in ALS history and they merit an unprecedented response from the FDA. That is the remedy we are seeking in this Citizens' Petition.

The ALS community has long been imploring the FDA to customize its regulatory process. Nearly a decade ago, when Matt Bellina was advocating for Right to Try, he too spoke of the clinical trial obstacles to assessing efficacy in a 100% terminal, rare disease with unmatched heterogeneity:

> *"The current FDA Guidelines are preventing innovation…. The problem with ALS and a lot of these cancers is that* ***everybody's a little different. Everybody manifests a little differently. So, you can't compare two patients against each other****. Our current system with the FDA is not tailored to create drugs for diseases like this.* ***ALS is never going to be cured by a one-size-fits-all drug.****"*

In Commissioner Makary's confirmation hearings before Senator Murkowski and in his interview with Megyn Kelly, he spoke about the regulatory process for rare diseases like ALS:

> *"We have to customize the regulatory process to the condition that we're trying to be able to offer hope for… we cannot require two randomized control trials. We have to customize the regulatory process to what we're trying to do. If our goal is to try to provide safe and effective therapies, and I do believe firmly in that approach, I think we can use some common sense to ask some big questions we've never asked before at the FDA."*

Petitioners believe the OCE's Rare Cancers Program is an apt template for how to address rare, terminal, heterogeneous neurodegenerative diseases like ALS. As a cancer patient himself, former Commissioner Gottlieb understood the need for a modified risk-benefit assessment. In his 2018 speech at the Annual Conference of the American Society of Clinical Oncology, he advocated for urgency and regulatory flexibility when the mortality data is ominous.

> *"There are critics who say we should hold drugs back from the market, & demand more pre-market studies proving overall survival endpoints, before we consider approving new drugs. I disagree. And I suspect some of the patients who face long odds -- for whom available therapy gives them just a slim chance of long-term survival -- might also disagree.*
>
> *I had Hodgkin lymphoma. I had a very curable tumor. At the time of my diagnosis, I was told my odds of a cure were 90% or better…. So, I understand why demanding large, pristine studies ultimately serves the interest of patients like me. But my situation was very different than being diagnosed with cancer & being told your chance of surviving five years is 50%, or 30%, or just 10%. Available therapy isn't very promising if that's your circumstance. The ability to access novel treatments becomes more urgent in these circumstances.* ***Waiting 3 more years for another large, prospective, randomized trial to be completed – to confirm highly promising results already observed in an earlier clinical trial -- may not sound as compelling to the patient who faces these long odds."***

People in the ALS community are facing even more daunting odds — they have a 100% chance of dying. Over 50% will die within 18 months and less than 20% have a chance of living five years.

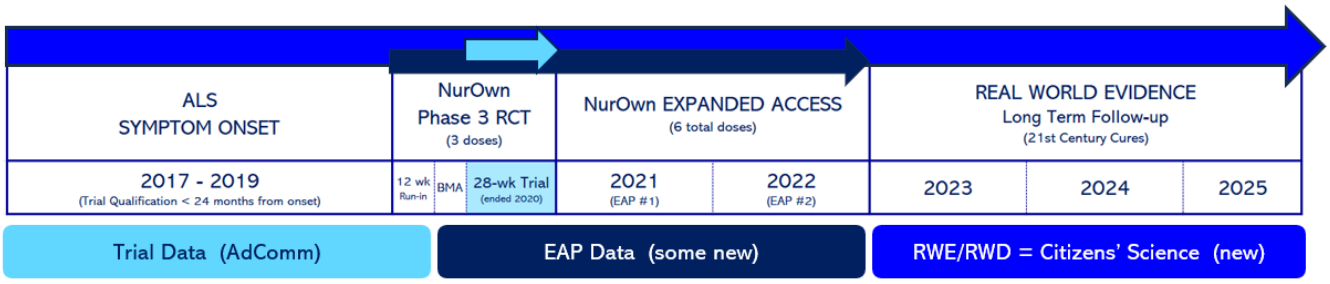
People with ALS can't wait another 3-5 years for yet another double-blinded, randomized controlled trial (RCT). Generations of people with ALS have already died waiting. Now is the time to change that inhumanity. Brainstorm's stem cell therapy is the way forward for thousands of people battling ALS.

In the keynote address at the National Organization for Rare Disorders (NORD) Rare Disease Scientific Symposium earlier in June 2025, Dr. Prasad outlined a framework aimed at accelerating access to therapies for rare diseases. He emphasized the FDA's commitment to approving promising therapies "at the first sign of promise," utilizing surrogate endpoints and regulatory flexibility to bypass traditional efficacy requirements for initial approvals, while relying on real-world data (RWD) to evaluate post-market outcomes. Petitioners submit that this policy framework is directly applicable to the FDA's review of NurOwn.

NurOwn has demonstrated evidence of efficacy in some people for over a decade. The ALS community desperately needs CBER to act on Commissioner Makary's promise to use both common sense and gold standard science; to emphasize urgency and regulatory flexibility; and to honor the spirit of Right to Try by ensuring people dying of ALS have access to promising therapies, while the FDA continues to study the promising therapy in rigorous and informative post-approval monitoring.

We respectfully urge the FDA to apply these principles to its evaluation of NurOwn. We are asking the FDA to consider the "totality of the evidence" from the short 28-week trial; the new evidence from the Expanded Access program; the unblinded real-world data and patient experiences spanning 6 to 8 years; and especially the new survival data that surpasses survival data of cancer therapies granted accelerated approval.

<u>Graphic</u> - NurOwn Totality of the Evidence from Phase 3 and EAP



Following is a summary of both unprecedented new and existing "substantial evidence" supporting our request for NurOwn's approval:

1. New EAP data demonstrating a 5.5 month Improvement in OS as of 2022
2. New EAP data demonstrating a 100% five-year survival rate far in excess of the 20% median ALS natural history
3. New and unprecedented data demonstrating years of improvement over median trach-free survival, as of June 2025
4. New, long-term respiratory function data that demonstrates a significant preservation of breathing function as evidenced by improvements in Forced Vital Capacity and significant extensions in Time-to-Event data for non-invasive ventilation
5. New long-term functional data that demonstrates a significant slowing in ALS progression (as much as 85%), outperforming any ALS therapy currently on the market
6. New survival data that far exceeds the survival data used to support accelerated approval of many cancer therapies
7. New, long-term progression free survival data that significantly outperforms any ALS therapy currently on the market
8. New, long-term functional data that demonstrates an ORR that meets or exceeds the ORR used to support accelerated approval of many cancer therapies
9. New EAP Neurofilament light data that demonstrates a significant decrease in neurodegeneration, and demonstrates a dose-dependent response in both the magnitude of change as well as the durability of those changes
10. Biomarker data that demonstrates target engagement and a plausible mechanism of action supporting accelerated or conditional approval
11. Biomarker data that demonstrates target engagement across ALS disease progression – regardless of ALSFRS-R score – but only in the NurOwn-treated arm, with no similar biological changes evidenced in the placebo arm
12. "Totality of the evidence" demonstrating that NurOwn had a dose-dependent response, with those who received the most doses of NurOwn the earliest in their ALS progression demonstrating the largest magnitude and longest durability of functional response
13. Expert opinions from world-renowned neurologists who opined that NurOwn caused unprecedented stabilization (and some improvements) in ways they had never seen in their 40-plus years as physician-scientists conducting ALS clinical trials
14. Expert opinions from treating neurologists, pulmonologists, respiratory and physical therapists who had never seen similar slowing, stabilization or improvements in function as they observed in clinic with their ALS patients who participated in the NurOwn trial
15. Real-world evidence, real-world data and newly unblinded lived patient experiences and PROs documenting that NurOwn interrupted, slowed and halted their lethal ALS progression and in some ways, improved how they felt and functioned
16. "Totality of the evidence" including dozens of "n of 1" case studies that demonstrate that NurOwn had a "clinically meaningful" impact on how people felt, functioned and survived

Just as the FDA recently did for Stealth Bio's drug, we are asking the FDA to invite Brainstorm to resubmit its BLA so Dr. Prasad's team at CBER can take a fresh look at and consider the "totality of the evidence" from the last 10 years – NOT just the evidence from the 28-week trial.

In their OpEd for JAMA Viewpoints, Doctors Prasad and Makary said:

> *"The FDA must have the courage to create new pathways for therapeutic developers to respond to the current forest fire that is worsening the health of the US population. We will rapidly usher to market new products with transformational potential."*

There is no forest fire creating more death and destruction than ALS. It is cheating people out of the decades of life they still had left to live and replacing their last years with inexplicable suffering as their paralyzed bodies slowly become their own coffins. NurOwn has not just the "potential" for transformational changes but based on the survival data and RWE/RWD we have submitted herein, it has already caused transformational changes.

Petitioners ask the FDA to honor Secretary Kennedy's pledge to end the war on stem cell therapies. Please rush NurOwn to market with a Phase 4 post-marketing study and patients' mandatory participation in a biorepository, with a disease-wide natural history and exposome database.

PETITIONERS

"A healthy person has a thousand dreams. The sick person only has one."
~ Secretary Robert F. Kennedy Jr.
(April 22, 2025)

For thousands of people battling ALS, that dream is to get a mesenchymal stem cell treatment called NurOwn. As Dr. Prasad has said: the American people are the FDA's *"number one stakeholder."* Nowhere are the stakes higher than among the people dying of ALS. As such, Petitioners are imploring the FDA to help make their dream of getting NurOwn become a reality.

The first group of Petitioners represent the class of people with ALS who received 3 doses of NurOwn in the Phase 3 trial and up to 6 more doses in the Expanded Access Program ("EAP"). Petitioners Matt Klingenberg, Josh Smith, Eric Stevens, and Roberto Muggli received the most doses in the US. When they screened for the trial, all four men were early in ALS progression, with an ALSFRS-R score above 40 on the 48-point functional rating scale. NurOwn worked on all. None got more. Roberto died waiting.

The second group of Petitioners represent the class of people who received 3 doses of NurOwn during the Phase 3 trial but not during the Expanded Access Program. Both Kade Simons and Justin Rogers were initially fast progressors. They began the trial screening with an ALSFRS-R score above 35 on the 48-point functional scale. NurOwn worked on them. They never got more. Both Kade and Justin died waiting.

The third Petitioner, Lesley Krummel represents the class of people who received NurOwn during the Phase 3 trial and were chosen to receive more in EAP, but their invitations to participate in EAP were withdrawn after the FDA's statement in March 2021. Lesley began the trial screening with an ALSFRS-R score above 40 on the 48-point functional scale. NurOwn worked on her. Lesley improved. But her EAP dosing was cancelled. She never received more. She has now declined and is dying waiting.

All the above Petitioners collectively are hereinafter referred to as " NurOwn Petitioners." They were in the subgroup of trial participants – earlier in ALS progression – where the clinical data met statistical significance on both the trial's primary and secondary endpoints. All these people told the FDA that NurOwn caused "clinically meaningful" improvements in how they "felt and functioned." But at the time of the NurOwn Advisory Committee ("AdComm") meeting in September 2023, the Phase 3 trial was still blinded; both the FDA and AdComm members appeared reluctant to give credence to the patient experiences and real-world evidence as outlined in 21st Century Cures.

But when the NurOwn Phase 3 trial was unblinded months after the AdComm, it was both validation and vindication. Everyone who testified that they could feel NurOwn working in their body was correct. All the above NurOwn Petitioners received confirmation from their trial sites that they received NurOwn in the Phase 3 trial. This is new information that the FDA has never considered.

Now, with this new proof in their possession, each of the above named NurOwn Petitioners can justifiably assert that NurOwn helped them "live better and live longer." Specifically, NurOwn:

- slowed or halted their lethal progression
- restored lost function in some
- caused long periods of progression-free survival (PFS)
- caused an increase in "trach-free" survival (TFS) that exceeds ALS natural history by 2x-3x
- caused a long-term slowing of ALS decline that was as much as 75-85% decrease
- caused an increase in overall survival (OS) that exceeds the disease's natural history

Many other unblinded Phase 3 trial participants experienced similar beneficial results when they received NurOwn. We hope that they will join in support of this Citizens' Petition.

The fourth Petitioner is Terri Pickering Saenz. She represents the people who participated in the NurOwn Phase 2 trial. Terri received one dose of NurOwn in 2015. She and many other people in Phase 2 reported that NurOwn improved how they "felt and functioned," albeit not with the same magnitude or durability as people in the Phase 3 trial and EAP who received more doses. For the last decade, Terri has been dying waiting for more NurOwn.

The fifth Petitioner is Mayuri Saxena. Mayuri was not in the NurOwn trial, but as a SOD1 carrier she tried repeatedly to get into the Tofersen expanded access program. She represents the thousands of people with ALS who have repeatedly and unsuccessfully tried to get access to investigational therapies via EAP or Right to Try but were refused access by drug sponsors. Today, Mayuri exemplifies the irreparable harm that results when access to a promising therapy is delayed. For years, she has

been unable to move, eat, drink or swallow. Today she is trached and on life support. She uses a feeding tube to eat, a suction device to remove excess mucus, a Tobii to talk, and a ventilator to breathe. She is now even losing the ability to use eye gaze to communicate. Her ALSFRS-R functional score is 0 on the 48-point scale. Her body is "locked in," but her mind is still as brilliant as ever.

The sixth group of Petitioners represent the class of people with ALS who were not eligible to participate in the trial and could not get NurOwn despite their valiant efforts. Petitioner Tara Collazo screened for the Phase 3 trial but was progressing too slowly to qualify; she is now a quadriplegic. Petitioners Patty Manhardt and Jamie Rose Berry were diagnosed too late to qualify for the Phase 3 trial; both died waiting. Anesthesiologist Shahriar Minokadeh, MD ("Shah") had ALS too long to qualify for either the Phase 2 or Phase 3 trial; he also tried unsuccessfully to get into the NurOwn "hospital exemption" program for cell therapeutics in Israel. Dr. Minokadeh has lost all limb function and now must use a trach to breathe.

The seventh Petitioner is Navy pilot Nick Warack. He represents the class of veterans with ALS, a service-related disease. Nick learned of the NurOwn trial too late to qualify. Along with Navy pilot Matt Bellina and thousands of others, Lieutenant Commander Warack served post-9/11 and had a significantly heightened risk of getting ALS.

The final group of "John Doe" Petitioners represent the class of approximately 33,000 people living with ALS in the US and the approximate 6,000 more who will be diagnosed each year in the future. Tens of thousands will die waiting for the completion of a Phase 3B trial. For all of these people still fighting ALS today, the ALS clock is a ticking time bomb. They cannot wait multiple years until the Phase 3B trial is fully funded, enrolled, completed, and then wait another year as the NurOwn BLA meanders its way through the FDA approval process. They need the FDA to act with the same urgency as ALS is killing their motor neurons.

You can find more details about each Named Petitioner starting at section "H" on page 91 below.

EMERGENT FACTS:
New Survival, Respiratory, and Neurofilament Light Data from Phase 3 and EAP

"ALS is notoriously difficult to treat….
One of the major challenges is the heterogeneity"
~ Dr. Merit Cudkowicz, MD

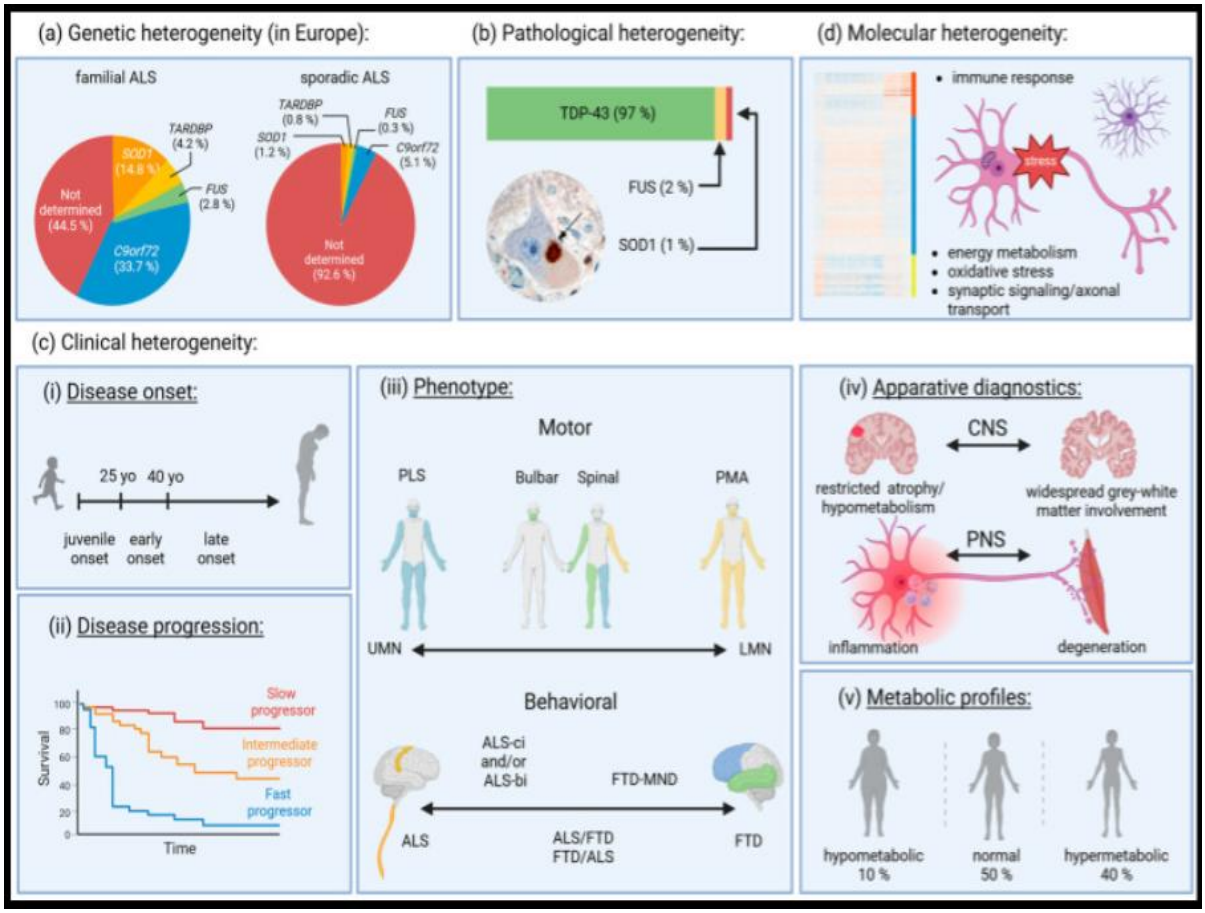
ALS is a 100% fatal, heterogeneous, rare neurodegenerative disease. As motor neurons die, the brain can no longer communicate with the voluntary muscles, which slowly become paralyzed. For reasons researchers don't fully understand, ALS impacts only the motor neurons, not the sensory neurons. Thus, people with ALS still feel cramping, sensations, fasciculations and pain, but they can't move to respond to them. Ultimately, people lose the ability to walk, talk, move, eat, drink, swallow, and eventually, breathe. Despite ALS being a clinical diagnosis with vastly heterogeneous phenotypes and cellular pathology, in the end, all people with ALS experience respiratory symptoms and almost all inevitably die from respiratory failure.[2]

A. ALS is a Vastly Heterogeneous, Terminal Rare Disease

ALS is a vastly heterogeneous disease in phenotype and genotype, and in pathology and penetrance. That's what caused Dr. Billy Dunn, CDER'S former Neuroscience Director, to concede that the biggest hurdle slowing ALS drug approvals is its complexity, calling heterogeneity *"the death of many clinical trials."* This graphic outlines some of that heterogeneity:[3]

[2] Andrews JA, Meng L, Kulke SF, Rudnicki SA, Wolff AA, Bozik ME, Malik FI, Shefner JM. Association Between Decline in Slow Vital Capacity and Respiratory Insufficiency, Use of Assisted Ventilation, Tracheostomy, or Death in Patients With Amyotrophic Lateral Sclerosis. JAMA Neurol. 2018 Jan 1;75(1):58-64.
[3] Tzeplaeff, L., Jürs, A. V., Wohnrade, C., & Demleitner, A. F. (2024). Unraveling the heterogeneity of ALS: A call to redefine patient stratification for better outcomes in clinical trials. Cells, 13(5), 452.

Graphic - ALS Heterogeneity

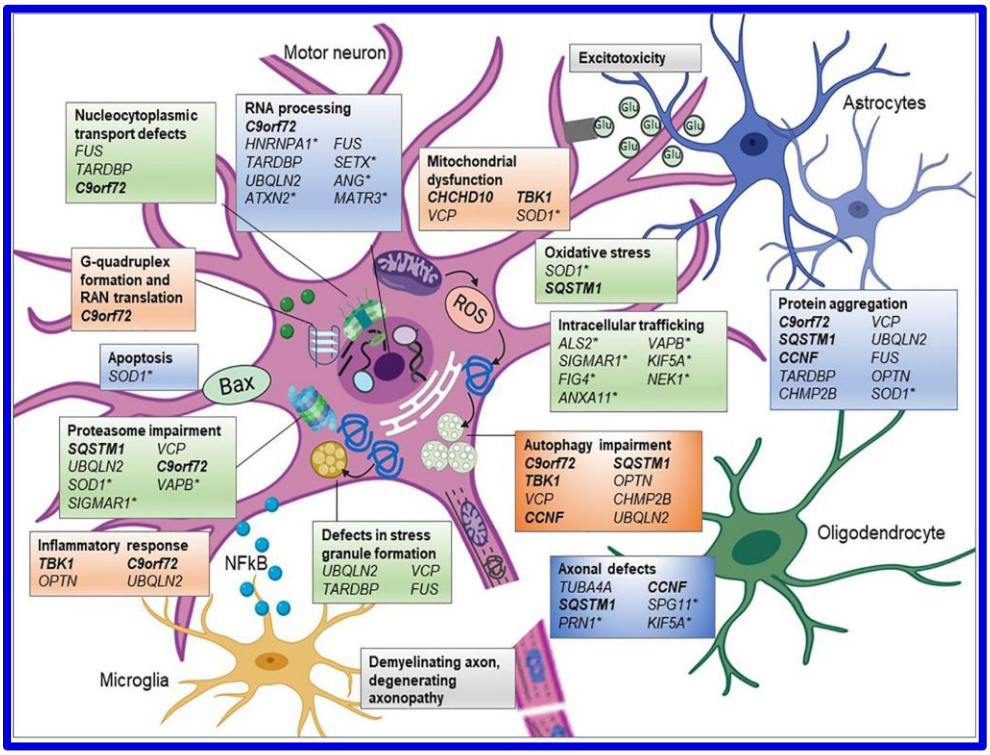


In the 2016 documentary, *"Die Trying: the Battle for ALS Treatments,"* ALS patient and VICE Producer Angelina Fanous said a *"one-size-fits-all system"* won't work for a heterogeneous neurodegenerative disease like ALS.

1. Cellular Heterogeneity

A 2023 article in Nature Reviews Drug Discovery underscored the need for multi-targeted approaches for ALS therapeutic development.[4] The failure of many single-agent trials reflects ALS's complexity, involving diverse cellular pathology. The consensus among researchers is that the heterogeneity of ALS — spanning genetic mutations and diverse pathological mechanisms — likely necessitates a cocktail of drugs targeting multiple aspects of the disease. As a result, the complexity of ALS likely requires better stratification of the patient population and a multi-drug approach to achieve meaningful therapeutic outcomes.

Graphic - ALS Cellular Heterogeneity



2. Genetic Heterogeneity

In addition to cellular heterogeneity, ALS is vastly diverse in genotype. Approximately 10-15% of cases are directly caused by 40+ genetic mutations;[5] but 85-90% of cases are sporadic of unknown etiology. The diagram above illustrates the varied pathophysiology affecting neurons and their glial cells in both sporadic and genetic forms of ALS, with boxes highlighting the genes associated with each pathological process. Notably, sporadic ALS displays similar pathological features despite its unclear origins.

[4] Mead, R. J., Shan, N., Reiser, H. J., Marshall, F., & Shaw, P. J. (2023). Amyotrophic lateral sclerosis: A neurodegenerative disorder poised for successful therapeutic translation. Nature Reviews Drug Discovery, 22(3), 185–212.

[5] Chiò, A., Logroscino, G., Traynor, B. J., Collins, J., Simeone, J. C., Goldstein, L. A., & White, L. A. (2020). Global epidemiology of amyotrophic lateral sclerosis: A systematic review of the published literature. Neuroepidemiology, 54(4), 300–310.

ALS can be both a polygenic and oligogenic disease. In fact, there are several reports of patients carrying two or more mutations of different ALS-related genes.[6] The distinction between ALS as an oligogenic or polygenic disease lies in the number and interaction of genetic factors contributing to its development. Oligogenic ALS involves a smaller number of genetic variants (typically 2–3 key mutations or rare variants) that interact to significantly increase disease risk or influence progression. For example, a patient might carry a rare mutation in a major ALS gene (e.g., C9orf72) alongside a modifier gene like SETX.

Polygenic ALS, on the other hand, arises from the cumulative effect of many common genetic variants (often single-nucleotide polymorphisms, or SNPs), each with a small individual effect, contributing to overall disease susceptibility in a more gradual manner, as seen in genome-wide association studies (GWAS) of sporadic ALS. While oligogenic cases are more common in familial ALS and linked to severe phenotypes, polygenic influences are prevalent in sporadic ALS, highlighting the complex genetic architecture of the disease.[7]

In a study of 391 patients with ALS that assessed variants in 17 genes, 3.8% had variants in more than one gene.[8] In that series, the burden of rare variants in known ALS genes significantly reduced the age at onset of symptoms. People with oligogenic expression are often faster progressors.[9] Petitioners Mayuri Saxena and Jamie Rose Berry are two examples of people with oligogenic heterogeneity. Both oligogenic and polygenic heterogeneity in ALS can significantly influence trial design and outcomes by introducing variability in disease progression and treatment response. Oligogenic ALS often leads to faster disease progression, thus necessitating stratification of participants by genetic profile to ensure balanced cohorts and accurate assessment of therapeutic efficacy, as highlighted by Iacoangeli et al. (2025). But this stratification is difficult to do with the many ultra-rare ALS variants with differing penetrance.

Polygenic ALS, driven by the cumulative effect of numerous common variants, contributes to a broader spectrum of disease severity in sporadic cases, requiring larger sample sizes and genetic risk scoring (GRS) to account for subtle genetic influences on outcomes (Feldman et al., 2022). This complex heterogeneity complicates endpoint selection, such as survival or functional decline, and underscores the need for personalized trial designs, including biomarker-driven approaches, to mitigate confounding factors and enhance the reliability of clinical results.

Even familial and sporadic ALS are impacted by genes that modify risk factors, impacting the onset, expression and progression of ALS. Besides “causative” genes, several other genes have been reported to modify ALS phenotype suggesting that variants in these genes modify the Gene-Time-Environment

[6] Lattante, S., Ciura, S., Rouleau, G. A., & Kabashi, E. (2015). Defining the genetic connection linking amyotrophic lateral sclerosis (ALS) with frontotemporal dementia (FTD). Trends in Genetics, 31(5), 263–273.
[7] Iacoangeli, A., … Cooper-Knock, J., … Glass, J. D., … Hardiman, O., … (2025). Oligogenic structure of ALS has genetic testing, counselling and therapeutic implications. Journal of Neurology, Neurosurgery & Psychiatry. Advance online publication.
[8] Cady, J., … Miller, T. M., Mitra, R. D., Ravits, J., Harms, M. B., & Baloh, R. H. (2015). Amyotrophic lateral sclerosis onset is influenced by the burden of rare variants in known ALS genes. Annals of Neurology, 77(1), 100–113.
[9] Iacoangeli, A., … Cooper-Knock, J., … Glass, J. D., … Hardiman, O.,… Farhan, S. M. K. (2025). Oligogenic structure of ALS has genetic testing, counselling and therapeutic implications. Journal of Neurology, Neurosurgery & Psychiatry.

theory that is unique to each person with ALS. Some examples of these "modifier" genes are: *UNC13A, ATXN2,*[10] and *CAMTA1.*[11] As Stanford's Aaron Gitler explained at this ALS One Research Symposium, UNC13A is the most common genetic risk factor across the sporadic ALS community. Dr. Gitler added that the two seminal NATURE studies about UNC13A connected the most common genetic risk factor (UNC13A) seen in approximately 60% of sporadic ALS[12] with the most common ALS pathology (TDP-43) that affects approximately 97% of people with ALS.

Van den Berg (2009) confirmed that people with at least one copy of the C allele have faster ALS progression, more frequent bulbar onset, higher incidences of ALS-FTD, lower FVC at diagnosis and resultantly, shorter survival. Thus, UNC13A variants could influence clinical trial outcomes by modifying disease severity, survival, or treatment response. While stratifying trial participants by UNC13A genotype could account for potential variability in efficacy or progression rates, Petitioners are unaware of any ALS trials that randomize patients based on their UNC13A status, and only a few who have assessed the possible impact.[13] Moreover, UNC13A is only 1 of 66 mis-splicing genes identified by Gitler's lab, further increasing the potential for heterogeneity to be impacting trial outcomes.

3. Heterogeneity by Age of ALS Onset

There is vast heterogeneity in age of onset as well. ALS is a disease typically associated with aging as the average age of diagnosis is 55 and the median is 58.[14] However, as demonstrated by many of the Petitioners, ALS does afflict people in their 20s and 30s. And recently the NIH identified some cases of pediatric ALS caused by a de novo mutation in SPTLC2. Sadly, there are no natural history studies evaluating why so many people are being diagnosed decades earlier than the average.

4. Heterogeneity by Speed of Progression

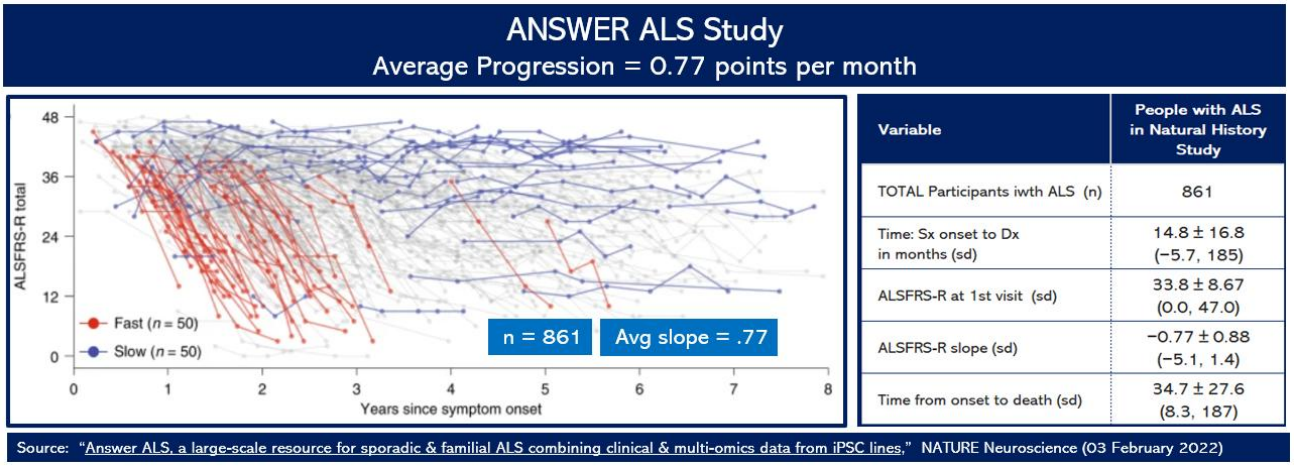
The Answer ALS study provides a comprehensive analysis of ALS progression and demographics, integrating clinical, multi-omics, and induced pluripotent stem cell (iPSC) data from over 850 sporadic

[10] Chiò, A., Calvo, A., Moglia, C., Ossola, I., Brunetti, M., Sbaiz, L., Lai, S. L., Abramzon, Y., Traynor, B. J., Restagno, G., & Al-Chalabi, A. (2015). ATXN2 polyQ intermediate repeats are a modifier of ALS survival. Neurology, 84(3), 251–258.
[11] Fogh, I., Lin, K., Tiloca, C., … Chiò, A., ... Hardiman, O. (2016). Association of a locus in the CAMTA1 gene with survival in patients with sporadic amyotrophic lateral sclerosis. JAMA Neurology, 73(7), 812–820.
[12] van Es, M. A., Veldink, J. H., … van den Berg, L. H. (2020). The distinct traits of the UNC13A polymorphism in amyotrophic lateral sclerosis. Annals of Neurology, 88(4), 796–806.
[13] While Brainstorm has published the UNC13A distribution in its Phase 3 trial, the trial sites have not yet released the UNC13A test results to the trial participants so we don't yet know which participants may have been a "C" allele carrier.
[14] Chiò, A., Logroscino, G., Traynor, B. J., … Goldstein, L. A., & White, L. A. (2020). Global epidemiology of amyotrophic lateral sclerosis: A systematic review of the published literature. Neuroepidemiology, 54(4), 300–310

and familial ALS patients. This large-scale database highlights ALS heterogeneity and identifies key factors influencing ALS progression.[15]

People with ALS lose function at different speeds of progression also called "change in slope." In ALS, a bounded scale called the ALS Functional Rating Scale (ALSFRS-R) is the patient-reported clinical outcome assessment used to assess change in function and ALS progression. Until recently the commonly accepted mean change in slope was 1.02 points per month, a statistic derived from the placebo arms of the PRO-Act clinical trial database. But the Answer ALS study of 861 people with ALS documented the now-commonly accepted mean rate of decline as 0.77 points per month.[16]

Graphic - Answer ALS Study Change in Slope diagram - Slow & Fast Progressors



In this 2023 study,[17] researchers compared key events in ALS progression in populations across the US, UK and EU. They stratified those time-to-event data by speed of progression:

- > 0.77 points/month = Fast Progressor
- 0.36 - 0.77 points/month = Intermediate Progressor
- <0.36 points/month = Slow Progressor

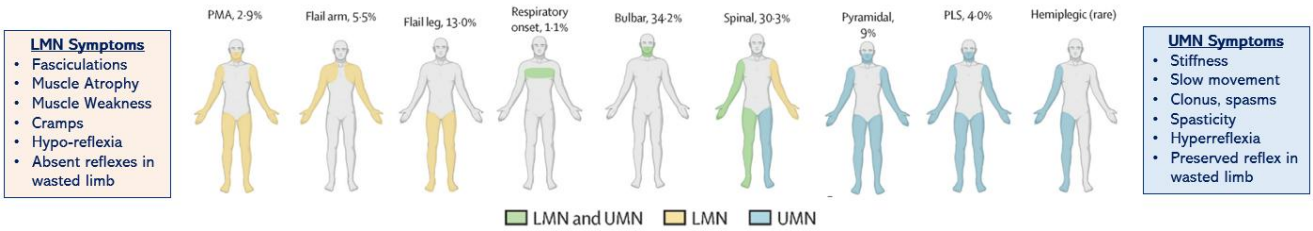
Comparatively, to qualify for the NurOwn trial, everyone had to have lost 3 points in the 12-week run-in period. As such – before receiving NurOwn – most of the people in the NurOwn trial would be characterized as "fast progressors." None would have been slow progressors as the trial sites screened to exclude those people (like Petitioner Tara Collazo).

[15] Baxi, E.G., … Ajroud-Driss, S., Baloh,R., Heitzman, D., Miller, T., Glass, J.D., … Cudkowicz, M.E., Maragakis, N., Finkbeiner, S., Berry, J., Fraenkel, E., Svendsen, C.N., & Rothstein, J.D., et al. (2022). Answer ALS, a large-scale resource for sporadic and familial ALS combining clinical and multi-omics data from induced pluripotent cell lines. Nat Neurosci 25, 226–237.
[16] Similarly the slope before baseline in the Healey ALS platform trials documented ALS progression that aligns with the Answer ALS database: (a) Zilucoplan = 0.75; (b) Verdiperstat = 0.77; (c) CNM-AU8 = 0.72; (d) Pridopidine = 0.75.
[17] Gebrehiwet, P., Brekke, J., Rudnicki, S. A., Mellor, J., Wright, J., Earl, L., Ball, N., Iqbal, H., Thomas, O., & Castellano, G. (2024). Time from amyotrophic lateral sclerosis symptom onset to key disease milestones: Analysis of data from a multinational cross-sectional survey. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 25(3-4), 345–357.

5. Heterogeneity by Site of ALS Onset

ALS heterogeneity can be classified by the site of onset, which influences not only phenotype of initial symptoms, but ALS progression as well. (Feldman et al., 2022).[18] These distinctions are significant as they impact symptom presentation and progression and thus, this heterogeneity can impact trial outcomes.

Graphic - ALS Heterogeneity by Site of Onset



The three most common types of ALS are:

(1) limb-onset: the most common, starting in arms or legs
(2) bulbar-onset: affects speech and swallowing muscles, often more rapid progression
(3) respiratory-onset: the rarest, beginning with breathing difficulties.

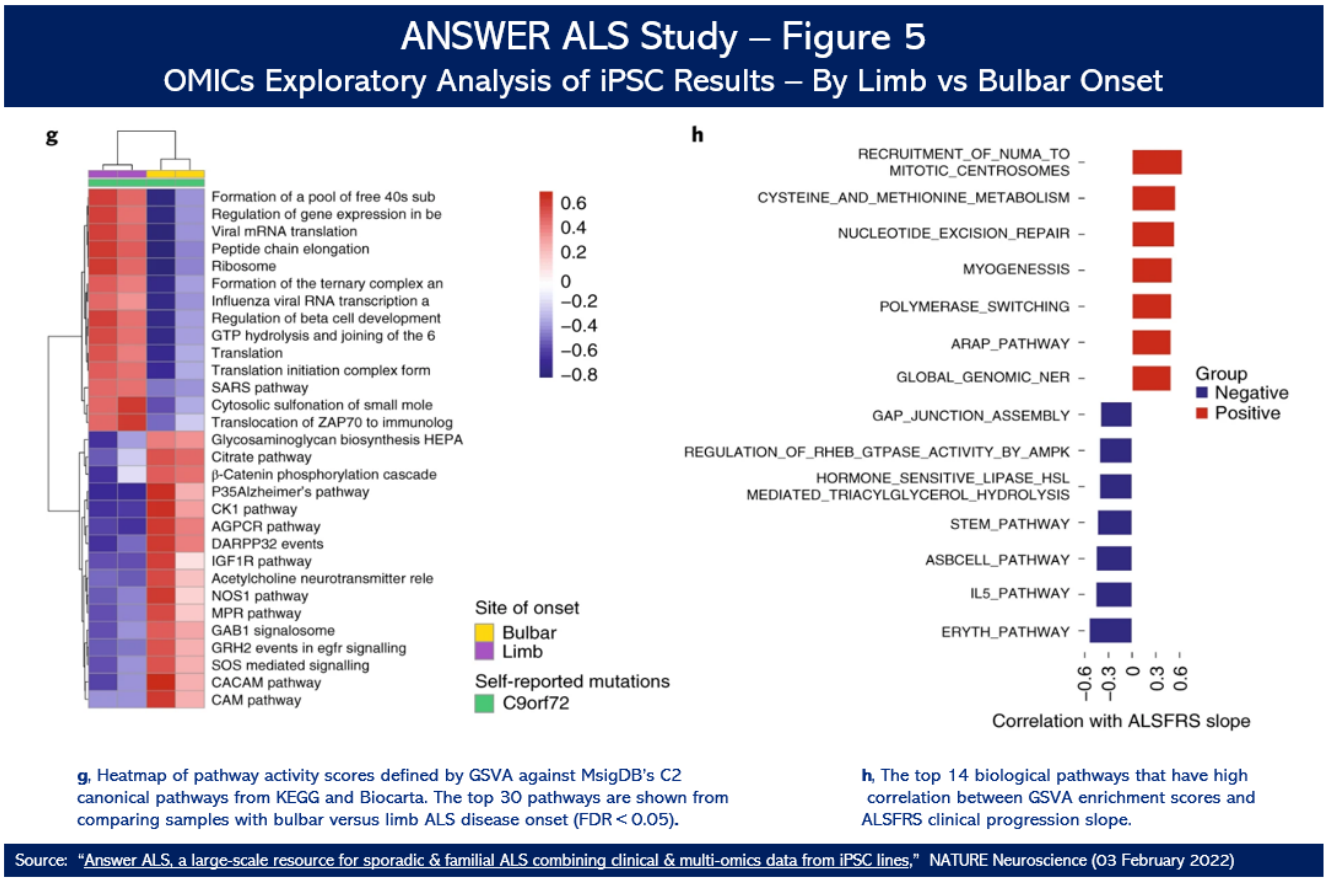
The differences between limb onset and bulbar onset aren't just what is evident from the outside. Rather, they reflect the vast heterogeneity about what is going on inside the diseased motor neurons in people with ALS.

Figure 5g below from the Answer ALS study is a heatmap that illustrates 30 of the top biological differences in the biological pathways between patients with bulbar versus limb onset ALS. This Gene Set Variation Analysis (GSVA) methodology looks at how active a biological pathway is in a patient's cells (specifically, motor neurons grown from iPSCs). An enrichment score is a number GSVA calculates for each pathway, showing how "turned on" or "turned off" that pathway is.

Higher scores mean the pathway is more active (e.g., genes in that pathway are working harder). These scores are what the heatmap visualizes, with colors indicating higher or lower activity (e.g., red for high activity, blue for low). For example, a high GSVA score for an inflammation pathway might mean that inflammation is very active in a patient's neurons, potentially damaging them.

[18] Feldman, E. L., Goutman, S. A., Petri, S., Mazzini, L., Savelieff, M. G., Shaw, P. J., & Sobue, G. (2022). Amyotrophic lateral sclerosis. The Lancet, 400(10360), 1363–1380.

Graphic - Answer ALS Study Figure 5 - Biological Pathways in ALS



Whereas Figure 5g illustrates 30 of the top biological differences in the biological pathways between patients with bulbar versus limb onset ALS, Figure 5h identified 14 key biological pathways where the level of activity (measured by GSVA scores) is strongly linked to how quickly ALS worsens (measured by the ALSFRS-R change in slope). In the context of clinical trial outcomes, these pathways are important because they may help explain why some patients decline faster. [19]

A summary of some of these pathways can be found at Exhibits. You will note that many of these pathways relate to neuroinflammation or neuroprotection – pathways on which NurOwn has a disease modifying impact. For example:

[19] Answer ALS is an innovative research-based non-profit founded by Johns Hopkins' Jeff Rothstein, MD PhD. It has collected biosamples from over 1000 people and is generating iPS cells from each patient, creating thousands of new and different iPS brain cell lines and performing the most comprehensive biological analytics ever—including DNA (genomics), RNA (transcriptomics) and protein (proteomics) analysis—to yield a personalized but open-access database of thousands of petabytes of new ALS-specific information. Then, in collaboration with experts in machine learning and big data informatics, this OMICs data will be mined to uncover ALS causes, subtypes, drug targets and biological pathways gone awry. It will serve as the foundation for new clinical trials, suggest new ways to subgroup patients to better discover successful drugs and to find drug-responsive biomarkers or diagnostics.

- IGF1R Pathway (Insulin-like Growth Factor 1 Receptor Pathway)
  Reduced IGF1R activity impairs neuroprotection. Dysregulation can amplify inflammatory responses in microglia and astrocytes (the brain's immune cells), while disrupting growth factor balance needed for motor neuron maintenance.[20]

- IL5 Pathway
  Overactive IL5 signaling is linked to immune responses that exacerbate neuroinflammation, contributing to motor neuron loss in ALS.[21]

- NOS1 Pathway (Nitric Oxide Synthase 1 Pathway)
  Overactive NOS1 produces toxic nitric oxide, causing oxidative stress and neuroinflammatory damage to motor neurons.[22]

- GRB2 Events in EGFR Signaling
  Dysregulated GRB2 events enhance neuroinflammation by promoting inflammation and growth factor imbalances, worsening motor neuron damage.[23]

- Cysteine and Methionine Metabolism
  Dysregulated cysteine and methionine metabolism impairs antioxidant defenses, increasing oxidative stress and indirectly promoting neuroinflammation while reducing neuroprotection.[24]

Petitioners include these graphics and pathways, not to have a complex scientific discussion about the biological processes involved in ALS, but instead to illustrate several points:

(1) the graphics exemplify why drug development in ALS is so difficult and why the ultimate treatments for ALS will likely take a drug cocktail that will be personalized to each person's own pathology;[25]

(2) there is no possible way to stratify a trial population and randomize for these multiple heterogeneous pathways; but using AI, researchers could analyze thousands of samples in Phase 4 biorepository to help identify why some patients are responding to certain therapies but not others; and

[20] Sakowski, S. A., Feldman, E. L., & Appel, S. H. (2012). Insulin-like growth factor-I for the treatment of amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis, 13(1), 1–7.
[21] Wood, H. (2020). Neuroinflammation in ALS: Cause or consequence? Nature Reviews Neurology, 16(2), 71.
[22] Tronel, C., & Rochefort, G. Y. (2014). Nitric oxide synthase in neurodegenerative diseases: From mechanisms to therapies. Molecular Neurobiology, 49(3), 1396–1407.
[23] Le Pichon, C. E., & Dominguez, S. L. (2017). Epidermal growth factor receptor: A potential therapeutic target for amyotrophic lateral sclerosis. Neurotherapeutics, 14(2), 351–356.
[24] Valle, C., (2017). Cysteine modifications in the pathogenesis of ALS. Frontiers in Molecular Neuroscience, 10, 5.
[25] For people who have sporadic (sALS), a major barrier to drug development has been the lack of a predictive preclinical human model for sALS. The Answer ALS program generates iPSC lines to understand the heterogeneity of sporadic AL .

(3) therapies like NurOwn that work on "some" must be rushed to market as its unprecedented results in a large proportion of patients can be a bridge to help people live longer and live better while scientists figure out how to develop drugs personalized for the vast heterogeneity of this heinous disease.

These scientific graphics also illustrate why Dr. Ajay Sampat, a young neurologist with ALS, submitted a Public Comment and reminded the FDA:

> *"The teaching I learned in residency is that **'if you have met one ALS patient, you have met one ALS patient.'** As a result of this, we cannot expect a drug to impact every individual the same way. And we should not deny an opportunity for treatment based on this flawed notion that a drug can and will help the majority of patients in this diverse condition."*

Some must be enough.

B. ALS Lifespan and Dying Motor Neurons

Every year, approximately 6,000 people are diagnosed with ALS and 6,000 die. The ALS community refers to this as the "turnstile of death." According to the most recent data from the CDC's ALS Registry, the incidence of ALS is 1.6 per 100,000. But because ALS is so rapidly lethal, the prevalence is approximately 32,000 instead of 1 million like MS. Thus, ALS meets the statutory definition as a "rare disease" and investigational therapies for ALS qualify for all benefits conferred with orphan drug status. But as Petitioner Patty Manhardt often shared: ***"it's only rare because we die so quickly."***

Early in ALS, as motor neurons are dying, people experience no symptoms because of the redundancies in the central nervous system. Surviving motor neurons can compensate by sprouting new connections to denervated muscle fibers, delaying symptom onset. Symptoms emerge only after this compensatory capacity is overwhelmed. By the time someone is diagnosed, researchers estimate that approximately 50% to 80% of motor neurons in affected regions are damaged or dead, with the higher end (70%–80%) more common in bulbar-onset cases or rapidly progressing disease.[26]

According to the NIH and CDC's ALS Registry, the average lifespan for people with ALS is 3-5 years.[27] But that survival statistic can be misleading as it encompasses a diverse population, including those who rely on life-support measures and opt for a tracheostomy to maintain breathing, which can significantly extend survival beyond the average. The inclusion of this "trached" population skews the overall figure, masking the variability in disease progression and the impact of advanced interventions. Thus, the more accurate assessment of a therapy's impact on survival outcomes in clinical trials is to consider "tracheostomy -free" ("trach-free") survival.

---

[26] Swash, M. (2013). Why are upper motor neuron signs difficult to elicit in amyotrophic lateral sclerosis? Journal of Neurology, Neurosurgery & Psychiatry, 84(6), 711–712.

[27] "Priorities of the NIH Amyotrophic Lateral Sclerosis (ALS) Strategic Planning Working Group" https://www.ninds.nih.gov/sites/default/files/documents/ALS%20Strategic%20Plan_11_20_23_508C.pdf

C. New Emergent Evidence of Long-Term Survival Data in NurOwn Phase 3 Trial and EAP

As Dr. Prasad has succinctly stated, the simple test of efficacy is whether a drug helps patients "live longer or live better." NurOwn does both.

For the first time, the NurOwn Petitioners are presenting critical new data that the FDA has never seen or considered.[28] In the sections below you will find compelling and unprecedented new evidence about:

- 5.5 month improvement in OS versus matched controls as of the end of EAP in 2022
- 100% five-year Survival data in EAP vs. 20% natural history
- Trach-free Survival (TFS) data that dwarfs median ALS natural history
- Respiratory data showing an extension in Time-to-NIV far beyond 15-month median
- Progression-free survival (PFS) data ranging up to 17 months
- Consistent long-term slowing in rate of decline to as low as 0.15 points per month
- Multiple "n of 1" stories

As one NurOwn EAP participant shared with the FDA-CBER's Dr. Marks, Dr. Witten and Dr. Bryan, nearly 4 years ago at the October 2021 PFDD meeting:

> *"We have seen firsthand that this therapy absolutely stopped my ALS progression and even gave me more ability to move, swallow, and speak. My family now has to watch me die in the cruelest way after witnessing a therapy that allowed me to live. This will be excruciating for them knowing there is a therapy that works… I would gratefully take an extra day, hour, even minute with my family. Nurown has given me extra time to be with them and selfishly, I want more…. People with ALS want to live. Nurown allows us to live longer than we would without it. Nurown has the ability to give people with ALS more time with the people that they love. In the forefront of every decision you make, please remember this - people with ALS want to live."*

1. Survival Data is the Gold Standard for Efficacy

Consensus guidelines suggest that **survival should be the primary end point for phase 3 trials**.[29] The FDA has long-considered Overall Survival (OS) as the "gold standard" primary endpoint.[30]

[28] The FDA's Briefing Document concedes that "The protocol did not include a plan for continued follow-up to comprehensively collect data on survival or functional status after the final study visit" in the Phase 3A trial; and further notes that the sponsor did not submit data from the EAP.

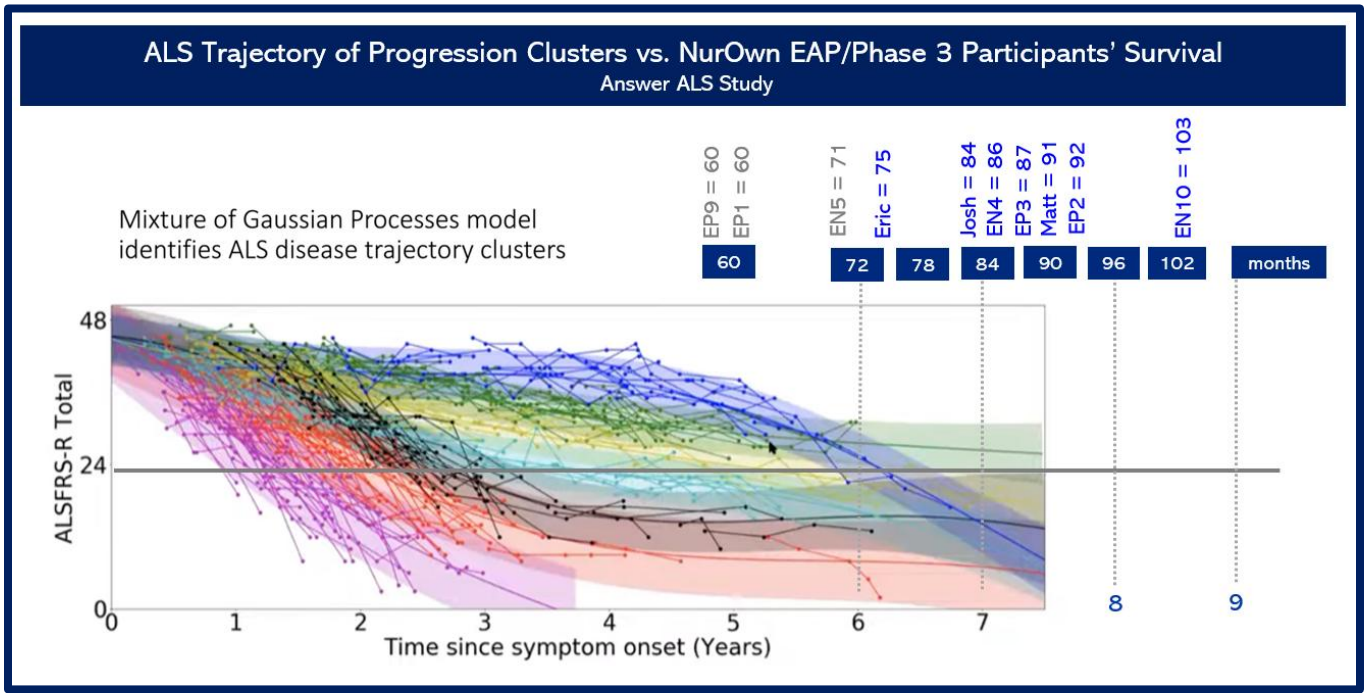
[29] World Federation of Neurology Research Group on Neuromuscular Diseases Subcommittee on Motor Neuron Disease. Airlie House guidelines. Therapeutic trials in amyotrophic lateral sclerosis. Airlie House "Therapeutic Trials in ALS" Workshop Contributors. J Neurol Sci. 1995 May;129 Suppl:1-10.

[30] U.S. Food and Drug Administration. (2018, December). Clinical trial endpoints for the approval of cancer drugs and biologics. Guidance for Industry.

In the FDA's 2024 final guidance *"Rare Diseases: Considerations for the Development of Drugs and Biological Products,"* it acknowledges the importance of selecting appropriate endpoints, including survival, but emphasizes regulatory flexibility due to the challenges of small patient populations and rapid disease progression.

The magnitude of the EAP participants' improvement in survival becomes apparent when you overlay the Petitioners' survival evidence atop the trajectory of progression clusters from the 867-person Answer ALS study.

<u>Graphic</u> - Answer ALS Trajectory of Slope/Progression Clusters



Dr. Jeff Rothstein presented this data on a 2020 webinar. Admittedly, the mortality data was not fully ripe at the time of that presentation 5 years ago. However, few people in the 867-person sample were on a trajectory to reach 7 years (84 months) survival. Moreover, recall that NurOwn trial participants had to be losing one point a month to qualify for the phase 3 trial. As such, all participants would have fallen in the trajectory at the bottom of the graphic colored in turquoise, black, orange or lavender.

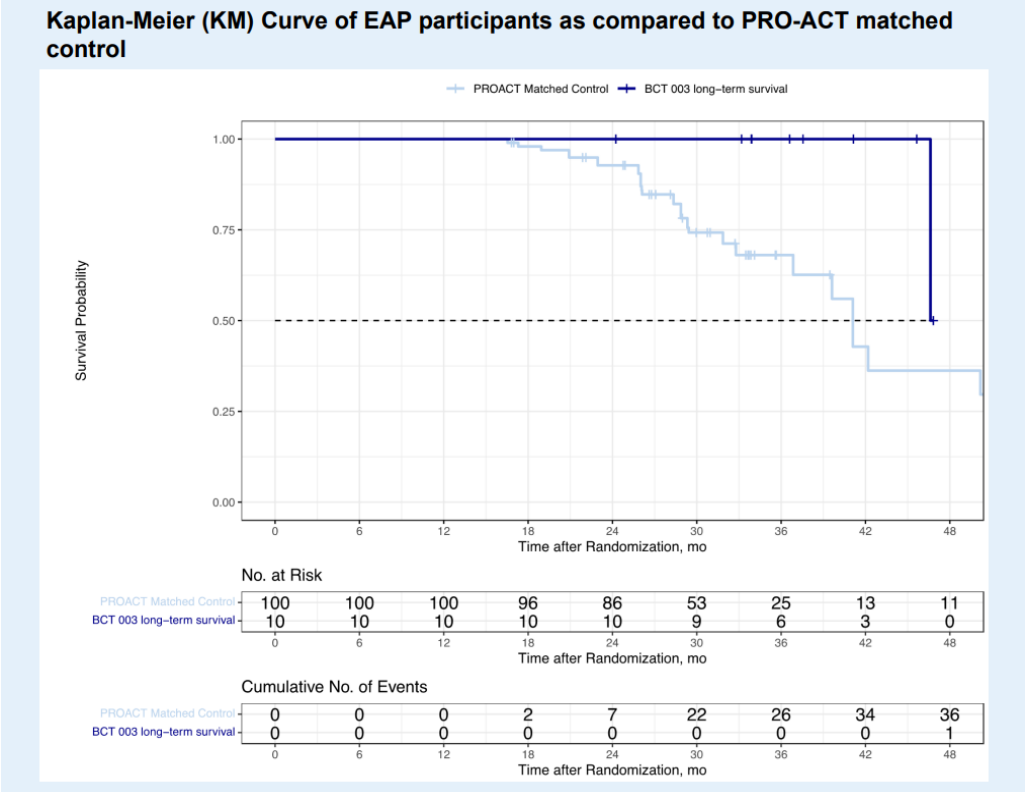
1. People in EAP had a 5.5 Month Improvement in OS vs. Matched Controls

In October 2024, Brainstorm presented a poster at the annual meeting of the Northeastern Amyotrophic Lateral Sclerosis (NEALS) Consortium Meeting. The poster was entitled: *"Debamestrocel Long-Term Benefits on Survival and Neurodegeneration in ALS Expanded Access Program."*
The EAP spanned two 28-week periods, in 2021 and 2022, with a break in time between the periods. EAP participants received an intrathecal dose of NurOwn (debamestrocel) every 8 weeks, for a maximum of 6 doses over the 2 periods. Of the 10 EAP participants, 6 received NurOwn and 4 were in the placebo arm in the Phase 3 trial.

At the last available visit in the EAP in the summer/fall of 2022:

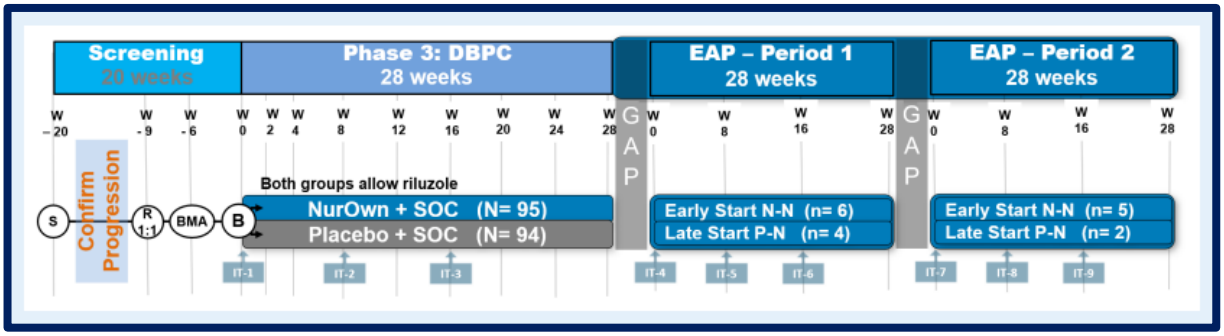
- 9/10 NurOwn EAP participants were alive
- 1/10 died (MAiD) after all doses in the EAP vs. 36/100 in the matched control
- 5.5 months extension of survival benefit
  (46.6 months for NurOwn vs. 41.1 months for the matched control)
- 5.5 months = Statistically significant difference in favor of NurOwn (LRT, p= 0.0379)

Graphic - EAP KM Survival Curve compared to Matched Controls



Above is the Kaplan Meier curve of EAP participants' survival as compared to PRO-ACT matched controls.[31] Below is the dosing schedule in the EAP. Both are excerpts of the poster presented at NEALS annual conference.

Graphic - EAP Trial Design



With the lifespan of matched controls at 41.1 months, a 5.5 month extension of survival is longer than both currently approved ALS therapies, Riluzole and MTP's Radicava (Edaravone) demonstrated when they were approved.

Note: the NurOwn Phase 3B trial that is supposed to start this year will not be able to collect similar survival data to corroborate the earlier EAP survival data. The trial and OLE are only 48 weeks (≈11 months) combined. The above survival data was examined at 48 months not 48 weeks. At 12 months, there were no deaths in the matched cohort or the NurOwn EAP. Thus, the only way to corroborate a long-term survival benefit is to approve NurOwn with a Phase 4 post-marketing study and biorepository -- just as is commonly done for cancer therapies.

And as promising as this EAP survival data is, it is incomplete. First, it only calculated survival through 2022 – nearly three years ago – when the EAP ended. Second, the graphic from Brainstorm poster doesn't depict the varying times for each gap in dosing between the Phase 3 trial and each round of EAP. Depending on whether they were in the early start or delayed start group that crossed over from placebo, some people in the EAP missed as many as 20-45 doses on the anticipated dosing schedule of every 2 months.

For example, Matt Klingenberg had a 25-month gap between the last dose in Phase 3 and the first dose in EAP in June 2021. Then again, there was an 8-month gap before he received doses 7-9 beginning in May of 2022. He has been unable to receive any more doses of NurOwn in the last 32 months. Because there was no OLE and the drug sponsor could not continue to manufacture the cells, in total, **Matt has missed 30 doses in the every two-month dosing schedule.** In addition to Matt's 30 missing doses, EAP

[31] According to Brainstorm, baseline characteristics from 10 EAP participants -- captured at the time they entered the Phase 3 trial -- were matched against a comparable cohort from the PRO-ACT historical database using matching covariates for propensity score matching (PSM). These covariates included time since disease onset, pre-baseline ALSFRS-R slope, age, Slow/Forced Vital Capacity (SVC/FVC), and site of onset, with a 10:1 matching ratio. A Kaplan-Meier (KM) plot was generated, and a log rank test (LRT) was performed to compare survival between the two groups

Petitioners Josh Smith (28), Eric Stevens (23), and Roberto Muggli (21) all missed doses but still contributed to the 5.5 month difference in OS. This makes the above OS data even more impressive.

Third, the four people in the placebo arm during the Phase 3 trial had multi-year delays (19 to 42 months) before they received their first EAP dose of NurOwn. Nonetheless, even in those with significant delays in dosing, NurOwn still impacted their OS.

Imagine the FDA evaluating the efficacy of chemotherapy after denying dying cancer patients access to it for 3 years! But that's what happened with NurOwn and nonetheless, it still slowed progression and improved survival – even on those who were more progressed at the time of their first dose.

The true impact of NurOwn on long-term ALS survival can only be determined through a Phase 4 post-marketing study – with consistent dosing – designed to evaluate the diverse responses driven by the extensive genotypic, phenotypic, pathophysiological, and multi-omics heterogeneity in this rare disease.

Graphic - Summary EAP Trach-Free Survival Data

NurOwn EAP - Trach-free Survival Data*

		Total EAP Population				EAP - Early vs Delayed Start			
SURVIVAL from	ALS Natural History	EAP Survival Range	EAP Survival		△ months	6/10 Early Start (P3 NurOwn)	△ months	4/10 Delayed Start (P3 Placebo)	△ months
Symptom Onset	30.0	60 - 103 months	Median	85	55	85	55	74	44
			Mean	81.0		85		75	
Diagnosis	18.0	51 - 87 months	Median	78	60	78	60	69	51
			Mean	73.0		76		69	

1. Traxinger / Glass (2013). Prognosis and epidemiology of ALS: analysis of a clinic population
2. Chio / Traynor (NIH) (2009). Prognostic Factors in ALS: a critical review
3. Knibb / Al Chalabi (2016). A clinical tool for predicting survival in ALS

* No one in NurOwn EAP received a tracheosotomy
10/10 people in EAP survived / are survivng trach-free ≥ 5 yrs.
6/10 still alive as of June 2025 - without trach

2. EAP's 100% Five-Year Survival Data Exceeds 20% Anticipated Survival Data in ALS Natural History

As seen in the table above, ten of ten people in the Expanded Access Program lived 5 years or longer. None were trached before death. Six are still living today without tracheostomies ("trachs") Following is an email excerpt that one of the EAP participants shared with us. It was a thank you note to Brainstorm:

"The only reason that you are hearing from me today is because of your product. I hit a huge milestone in August which was the celebration that ***I have been here for 5 years since symptom onset****.* ***I absolutely believe that the only reason my family and I were able to celebrate my ALS anniversary was because of the investment and brilliance that you put into NurOwn.*** *First I would like to thank you as* ***I am living proof that your therapy works*** *and I have been trying to tell anybody who will listen that I know that NurOwn works….*

I truly believe that we will look back at this time as a very dark period in which ***we had a therapy that would prolong the lives of people living with ALS but we got so caught up with the bureaucratic nonsense that we let this 'ALS vintage' die.*** *I hope that some shame is felt by those who held us back."*

Sadly, less than 20% of people with ALS survive 5 years or more. And even this statistic is buoyed by those who get life-sustaining tracheostomies. When excluding tracheostomy patients, researchers at Mayo and Johns Hopkins reported a five-year tracheostomy-free survival as low as 14%.[32] In 94 patients, the mean survival from symptomatic onset was 2.95 years; the mean survival from diagnosis was 1.89 years.

On June 16, 2025, Brainstorm issued a Press Release announcing a 90% EAP five-year survival rate. It analyzed survival from the time of first symptom onset through participation in the Phase 3 trial and EAP – followed by additional survival data collected through publicly available records.

In calculating the 5-year survival rate, Petitioners are in possession of not only publicly available records but also personal records provided directly by EAP participants – records that Brainstorm does not have access to – and they included outside electronic medical records and ALS-TDI PMP records, all of which provided the foundation for the analysis Petitioners have done herein.

From those records, Petitioners can document that:

- **100% of participants (10/10) survived trach-free ≥60 months (5 years) from symptom onset**
    - 60 - 103 month range (two people at 60 months)

- **80% of participants (8/10) survived trach-free ≥60 months (5 years) from diagnosis**
    - 51 - 87 month range

[32] Mateen, F. J., Carone, M., & Sorenson, E. J. (2010). Patients who survive 5 years or more with ALS in Olmsted County, 1925–2004. Journal of Neurology, Neurosurgery & Psychiatry, 81(10), 1144–1146.

Graphic - EAP Trach-Free Survival Data

Name	x	Matt	x	Josh	Eric	Roberto	x	x	x	x	EAP (n=10)		
Trial Participant ID	EN10	EN8	EN4	EN6	EN7	EN5	EP2	EP3	EP1	EP9	MEAN	MEDIAN	Δ
ONSET - Limb or Bulbar	LL	UL	UL	UL	B & UL	UL	LL	UL	LL	B & UL			
NurOwn (N/N) or Crossover Placebo (N/P)	N-N	N-N	N-N	N-N	N-N	N-N	N-P	N-P	N-P	N-P			
Baseline ALSFRS-R - Phase 3	≥32	≥40	≥40	≥40	≥40	≥40	≥40	33	37	≥32			
Trach-free Survival (months) - Sx Onset Symptom Onset to Death or June 2025	103	91	86	84	75	71	92	87	60	60	81	85	55
Δ - Trach-free Survival SURVIVAL from Sx Onset	2.9x	2.5x	2.4x	2.3x	3.1x	2.0x	2.6x	2.4x	1.7x	2.5x			
Trach-free Survival (months) - Dx Diagnosis to Death or June 2025	85	87	81	75	70	60	87	82	55	51	73	78	60
Δ - Trach-free Survival SURVIVAL from Dx	2.7x	2.8x	2.6x	2.4x	4.1x	1.9x	2.8x	2.6x	1.8x	3.0x			
Time without NIV		85		84	38	71	92				74	84	69
Sx Onset to Dx (months)	18	4	5	10	5	11	5	5	5	9			
GAP - Sx Onset to Dose #1	25	14	13	16	11	20	41	35	42	19			
Source of Data (Public Comments, Medical Records, Media & Iview Notes)	PC Notes & Media	EMR PC & Notes	Media	EMR PC & Notes	EMR PC & Notes	EMR PC & Notes	Notes & Media	EMR PC & Notes	EMR PC & Notes	PC Notes & Media			
* Median Trach-Free Survival from SX Onset = 30 months (Traxinger/Glass 2013); 20-36 months (Chio / Traynor 2009). Median Trach-Free Survival from Dx ≈ 18 months (Knibb /Al Chalabi 2016) ; 16 mos (Traxinger /Glass 2013).													

3. Standardized Mortality Ratio: Five-Year EAP Data

The **Standardized Mortality Ratio (SMR)** is a statistical measure used to compare the observed number of deaths in a specific population (e.g., EAP participants) to the expected number of deaths in the reference ALS population. As you know, it's commonly used in epidemiology to assess whether a group has a higher or lower mortality rate than expected.

Comparing the 5-year survival data for the EAP population, 20% of the ALS population is expected to survive 5 years. However, 100% of the NurOwn EAP population survived 5 years. This results in an SMR of zero. (0/8 x 100 = 0) . When no deaths are observed, the SMR is 0, which is highly unusual. This may indicate a small sample size, not a long enough time frame to assess mortality, a highly selected group -- **or an exceptional treatment outcome.**

The EAP sample size is small (n = 10) but the survival data spans ~ 5-7 years after the end of the RCT. People unfamiliar with ALS trials in general, or the NurOwn trial population specifically, might suggest the EAP survival data isn't valid because it was highly selected to favor survival. In fact, quite the opposite is true.

Slow progressors were excluded from the Phase 3 trial (as they are in most ALS trials) because it's hard to assess a treatment effect in slow progressors in a short six-month trial. As such, to qualify for the Phase 3 trial, people had to be losing at least 1 point per month during the trial's run-in phase. In ALS natural history, the mean decline per month is 0.77. As such, one would expect a higher – not lower – mortality rate in the NurOwn EAP than the general ALS natural history.

One potential confounding factor could be that people had to have survived the Phase 3 trial to be selected for EAP. But as the FDA's AdComm briefing document points out, there were 13 deaths during the trial (6.9%). Moreover, the EAP enrolled 4/10 people who were crossovers from the placebo arm and had lower ALSFRS-R scores at the EAP baseline, making mortality more likely. Additionally, one person had a baseline score of 13/48 at first EAP dose of NurOwn. This again would skew expected results to more, not less deaths, at 5 years in EAP. Even among the 4 EAP participants who eventually died after five years, 2 were in the NurOwn arm and 2 were in the placebo crossover arm. Finally, none of the people in EAP had tracheostomies, which artificially extends survival statistics.

The EAP population was NOT selected to favor survival. Instead, all the above factors made the EAP population favor mortality. As such, **the five-year survival data is all the more impressive evidence of an exceptional treatment response on NurOwn.**

Based on 0 observed deaths at 60 months, with 8 expected deaths:

- 95% Confidence Interval for SMR: [0, 0.461]
- p-value: ~0.000335 (one-sided) or ~0.000671 (two-sided)

These results indicate a statistically significant reduction in mortality compared to the expected rate.

4. New Trach-free Survival Data Far Exceeds Median ALS Natural History

According to the NIH and CDC's ALS Registry, the average lifespan for people with ALS is 3-5 years.[33] But that survival statistic can be misleading as it includes people who use machines to help them breathe. The "tracheostomy-free" survival data is more ominous than the oft-repeated 3-5 years statistic.

In a review summarizing survival data from dozens of population studies – **from symptom onset** – Bryan Traynor and Chiò (2009) reported that 20-36 months was the range of "trach-free" survival.[34] According to a survival analysis of 733 patients at Emory's ALS clinic, the median trach-free survival of their clinic's patients was **30 months from symptom onset and 16 months from diagnosis.**[35] A similar study of 575 patients was authored by Professor Ammar Al-Chalabi out of the UK. **From diagnosis, the median survival was 17.7 months.**[36] The consistency of these studies demonstrates the commonly accepted statistic that median ALS survival from diagnosis is just under 18 months.

[33] "Priorities of the NIH Amyotrophic Lateral Sclerosis (ALS) Strategic Planning Working Group" https://www.ninds.nih.gov/sites/default/files/documents/ALS%20Strategic%20Plan_11_20_23_508C.pdf

[34] Chiò, A., Logroscino, G., Hardiman, O., Swingler, R., Mitchell, D., Beghi, E., & Traynor, B. J. (2009). Prognostic factors in ALS: A critical review. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 10(5–6), 310–323.

[35] Traxinger, K., Kelly, C., Johnson, B. A., Lyles, R. H., & Glass, J. D. (2013). Prognosis and epidemiology of ALS: Analysis of a clinic population, 1997–2011. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 14(7–8), 584–588.

[36] Knibb, J. A., Keren, N., Kulka, A., Leigh, P. N., Martin, S., Shaw, C. E., Tsuda, M., & Al-Chalabi, A. (2016). A clinical tool for predicting survival in ALS. Journal of Neurology, Neurosurgery & Psychiatry, 87(12), 1361–1367.

In comparison, below is the trach-free survival data of the 10 people in EAP. **No one in EAP has undergone a tracheostomy or uses permanent ventilation to survive**. As you can see by the data below, in NurOwn EAP participants, the trach-free survival:

- **From Symptom onset**
  - ALS Median = 30 months (2.5 years)
  - EAP Median = 85 months (7.1 years)
  - Ranges from 60 - 103
  - △ ≈ 4.6 years longer than median

- **From Diagnosis**
  - ALS Median = 18 months (1.5 years)
  - EAP Median = 78 months (6.5 years)
  - Ranges from 51 - 87
  - △ = 5 years longer than median

Graphic - NurOwn's NEW Trach-free Survival versus Median ALS Natural History

NurOwn EAP - Trach-free Survival Data*

		Total EAP Population			EAP - Early vs Delayed Start				EAP - Living vs Deceased			
SURVIVAL from	ALS Natural History	EAP Survival Range	EAP Survival	△ months	6/10 Early Start (P3 NurOwn)	△ months	4/10 Delayed Start (P3 Placebo)	△ months	6/10 Living June 2025	△ months	4/10 Died after EAP	△ months
Symptom Onset	30.0	60 - 103 months	Median 85	55	85	55	74	44	89	59	66	36
			Mean 81.0		85		75		89		69	
Diagnosis	18.0	51 - 87 months	Median 73	55	78	60	69	51	84	66	58	40
			Mean 73.0		76		69		81		62	

1. Traxinger / Glass (2013). Prognosis and epidemiology of ALS: analysis of a clinic population
2. Chio / Traynor (NIH) (2009). Prognostic Factors in ALS: a critical review
3. Knibb / Al Chalabi (2016). A clinical tool for predicting survival in ALS

* No one in NurOwn EAP received a tracheosotomy
10/10 people in EAP survived / are survivng trach-free ≥ 5 yrs.
6/10 still alive as of June 2025 - without trach

All 10 people in EAP lived or are still living trach-free a minimum of 5 years from symptom onset.

- **From Symptom onset**
  - **△ ≈ 11 months longer survival in Early Start Population**
  - ALS Median = 30 months (2.5 years)
  - N/N - EAP Early Start Median = 85 months (≈ 7.1 years)
    - △ ≈ 4.6 years (55 months) longer than median
  - N/P – Delayed Start Median = 74 months (≈ 6.2 years)
    - △ ≈ 3.7 years (44 months) longer than median

- **From Diagnosis**
    - **△ ≈ 9 months longer survival in Early Start Population**
    - ALS Median = 18 months (1.5 years)
    - EAP Median = 78 months (6.5 years)
        - △ ≈ 5 years (60 months) longer than median
    - N/P – Delayed Start Median = 69 months (≈ 5.75 years)
        - △ ≈ 4.25 years (51 months) longer than median

After hitting the 5-year survival threshold, over the last few years, 4 of 10 EAP participants eventually died waiting for more doses of NurOwn. But equally tragic and impressive is that even among those 4 people who died, they lived a median of 5.5 years trach-free from symptom onset – which is nearly 3 years longer than median trach-free natural history.

The unfathomable tragedy is that they died waiting, despite knowing that a drug was helping them live. Sadly, our regulatory system doesn't act with the same urgency as ALS is killing their motor neurons.

5. Improved Survival - by Site of Onset

The survival rate in ALS varies, depending on phenotypic onset. People with limb-onset ALS generally have a longer survival time than bulbar-onset. Bulbar-onset ALS (20–30% of cases) affects speech and swallowing early, leading to faster respiratory and nutritional complications. A 2009 meta-analysis by Chio, including NIH's Bryan Traynor, reported a five-year survival of 20–30% for limb-onset versus 5–10% for bulbar-onset.[37] One study of 150 Japanese ALS patients found the five-year survival rate was 21% for lower limb onset, 18% for upper limb onset and 5% for bulbar onset.[38]

[37] Traynor, B. J., Codd, M. B., Corr, B., Forde, C., Frost, E., & Hardiman, O. (2000). Clinical features of ALS according to the El Escorial and Airlie House diagnostic criteria: A population-based study. Archives of Neurology, 57(8), 1171–1176.
[38] Fujimura-Kiyono C, Kimura F, Ishida S, et al. Onset and spreading patterns of lower motor neuron involvements predict survival in sporadic ALS. Journal of Neurology, Neurosurgery & Psychiatry 2011;82:1244-1249.

Graphic - NurOwn's Trach-free Survival vs Median ALS Natural History - by Participant

Name	x	Matt	x	Josh	Eric	Roberto	x	x	x	x	Lesley	Kade	Justin
Trial Participant ID	EN10	EN8	EN4	EN6	EN7	EN5	EP2	EP3	EP1	EP9	N3	N2	N1
ONSET - Limb or Bulbar	LL	UL	UL	UL	B & UL	UL	LL	UL	LL	B & UL	LL	B & UL & LL	B & UL
NurOwn (N/N) or Crossover Placebo (N/P)	N-N	N-N	N-N	N-N	N-N	N-N	N-P	N-P	N-P	N-P	N	N	N
Baseline ALSFRS-R - Phase 3	≥32	≥40	≥40	≥40	≥40	≥40	≥40	33	37	≥32	≥40	34	≥40
Trach-free Survival (months) - Sx Onset Symptom Onset to Death or June 2025	103	91	86	84	75	71	92	87	60	60	94	78	50
△ - Trach-free Survival SURVIVAL from Sx Onset	2.9x	2.5x	2.4x	2.3x	3.1x	2.0x	2.6x	2.4x	1.7x	2.5x	2.6x	3.3x	2.1x
Trach-free Survival (months) - Dx Diagnosis to Death or June 2025	85	87	81	75	70	60	87	82	55	51	84	68	47
△ - Trach-free Survival SURVIVAL from Dx	2.7x	2.8x	2.6x	2.4x	4.1x	1.9x	2.8x	2.6x	1.8x	3.0x	2.7x	4.0x	2.8x
Speed of Progression - Pre-Treatment	Average	Average	Average	Average	Fast	Average	Average	Average	Average	Fast	Average	Fast	Fast
Sx Onset to Dx (months)	18	4	5	10	5	11	5	5	5	9	9	10	3
GAP - Sx Onset to Dose #1	25	14	13	16	11	20	41	35	42	19	25	17	7
Source of Data (Public Comments, Medical Records, Media & Iview Notes)	PC Notes & Media	EMR PC & Notes	Media	EMR PC & Notes	EMR PC & Notes	EMR PC & Notes	Notes & Media	EMR PC & Notes	EMR PC & Notes	PC Notes & Media	EMR PC & Notes	EMR PC & Notes	EMR Notes & Media
* Median Trach-Free Survival from SX Onset = 30 months (Traxinger/Glass 2013); 20-36 months (Chio / Traynor 2009). Median Trach-Free Survival from Dx ≈ 18 months (Knibb /Al Chalabi 2016) ; 16 mos (Traxinger /Glass 2013).													

6. Improved Survival - Bulbar Onset Subgroup

Because of the vast heterogeneity of ALS, when evaluating a therapy's efficacy, it is important to compare people who have similar phenotypes. As seen in the Answer ALS heat map above, biological pathways impact people differently depending on whether they have limb or bulbar onset. And from natural history, we know that people with bulbar onset have a much quicker trajectory to death.

From symptom onset, median survival time for bulbar onset patients is approximately 2 years. In population-based studies, Chiò and Traynor (2009) reported median survival for bulbar-onset from symptom onset to death or tracheostomy was **20–24 months.** According to Knibb, al Chalabi (2009), the median survival time from diagnosis is **17 months** for bulbar patients.[39] In the table below you can see the de-identified EAP population as well as the three Petitioners from the Phase 3 trial.

Although it's admittedly a small sample size, 2 of the 10 men in EAP had bulbar onset. With the addition of Petitioners Justin Rogers and Kade Simons, we are able to analyze how NurOwn may have impacted their bulbar function and survival. Additionally, 3 of the 4 men received different doses. Each man had different timelines from symptom onset to diagnosis and from diagnosis to their first dose of NurOwn. All 4 men, concurrently, had upper limb and bulbar onset. This is significant because onset in multiple regions is typically associated with rapid progression.

[39] Knibb, J. A., Keren, N., Kulka, A., Leigh, P. N., Martin, S., Shaw, C. E., Tsuda, M., & Al-Chalabi, A. (2016). A clinical tool for predicting survival in ALS. Journal of Neurology, Neurosurgery & Psychiatry, 87(12), 1361–1367.

The interval between site of onset and involvement of the second region is also an important predictor of survival. For patients with a rapid spread pattern (two regions within 3 months from onset), it is exceedingly rare to survive more than 5 years.

Fujimura-Kiyono et al. (2011) defined "rapid spread" as two regions (e.g., limb to bulbar or contralateral limb) affected within 3 months from onset. Of the 150 patients with rapid spread, ***"No patient with a rapid spread pattern survived >5 years."***[40] Gargiulo-Monachelli et al. (2012) found that rapid spread (e.g., interposed or non-contiguous patterns) was associated with worse prognosis, with median OS ~2.5–3 years.[41] Chiò et al. (2020) used the PARALS registry to assess survival by the number of body regions involved at diagnosis. Patients with two regions affected early (akin to rapid spread) had 5-year survival rates near 0% for those with early multi-region involvement.[42]

In this "n of 4," there are some compelling post hoc observations about the impact of NurOwn on bulbar function and survival. Not surprisingly, the man who received the most doses of NurOwn and received them earliest in his ALS progression has retained the most bulbar function and lived the longest.

As you can see by the data below, **<u>for people with Bulbar Onset, NurOwn caused ≥ 3.5 years of trach-free survival benefits:</u>**

- **From Symptom onset**
  - ALS Median = 20-24 months (≈ 2 years)
  - EAP Median = 67.5 months (≈ 5.6 years)
  - Ranges from 50-75 months
  - **△ ≈ 3.6 years longer lifespan**

- **From Diagnosis**
  - ALS Median = 17 months (≈ 1.5 years)
  - EAP Median = 59.5 months (≈ 5 years)
  - Ranges from 47-70 months
  - **△ ≈ 3.5 years longer lifespan**

[40] Fujimura-Kiyono, C., … Hanafusa, T. (2011). Onset and spreading patterns of lower motor neuron involvements predict survival in sporadic ALS. Journal of Neurology, Neurosurgery & Psychiatry, 82(11), 1244–1249.
[41] Gargiulo-Monachelli, G. M., Janota, F., … & Sica, R. E. (2012). Regional spread pattern predicts survival in patients with sporadic amyotrophic lateral sclerosis. European Journal of Neurology, 19(6), 834–841.
[42] Chiò, A., Calvo,, ... & PARALS Group. (2020). Regional spreading of symptoms at diagnosis as a prognostic marker in amyotrophic lateral sclerosis: a population-based study. Journal of Neurology, Neurosurgery & Psychiatry, 91(6), 585–592.

Graphic - NurOwn's Trach-free Survival vs Median ALS Natural History - by Bulbar Onset

Name	Eric	x	Kade	Justin	BULBAR Subgroup		BULBAR Natural History	△ Median SURVIVAL
Trial Participant ID	EN7	EP9	N2	N1	MEAN	MEDIAN		
ALS genes	CAMTA1	MAPT - VUS	SETX-VUS					
ONSET - Limb or Bulbar	B & UL	B & UL	B & UL & LL	B & UL				
NurOwn (N/N) or Crossover Placebo (N/P)	N-N	N-P	N	N				
Baseline ALSFRS-R - Phase 3	≥40	≥32	34	≥40				
Trach-free Survival (months) - Sx Onset Symptom Onset to Death or June 2025	75	60	78	50	65.8	67.5	20-24	43.5
△ - Trach-free Survival SURVIVAL from Sx Onset	3.1x	2.5x	3.3x	2.1x				
Trach-free Survival (months) - Dx Diagnosis to Death or June 2025	70	51	68	47	59	59.5	17	42.5
△ - Trach-free Survival SURVIVAL from Dx	4.1x	3.0x	4.0x	2.8x				
Speed of Progression - Pre-Treatment	Fast	Fast	Fast	Fast				
SLOPE Before NurOwn (points/month) - from Sx Onset	1.25	≥1.0	1.0	1.15				
Time without NIV - (Fast Progressors =15 months median)	38	?	78	25	47	38	15	23
Sx Onset to Dx (months)	5	9	10	3	6.75	7		
GAP - Sx Onset to Dose #1	11	19	17	7	13.5	14		
Source of Data (Public Comments, Medical Records, Media & Iview Notes)	EMR PC & Notes	PC Notes & Media	EMR PC & Notes	EMR Notes & Media				

- **<u>EN7 - Petitioner Eric Stevens</u>** received 8 doses of NurOwn in the trial and EAP. Eric has a genetic mutation, CAMTA1, that speeds up ALS progression. Consistent with that mutation, his early progression was fast, losing 1.25 points per month on the 48-point functional rating scale. He was on a trajectory to die within 3 years. Thankfully however, Eric's first dose of NurOwn was just 6 months after symptom onset and his baseline score was still ≥40. Eric's bulbar symptoms were noticeable during their multiple appearances on the ELLEN Show. His speech was slow, softer, and had an irregular cadence. But then it audibly improved in a subsequent appearance on the show in 2021. Today Eric takes all nutrition through his feeding tube, but he **is still speaking and intelligible – 6 years from symptom onset**. He is also the only one of these four men with bulbar onset who is still alive today.

- **<u>N2 - Petitioner Kade Simons</u>** received 3 doses of NurOwn in the Phase 3 trial only. He is the only one of the four men who had symptom onset in three regions concurrently. Kade was a fast progressor, losing 1 point per month before receiving NurOwn. Kade's first bulbar symptoms occurred in May of 2018, when his voice began to get nasally. By the time Kade received NurOwn in July of 2019, his ALSFRS-R score had plummeted to 34. But the morning after his first precious dose of NurOwn, Kade felt it working systematically throughout his body.

  NurOwn caused the most durable impact on Kade's respiratory and bulbar function. He continued to join family at restaurants throughout 2023. Ultimately, Kade didn't get a feeding tube until February of 2024, and even then he still continued to eat things like pizza and Jersey Mike's Subs up until a few months before his death in August of 2024. Most impressively, Kade did not use NIV up until the time of his death. **This long-term, durable impact on bulbar and respiratory function lasted 6.5 years from symptom onset – nearly 4x longer than the median natural history of bulbar ALS.**

- **N1 - Petitioner Justin Rogers** With acute onset in multiple regions, Justin was diagnosed within 3 months from symptom onset; however, his prognosis was not hopeful. His first symptom was when he slurred his words and a hockey teammate asked him if he had been drinking. At one year post-diagnosis, Justin's ALSFRS-R had fallen to 33. His progression was so rapid that his neurologist's notes (RWD) documented having a hospice and DNR discussion, giving him only 6 to 12 months to live, consistent with the natural history of bulbar onset ALS. Concurrently, however, Justin had begun the NurOwn Phase 3 trial, where he received 3 doses. His last dose was in June 2020 then Justin survived until June 2023. Although he rapidly lost his speech, Justin survived 3 years from that ominous neurologist visit and more than 4 years from symptom onset. With NurOwn, Justin doubled his neurologist's prognosis and the median natural history of bulbar onset ALS.

- **EP9** - De-identified (MAPT-VUS carrier). EP9 was in the placebo arm in the phase 3 trial but eventually received 6 NurOwn doses in the EAP. Of these three men, he had the longest delay before receiving NurOwn. His first dose in EAP was in June 2021, 19 months after symptom onset. He told CBER at the PFDD meeting that his speech was "very weak and hard to understand" at the start of EAP. After receiving NurOwn, his FVC remained within the normal range at 90%. At his annual appointment (RWD), his neurologist was quite happy and told him it was *"not common to maintain normal breathing capacity after 2 years."* Ultimately, despite having bulbar onset and a 1.6-year delay in getting his first NurOwn dose, **EP9 survived to hit that 5-year milestone**.

When trying to assess efficacy in a vastly heterogeneous terminal disease, it is important to compare homogeneous subgroup populations - even if it's post hoc. And it's important to consider real-world evidence and real-world data. Statisticians may call this data dredging, but Petitioners must remind those same statisticians about the implications of a statistical Type 2 error in 100% fatal disease.

People with ALS are dying and every scrap of evidence is important to see if a drug will help them live. That's why this post hoc analysis of this small "n of 4 matters." That's why 8 years of real-world evidence outside the 28-week trial matter as this is evidence too. But most of all, those extra years of life matter.

For example, when compared to the entire ALS population, Justin's 4 years of survival may not have seemed impressive. But when compared to the bulbar onset population, it is. NurOwn interrupted and slowed Justin's rapid lethal progression. NurOwn defied the hospice prognosis of Justin's experienced ALS neurologist. NurOwn gave Justin at least two more years to make memories with his wife and young daughter. Nothing could be more clinically meaningful.

Similarly, Eric was on a 3-year trajectory to death. Instead, here we are 6 years later and Eric has become a dad not once but twice. Those early doses of NurOwn restored some limb, respiratory function and speech. That 5-year survival threshold is more than a statistic on a spreadsheet. The man who was diagnosed one month after his honeymoon is still able to tell his wife he loves her. He is still able to read books to his kids, sing happy birthday and cheer them on at their soccer games. NurOwn gave him that gift.

7. Improved Survival - Limb Onset Subgroup

Chiò (2009) reported median trach-free survival from symptom onset in limb-onset ALS ranged from 36 to 48 months across studies, with population-based studies reporting a median of **36 months from symptom onset**. According to Knibb, al Chalabi (2016), the median survival time **from diagnosis is 31 months for limb onset.**

Graphic - NurOwn's Trach-free Survival vs Median ALS Natural History - by Limb Onset

Name	Matt	Josh				Roberto			Lesley	Limb Onset		LIMB Natural History	△ Median SURVIVAL
Trial Participant ID	EN8	EN6	EN4	EN10	EP3	EN5	EP1	EP2	N3	MEAN	MEDIAN		
ONSET - Limb or Bulbar	UL	UL	UL	LL	UL	UL	LL	LL	LL				
NurOwn (N/N) or Crossover Placebo (N/P)	N-N	N-N	N-N	N-N	N-P	N-N	N-P	N-P	N				
Baseline ALSFRS-R - Phase 3	≥40	≥40	≥40	≥32	33	≥40	37	≥40	≥40				
Trach-free Survival (months) - Sx Onset Symptom Onset to Death or June 2025	91	84	86	103	87	71	60	92	94	84.25	84.5	36	48.5
△ - Trach-free Survival SURVIVAL from Sx Onset	2.5x	2.3x	2.4x	2.9x	2.4x	2.0x	1.7x	2.6x	2.6x				
Trach-free Survival (months) - Dx Diagnosis to Death or June 2025	87	75	81	85	82	60	55	87	84	81.5	82.0	31	51.0
△ - Trach-free Survival SURVIVAL from Dx	2.8x	2.4x	2.6x	2.7x	2.6x	1.9x	1.8x	2.8x	2.7x				
Time without NIV	85	84				71		92	94	85.2	84		
Sx Onset to Dx (months)	4	10	5	18	5	11	5	5	9	6.5	5.0		
GAP - Sx Onset to Dose #1	14	16	13	25	35	20	42	41	25	25.7	25.0		
Source of Data (Public Comments, Medical Records, Media & Iview Notes)	EMR PC & Notes	EMR PC & Notes	Media	PC Notes & Media	EMR PC & Notes	EMR PC & Notes	EMR PC & Notes	Notes & Media	EMR PC & Notes				
1. Knibb, al Chalabi (2016), the median survival time from Dx = 31 months for limb onset. 2. Chio (2009) - median trach-free survival from Sx onset in limb-onset = 36 to 48 months across studies, with population-based studies = median 36 months from symptom onset.													

As you can see by the data above, NurOwn's trach-free survival for people in EAP with limb onset shows ≥ 4 years of extended survival benefits:

- **From Symptom onset**
  - ALS Median = 36 months (3 years)
  - EAP Median = 84.5 months (7 years)
  - Ranges from 60-103 months
  - **△ = 4 years longer lifespan**

- **From Diagnosis**
  - ALS Median = 31 months (2.6 years)
  - EAP Median = 82 months (6.8 years)
  - Ranges from 55-87 months
  - **△ = 4.25 years longer lifespan**

D. Emergent Evidence of Improvement in Respiratory Function

People in the NurOwn trial and EAP have also consistently reported that NurOwn improved their respiratory function. Because loss of respiratory function is typically what causes death in ALS, especially relevant to any efficacy determination is the time-to-tracheostomy but also the time to non-invasive ventilation (NIV). NIV helps compensate for diaphragm weakness. NIV delivers positive airway pressure to assist breathing, improving oxygenation and eliminating CO2.[43] This reduces symptoms like dyspnea and fatigue, improves sleep quality, and extends survival by months, particularly when initiated early.[44] Thus, respiratory data are critical to efficacy determinations because they provide objective data about life-sustaining function.

1. The Phrenic Nerve and Neurotrophic Factors Impact Respiratory Function

In ALS, Andrews and Shefner (2018)[45] reported that *"death is usually caused by respiratory failure owing to loss of motor neurons supplying innervation to the diaphragm and chest wall muscles."* The phrenic nerve innervates the diaphragm and is critical for respiratory function. Hardiman, Al-Chalabi, and Chiò (2017) reported that the progressive loss of motor neurons -- especially in the phrenic nerve -- impairs diaphragm function, leading to hypoventilation, hypercapnia, and ultimately respiratory failure, the leading cause of mortality.[46]

Phrenic nerve survival and function are supported by neurotrophic factors, a subtype of growth factors that primarily support the growth, survival, maintenance, and differentiation of neurons and glial cells in the nervous system. For example, brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), and insulin-like growth factor 1 (IGF-1), play essential roles. BDNF promotes neuronal survival and synaptic plasticity, potentially mitigating phrenic motor neuron loss. GDNF enhances motor neuron protection and axonal growth, which may help maintain diaphragm

[43] Bourke, S. C., Tomlinson, M., Williams, T. L., Bullock, R. E., Shaw, P. J., & Gibson, G. J. (2006). Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: A randomized controlled trial. The Lancet Neurology, 5(2), 140-147

[44] Andersen, P. M., Abrahams, S., Borasio, G. D., de Carvalho, M., Chio, A., Van Damme, P., ... & Weber, M. (2012). EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS) – revised report of an EFNS task force. European Journal of Neurology, 19(2), 360-375.

[45] Andrews JA, Meng L, Kulke SF, Rudnicki SA, Wolff AA, Bozik ME, Malik FI, Shefner JM. Association Between Decline in Slow Vital Capacity and Respiratory Insufficiency, Use of Assisted Ventilation, Tracheostomy, or Death in Patients With Amyotrophic Lateral Sclerosis. JAMA Neurol. 2018 Jan 1;75(1):58-64.

[46] Hardiman, O., Al-Chalabi, A., Chio, A., Corr, E. M., Logroscino, G., Robberecht, W., ... & van den Berg, L. H. (2017). Amyotrophic lateral sclerosis. Nature Reviews Disease Primers, 3, 17071

innervation.[47] IGF-1 supports motor neuron survival and has shown potential in slowing ALS progression by preserving phrenic nerve function.[48]

Recall that NurOwn works by using mesenchymal stem cells to deliver packages of neurotrophic factors throughout the CNS, directly to the damaged and dying motor neurons.

2. Measuring Respiratory Function as a Predictor of ALS Survival

The American Academy of Neurology (AAN) guideline recommends NIV when FVC is ≤50% predicted. Because degeneration of phrenic motor neurons leads to weakened diaphragm muscles, and ultimately respiratory failure, the time-to-NIV is an important data point in evaluating long-term respiratory function.

NEALS neurologists Jinsy Andrews and Jeremy Shefner (2018) reported:

> *"Respiratory muscle function is commonly assessed in the clinic and in ALS clinical trials by measuring vital capacity (VC), the maximal volume displaced from the lung (often reported as percentage predicted instead of absolute volume), using either a forced VC (FVC) or a slow VC (SVC) maneuver…. **The rate of decline of FVC predicts survival of patients with ALS.** The importance of respiratory dysfunction in ALS has long been recognized … [and] direct measurements of respiratory function using measures like VC are also important. While **FVC** has been the most widely used method for respiratory assessment in ALS, the patient must expel air quickly and forcefully, which may cause fatigue and induce bronchospasm and **may result in an underestimation of actual lung capacity**."*

As such, Andrews and Shefner recommend using SVC and found that rate of decline in SVC is associated with clinically meaningful events in ALS, including respiratory failure, tracheostomy, or death. This suggests that vital capacity is an important predictor of clinical progression.

Petitioners believe their study is one of the largest and most comprehensive to ever study the connection between vital capacity and survival in ALS. Among 893 placebo-treated patients in the PRO-Act trial database, the mean (SD) SVC was 90.5% (17.1%) at baseline and the average decline of SVC from baseline through 1.5-year follow-up was -2.7% per month. With over 2300 observations, they also reported that the average slope of SVC decline for 2.6% points per month for limb onset versus 3.2% points per month for bulbar onset. (p=0.06).

---

[47] Lladó, J., Haenggeli, C., & Kato, A. C. (2006). Neurotrophic factors and gene therapy in ALS. Amyotrophic Lateral Sclerosis, 7(2), 65-73; Aebischer, P., Schluep, M., Déglon, N., Joseph, J. M., Hirt, L., Heyd, B., ... & Kato, A. C. (1996). Intrathecal delivery of CNTF using encapsulated genetically modified xenogeneic cells in amyotrophic lateral sclerosis patients. Nature Medicine, 2(6), 696–699.

[48] Sakowski, S. A., Schuyler, A. D., & Feldman, E. L. (2009). Insulin-like growth factor-I for the treatment of amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis, 10(2), 63–73; Vincent, A. M., Mobley, B. C., Hiller, A., & Feldman, E. L. (2004). IGF-I prevents glutamate-induced motor neuron programmed cell death. Neurobiology of Disease, 16(2), 407–416.

Age also impacted SVC. People <50 years old had an average decline of −2.3% (−2.7 to −1.8); people 50-65 years old had −2.6% decline; whereas those over 65 had a −3.6 decline. People ≤ 65 years old had an average loss of 15% of SVC over six months and the authors concluded that these changes were related to OS.[49]

The findings in this large study are important as the NurOwn Phase 2 trial was 24 weeks and the Phase 3 trial and EAP were 28 weeks (approximately 6 months). As such, one would expect to see similar decline in FVC over those time periods if NurOwn didn't work. But as you will see below, the impact was just the opposite.

Similarly, another way to assess the impact on respiratory function is to utilize time-to-event data such as time-to-trach and time-to-NIV. Those statistics are outlined in this May of 2024 review*, "Time from ALS symptom onset to key disease milestones: analysis of data from a multinational cross-sectional survey."* In it, researchers found in the US, **time to NIV -- from symptom onset -- was approximately 15 months for fast progressors and 27 months for intermediate progressors:**[50]

- NIV - Fast Progressor losing > 0.77 points/month ALSFRS-R
  - 14.9 months from Symptom Onset = US Population
  - NurOwn Trial Qualification losing ≥ 1 point/month ALSFRS-R

- NIV - Intermediate Progressor losing 0.36 - 0.77 points/month ALSFRS-R
  - 26.9 months from Symptom Onset = US Population
  - Ex: Tara Collazo and Nick Warack who were excluded from NurOwn trials

- NIV – Slow Progressor losing < 0.36 points/month ALSFRS-R
  - 79.5 months from Symptom Onset = US Population
  - Ex: Navy pilot Matt Bellina

[49] Andrews JA, Meng L, Kulke SF, Rudnicki SA, Wolff AA, Bozik ME, Malik FI, Shefner JM. Association Between Decline in Slow Vital Capacity and Respiratory Insufficiency, Use of Assisted Ventilation, Tracheostomy, or Death in Patients With Amyotrophic Lateral Sclerosis. JAMA Neurol. 2018 Jan 1;75(1):58-64.

[50] Gebrehiwet, P., Brekke, J., Rudnicki, S. A., Mellor, J., Wright, J., Earl, L., Ball, N., Iqbal, H., Thomas, O., & Castellano, G. (2024). Time from amyotrophic lateral sclerosis symptom onset to key disease milestones: Analysis of data from a multinational cross-sectional survey. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 25(3-4), 345–357.

Graphic __ - Time-to-Event Data in ALS

MILESTONE Symptom Onset to…	Month to Hit Milestone						
	AVERAGE All Progessors	Int'l Fast Progressors (>0.77)	US FAST Progressors (>0.77)	Int'l Intermediate Progressors (>0.36 – <0.77)	US INTERMEDIATE Progressors (>0.36 – <0.77)	Int'l Slow Progressors (≤0.36)	US SLOW Progressors (≤0.36)
Wheelchair	22.8	14.7	13.7	30.8	28.9	58.6	40.2
NIV - Respiratory aid	27.3	17.6	14.9	33.7	26.9	80.0	79.5
Feeding Tube	28.6	19.0	16.6	39.6	31.4	102.0	110.3
24 Hr Care facility	30.3	18.2	18.3	36.3	44.5	75.4	67.7

3. Preserved and Improved Respiratory Function in NurOwn Trial and EAP Recipients

Comparing the Time-to-NIV data with NurOwn recipients' real-world evidence provides astonishing insights to corroborate NurOwn's plausible mechanism of action on the phrenic nerve, and in turn, one way in which NurOwn causes an unprecedented improvement of survival.

Multiple people in the NurOwn trials and EAP reported "significant improvements" in breathing function. For example, after additional doses in Expanded Access, Josh Smith, Eric Stevens and Phil Green reported improved VC. And Matt Bellina stopped using NIV altogether after he received 7 doses via Right to Try. People with ALS don't spontaneously regain VC or stop using NIV. It just doesn't happen. But it did with NurOwn.

a. Time-to-NIV

The table below summarizes how NurOwn impacted the respiratory capacity of many of the Petitioners. This is new evidence not only because it is long-term data about the impact of NurOwn on the phrenic nerve, but also because the collection of FVC/SVC was halted during the trial because of COVID.

Graphic - NurOwn's Time-to-NIV

Name	Lesley	Matt	Josh	Roberto	Kade	Eric	Justin
Trial Participant ID	N3	EN8	EN6	EN5	N2	EN7	N1
ONSET - Limb or Bulbar	LL	UL	UL	UL	B UL & LL	B & UL	B & UL
NurOwn (N/N) or Crossover Placebo (N/P)	N	N-N	N-N	N-N	N	N-N	N
Baseline ALSFRS-R - Phase 3	≥40	≥40	≥40	≥40	34	≥40	≥40
Trach-free Survival (months) - Sx Onset Symptom Onset to Death or June 2025	94	91	84	71	78	75	50
Trach-free Survival (months) - Dx Diagnosis to Death or June 2025	84	87	75	60	68	70	47
ACTUAL Time to NIV from Dx Dx to Death or June 2025	84	78	75	60	68	33	22
Time to NIV from Dx - by Site of Onset	23	23	23	23	13.5	13.5	13.5
△ - Time to NIV - from Dx (months)	61	55	52	37	54.5	19.5	8.5
△ - Time to NIV - from Dx	3.7x	3.4x	3.3x	2.6x	5.0x	1.7x	1.6x

In the journal Respiratory Medicine, Carratù (2019) reported that **median time-to-NIV is 13.5 months post-diagnosis for bulbar-onset**.[51] Three Petitioners in the table above had bulbar onset.

Kade Simons never used NIV up until the time of his death 68 months after diagnosis. That is 5x longer than natural history for bulbar onset patients. It's especially impressive because Kade received only 3 doses of NurOwn. Kade's pulmonologist was so surprised that Kade's breathing was so still so strong that he jokingly asked, *"are you sure you have ALS?"*

Similarly, Eric Stevens and Justin Rogers both had bulbar onset. With just 3 doses of NurOwn and fast - progressing bulbar onset, Justin began using NIV at 22 months from diagnosis (1.6x longer than natural history). Eric didn't start using NIV at night until 33 months from diagnosis (2.4x longer than natural history). Even three years after symptom onset, NurOwn still helped Eric. During the second round of EAP in 2022, **Eric's FVC improved by 13 points**.

Carratù (2019) reported that **median time-to-NIV is 23 months post-diagnosis for limb-onset patients.** After receiving just 3 NurOwn doses in the trial, Lesley Krummel still doesn't use NIV 84 months from diagnosis. Both Roberto Muggli and Josh Smith were in EAP and received 9 total doses. Roberto never used a bipap up until his death -- 60 months after diagnosis. To this day, Josh still doesn't use NIV 75 months from diagnosis.

[51] Carratù, P., Spicuzza, L., Cassano, A., Maniscalco, M., Gadaleta, F., Lacedonia, D., & Carpagnano, G. E. (2019). Early treatment with noninvasive ventilation in amyotrophic lateral sclerosis. Respiratory Medicine, 152, 1–6.

b. Real World Evidence of Improved Respiratory Function

Over the last decade, people in the NurOwn trials have reported improved respiratory function. Not just slowing of progression. Not just stabilization. Improvement.

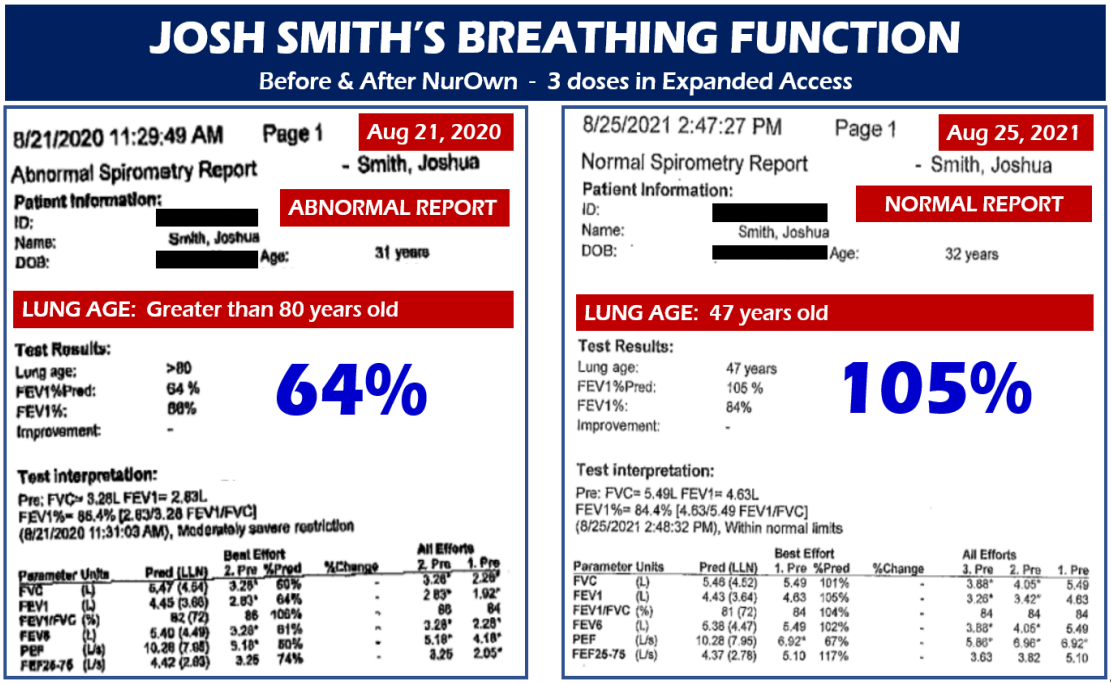
As detailed in the Phase 2 data below, Bobby Forster reported "significant improvements" in his FVC with just one dose of NurOwn. After receiving additional doses of NurOwn in EAP, Josh Smith, Phil Green and Eric Stevens all reported improvements in FVC. People with ALS don't spontaneously regain VC. It just doesn't happen in ALS. But it did with NurOwn.

Recall that the study by Andrews and Shefner concluded that the average loss of SVC is approximately 15% over 6 months, and FVC may underestimate that loss.

In August of 2020, Josh Smith had his FVC tested by Emad Kamel MD, FACP/FCCP at Ocean Pulmonary and it was 64%. His breathing function was akin to a man >80 years old. This was about 17 months post-diagnosis. Josh was approaching the 50% threshold where NIV would have been recommended. This decline was aligned with the time-to-event studies mentioned above as well as the Andrews/Shefner paper documenting a 15% decrease (in SVC) over a 6-month timeframe.

Then from April 6th through July 20th in 2021, Josh received 3 more doses of NurOwn in EAP from Dr. Brown at UMass and the trajectory of his loss of breathing function was upended. As a then 32-year-old with limb onset, Josh's results were astounding!

Graphic - Josh Smith's FVC Tests 2020 Pre-EAP vs. 2021 Post-EAP



J

Based on Andrews/Shefner study above, Josh should have lost respiratory function in the year between these two pulmonary assessments but instead, he regained an unprecedented improvement in breathing capacity.

Below are the results of Josh's FVC tests:

- September 2019 – January 2020: NurOwn Phase 3 Trial Doses #4-6
- August 2020: Pre-EAP Round1 FVC = **64%**

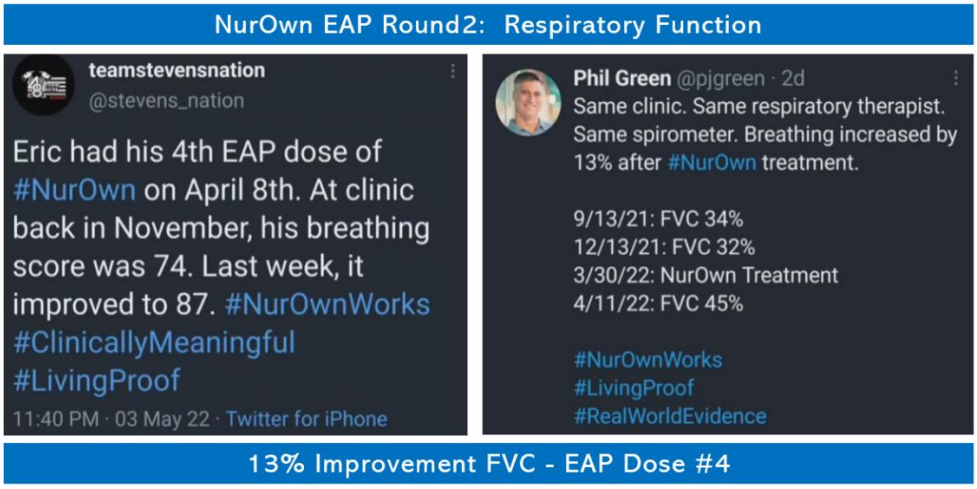
- April – July 2021: NurOwn Doses #4-6
- August 2021: Post EAP FVC = **105%**
- February 2022: Pre-EAP Round2 FVC = **87%**

- May – June 2022: NurOwn Doses #7-8
- July 2022: EAP FVC = **86%**

- August 2022: NurOwn Doses #9
- October 2022: Post EAP FVC = **92%**

Josh's pulmonary function tests were submitted as part of the Exhibits to his Josh's Public Comment at the AdComm. One attachment was entitled "Joshua Smith Medical Records Summary." This is real-world data collected outside the trial. Yet it was never discussed or even mentioned by the FDA nor AdComm members. But Josh wasn't the only one who had improvements in FVC. So too did others. Phil Green and Eric Stevens both posted on social media about their results during the second round of EAP in 2022 with Dr. Namita Goyal at UC Irvine. By that time, their ALS was more advanced than it had been in the trial in 2019, but NurOwn helped them once again – just as Dr. Windebank testified at the AdComm. They too shared their results with the FDA at the AdComm.

Graphic - FVC Tests 2021 vs. 2022 Post-EAP for Eric Stevens and Phil Green



Similarly, in October 2021, EAP participants met with FDA-CBER leadership to share their experiences during the first round of EAP and to request more EAP access. The transcript of this meeting was shared with FDA-CBER in advance of the meeting. In it, one man spoke about his gross motor function but also shared his neurologist's perspective on his respiratory function.

> *"I received my second treatment of NurOwn on August 16th and will receive my final treatment on October 21st…. I just had a breathing test at my ALS clinic and* ***my FVC remains within the normal range at 90%. My neurologist, Dr. Jinsy Andrews, says it is not common to still have normal breathing capacity more than 2 years after diagnosis*** *and she is quite happy about it."*

Sadly, without the ability to get more NurOwn, he died waiting two years later – just a few short months after the tragic AdComm.

4. NurOwn Improved Matt Bellina's Respiratory Function when He Received 7 Doses via Right to Try

Coupled with the Time-to-NIV and VC data above, Matt Bellina's real-world respiratory data is supporting evidence to corroborate what NurOwn trial and EAP participants have long said: NurOwn helps them breathe better.

As Matt Bellina shared in this I AM ALS Press Release from Veterans to the FDA in 2022: *"My lung capacity is 37% higher than it was before my first injection, so I no longer need the assistance of a breathing machine."* Previously, Matt's ALS had progressed to a point where he needed NIV. Then he received NurOwn. His breathing function rebounded and stabilized for years afterwards.

People with ALS don't spontaneously come off non-invasive ventilation. No placebo effect can make you breathe better. It just doesn't happen. But it did with NurOwn.

In his March 2021 blog, after the FDA publicly commented that there was not enough evidence to support the filing of a BLA, Matt Bellina provided evidence to the contrary. In an ode to the Latin phrase RES IPSA LOQUITIR ("the thing speaks for itself"), Matt publicly disclosed his real-world data from his VA medical records, which documented his profound improvements in breathing. Matt also signed an agreement with the VA and Brainstorm giving them permission to disclose his information.

And for any critics who would challenge the reliability of this open-label "n of 1," Matt also clarified that the Philadelphia VA treated *him "in accordance with the clinical trial protocols."* Matt then documented his improvements in his ALSFRS-R and FVC.

> *"Here is the data from my VA medical records…. Unfortunately, I have not seen Pulmonary since this whole Covid thing started. I have been doing virtual clinic so the last data point is the end of 2019:"*

<u>Dose #1</u> – December 27, 2018
12/27/2018 PFTs: FEV1 1.83 (42% pred), FVC 2.61 (48% pred), FEV1/FVC 70%
1/25/2019 PFTs: FEV1 3.12 (72% pred), FVC 3.81 (70% predicted), FEV1/FVC 82%

<u>Dose #2</u> – February 12, 2019
2/12/2019 PFT: FEV1 2.55 (59% pred), FVC 3.11 (57% predicted), FEV1/FVC 82%
3/8/2019 PFT: FEV1 2.79 (XX% pred), FVC 3.85 (XX% predicted), FEV1/FVC 72.5%

<u>Dose #3</u> – April 18, 2019
5/17/2019 PFT: FEV1 2.54 (58% pred), FVC 3.84 (71% predicted), FEV1/FVC 66%

<u>Dose #4</u> – July 18, 2019
7/18/2019 PFT: FEV1 2.45 (56% pred), FVC 2.89 (53% predicted), FEV1/FVC 85%
8/23/2019 PFT: FEV1 2.71 (XX% pred), FVC 3.46 (XX% predicted), FEV1/FVC XX%

<u>Dose #5</u> – September 18, 2019

<u>Dose #6</u> – November 21, 2019
11/1/2019 PFT: FEV1 2.80 (65% pred), FVC 3.69 (68% predicted), FEV1/FVC 76%
12/19/2019 PFT: FEV1 2.51 (58% pred), FVC 3.21 (60% predicted), FEV/FVC 78%

<u>Dose #7</u> – August 12, 2020

Importantly in his March 2021 blog, Matt noted: *"I still have not gone back on the Trilogy despite being hospitalized for pneumonia for 8 days in February 2020."*

In her Public Comment to the NurOwn AdComm, Matt's mother added more context to how powerful of an effect NurOwn had on Matt's bulbar function and breathing function, which were already compromised on that December day of his first dose of NurOwn.

> *"On that day, Matt nearly choked to death while eating dinner. This incident is documented in his post-procedure medical records. Fast-forward one-month to mid-January 2019, Matt stopped choking while eating, he was **<u>breathing without mechanical assistance, the "huffing" was gone. He was completely off the trilogy machine…. His breathing improved, his swallowing improved</u>**."*

As of May 2023, his mother Deb Bellina again shared news about the long-term durability of NurOwn's impact on Matt's respiratory function: ***"He is breathing and eating with no intervention 4 1/2 years AFTER his first dose of NurOwn."*** That is more than 4 years of impact on respiratory function!

In sum, these new respiratory data are especially important real-world evidence. Most clinics halted collection of vital capacity assessments during COVID, and as such, Brainstorm was deprived of the chance to collect and assess the impact of NurOwn on respiratory function in both the trial and EAP. But this long-term RWE fills that information gap. Thus, this is new evidence for the FDA to consider.

The other critical thing demonstrated by these data are that patient experiences and real-world evidence matters. When ALS patients have difficulty breathing and are gasping for air, they know when a therapy helps them breathe better. The NurOwn Petitioners know that NurOwn helped them breathe better, and when you breathe better, you live longer.

E. Emergent Data of Significant Reduction in Harmful Neurofilament Light in EAP Participants who Received Additional Doses of NurOwn

Neurofilament light (NfL) is a biomarker that measures the amount of neurodegeneration in people with ALS and other neurodegenerative diseases. As ALS progresses and motor neurons start dying, the levels of neurofilament light increase.[52]

Brainstorm presented the following EAP neurofilament light data at the ALS Drug Development Summit in May 2024 where Mitze Klingenberg was in attendance. Then in October 2024, Brainstorm presented the data again in a NEALS Poster where you can see the compelling changes in the neurodegeneration biomarker NfL.

At the end of the 28-week Phase 3 trial, the NurOwn arm of the trial population experienced a small but beneficial reduction from baseline neurofilament light (NfL) levels: a small 9.4% delta in neurofilament light (NfL) levels compared to those in the placebo arm. But in the subgroup of 10 people who were eventually enrolled in the EAP, at the end of Phase 3, there was a 41% delta in NfL levels in favor of the 6 people in NurOwn arm versus the 4 people in the placebo arm.

Graphic - NurOwn's NfL Change from Baseline Table

Percent Change from Baseline NFL in NurOwn Phase 3 & EAP								
	Phase 3					EAP Round 1		EAP Round 2
Trial Status	TOTAL Phase 3 Population		Sx to Trial Dose #1 (months)	EAP Participants in Phase 3 (2017-2020)		Gap to EAP Dose #1 (months)	EAP 1 (2021)	Gap to EAP Dose #4 (months)	EAP 2 (2022)
NurOwn P3	95	<11%>	12 - 25	6	<4%>	9 - 28	<27%>	7 - 9	<36%>
Placebo P3	94	<1.6%>		4	37%	29 - 42	17%	6 - 9	<5%>
Difference	189	9.4%		10	41%		44%		31%

[52] The NurOwn trial, uniquely, enrolled people across the ALS disease spectrum, including those late in ALS progression. The lowest baseline score was 16/48 when dosing began. The 10 people in the EAP were earlier in disease progression at the start of the NurOwn trial. Brainstorm reported that everyone in EAP had a baseline score ≥32 on the 48-point functional rating scale. Thus, it should be expected to see a wide range of baseline neurofilament light levels at the start of the Phase 3 trial.

And as was exemplified by the people in EAP, the more NurOwn doses that people received, the more their harmful NfL levels decreased. Ultimately, he 6 people in the "early start" NurOwn EAP arm demonstrated a 27% beneficial decrease in NfL levels at the end of Round 1 in EAP. Thereafter at the end of Round 2 of EAP, both arms continued to experience beneficial decreases in NfL: 36% in the NurOwn "early start" arm and 5% in the "delayed start" arm.

In EAP Round 2, people in the "delayed start" arm (aka crossover from EAP) started to experience a dose-dependent response and began to make up that delta. By the end of Round 2, there was a 31% delta in favor of those who had received NurOwn both in the trial and in the EAP.

The lesson: treat people early and often to see the largest reduction in harmful neurofilament light. But recognize that people later in progression can also experience benefits! Imagine if all these people could have received NurOwn every two months on the prescribed dosing schedule. The only way we will know what these NfL data would look like with long-term use and consistent dosing is if NurOwn is approved with a Phase 4 post-marketing study.

(See section M below for more detailed biomarker and NfL discussion).

F. Other Emergent Data from EAP

The evidence related to slowing of functional decline and extended time of "progression-free" survival demonstrate that NurOwn caused a PROFOUND clinically meaningful change in how people feel, function and survive.

Unfortunately, Petitioners do not possess ALSFRS-R data for all people in EAP. Some treating neurologists don't use the ALSFRS-R. Some people didn't personally track their scores. Some had missing scores. Some trial and EAP participants didn't see a neurologist outside the trial. And Brainstorm has not yet authorized the trial and EAP sites to release the trial participants' ALSFRS-R and FVC/SVC scores.

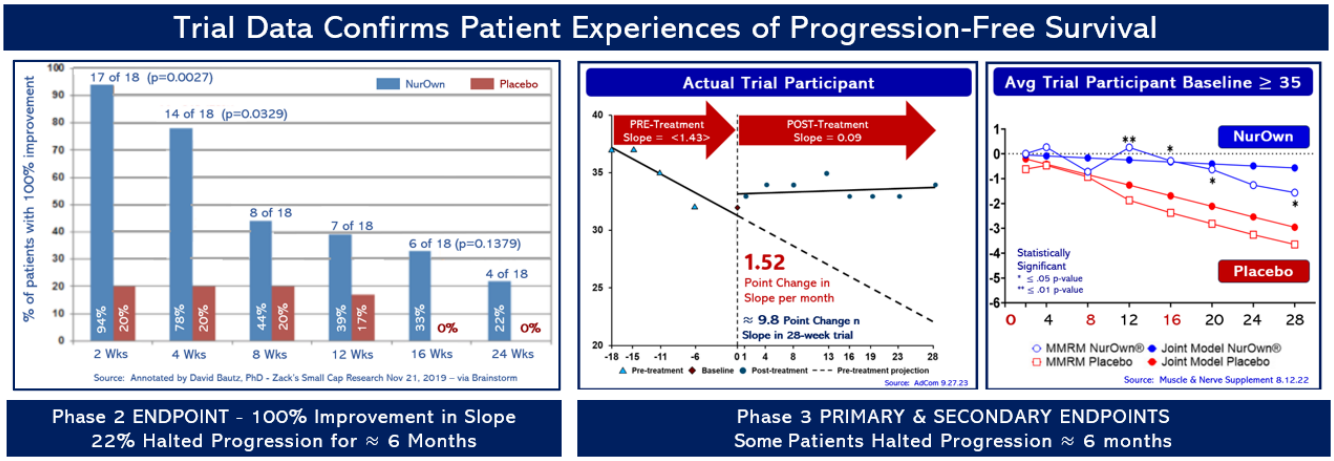
As such, Petitioners are quite aware that the below data are not a perfect data set and that, alone, the data do not have the same reliability as the unequivocal survival data. But in the people who did track their scores, the long-term data we do have is so unprecedented in the history of ALS and ALS clinical trials that it adds to the mountain of supporting evidence of efficacy. It is also corroborated by real-world data and patient experiences that trial and EAP participants documented contemporaneously in writing, in videos, and on social media as "present sense impressions" and "excited utterances." And strengthening that data even more, the trial participants' treating neurologists offered real-world data and evidence supporting their unprecedented changes.

1. New Evidence of Progression-free Survival (PFS)

Just as Dr. Anthony Windebank testified at the AdComm, people halted their progression when they received NurOwn and declined when they didn't. Now that the trial has been unblinded, some Petitioners individually have proof that they were in the population of people about whom Dr. Windebank spoke.

The trial data in both Phase 2 and Phase 3 showed approximately 6 months of progression-free survival in some and a dose-dependent response by the times those trials ended at 24 and 28 weeks, respectively.

Graphic - Phase 2 and 3 Data Confirms Some Patients Halted Progression



Approximately 20% of fast progressors in Phase 2 halted the progression for 6 months – with just one dose. Then in Phase 3 with 3 doses, again people reported halting progression for up to 17 months, including Petitioner Matt Klingenberg. Matt Bellina also halted his respiratory progression for years. The stories are endless.

But until Brainstorm allows trial sites to release the ALSFRS-R and FVC/SVC scores, we cannot accurately and retrospectively assess the magnitude of progression-free survival for everyone. Likewise, in the future the best way to assess PFS is the same way regulators do in cancer -- with a large Phase 4 post-marketing study with consistent dosing over several years.

2. 75-85% Slowing in Long-term Rate of Decline

Recall that the average rate of decline in ALS is 0.77 points per month and that people had to lose ~ 1 point per month to qualify for the NurOwn trial. Against that backdrop, the significant slowing in the rate of decline is notable. For example, Matt, Josh, Eric, Kade and Lesley all decreased their rate of progression to approximately 0.16 points per month over years. But those periods of time were at different points in the dosing schedule and lasted different periods of time. As such, to accurately

compare and report this improvement to the FDA, and to minimize recall bias and other errors, we hope Brainstorm will consider allowing us to have access to our own medical records from the trial and EAP.

Name	Josh	Matt	Eric	x	x	Roberto	Lesley	Kade	Justin	NurOwn Early Start (n=6)			Early Start P3 & EAP (n=9)		
Trial Participant ID	EN6	EN8	EN7*	EN10	EN4	EN5	N3	N2*	N1*	MEAN	MEDIAN	Δ median	MEAN	MEDIAN	Δ median
ONSET - Limb or Bulbar	UL	UL	B & UL	LL	UL	UL	LL	B & UL & LL	B & UL						
NurOwn (N/N) or Crossover Placebo (N/P)	N-N	N-N	N-N	N-N	N-N	N-N	N	N	N						
Baseline ALSFRS-R - Phase 3	40	43	40	32	≥40	≥40	≥40	34	≥40						
Trach-free Survival (months) - Sx Onset** Symptom Onset to Death or June 2025	84	91	75	103	86	71	94	78	50	85	85	55	81	84	54
Trach-free Survival (months) - Dx**	75	87	70	85	81	60	84	68	47	76	78	60	73	75	57
SLOPE After NurOwn (mean = 0.77 pts/month)	0.15	0.15	0.16	0.16			0.17	0.16	0.75	0.24	0.16	-0.61	0.24	0.16	-0.61
Time without NIV (median = 15 months)	84	85	38			71	94	78	25	68	78	63	68	78	63
PROGRESSION FREE SURVIVAL (months)	9	17	5	3			11	0	0	6.4	5.0				
Source of Data (Public Comments, Medical Records, Media & Iview Notes)	EMR PC & Notes	EMR PC & Notes	EMR PC & Notes	PC Notes & Media	Media	EMR PC & Notes	EMR PC & Notes	EMR PC & Notes	EMR Notes & Media						

G. RWE from Ten People in EAP and One Person in Right to Try Resulted in Unprecedented Proof that Can Meet the "Substantial Evidence" Threshold as Multiple Unprecedented and Probative "n of 1" Stories Exist

"We want to focus the agency on cures and meaningful treatments.
We believe in the letter and the spirit of Right to Try."
-Commissioner Marty Makary
(FOXNews - May 8, 2025)

As Commissioner Makary stated recently: *"we can learn from individual cases."* To wit, from Matt Bellina's 7 doses in Right to Try, the ALS community learned a lot that we didn't learn in the short Phase 3 trial with just 3 doses of NurOwn. We learned:

- How NurOwn impacts slow progressors
- What the long-term durability of NurOwn might be based on Matt's 7 total doses
- How someone with a baseline score of 21/48 might respond to NurOwn
- How the magnitude of response to NurOwn seemed directly correlated to his Matt's 6 consecutive doses of the total 7 doses.

And most importantly, when Matt stood up out of his wheelchair for the first time in years and stopped using a bipap to breathe for more than 4 years – all after receiving NurOwn -- we learned that it is possible for some people with ALS to regain function. Something no one previously thought possible.

Likewise, from the "n of 10" in EAP, we have -- for the first time in ALS history – profound, disease-modifying respiratory and survival data.

As the current Commissioner believes there is value in learning from "n of 1" cases, so too does former Commissioner Woodcock, who is working with the Haystack Project on rare disease legislation. At a recent BIO conference, Pink Sheet reported on Dr. Woodcock's speech:

> ***"[If] a person who was bedridden walks, nobody's going to be that impressed…. But if you do it seven times and five out of seven walk, you're going to carry the day."***

Dr. Woodcock went on to explain that for very small, heterogeneous diseases, "sequential n of 1 studies," can constitute "substantial evidence." She argued her advice is consistent with the FDA's drug approval authority and added:

> *"The statute governing efficacy says 'adequate and well controlled investigations that will convince experts' but '**it does not say anything about a p-value. It does not say anything about randomization**'. It says adequate and well-controlled and there are different ways to do that."*

Petitioners submit that Matt Bellina's "n of 1" real-world study is so unprecedented that it should be part of the totality of the supporting evidence that the FDA considers for NurOwn's approval. Instead, Matt's unprecedented RWE was not even mentioned in the FDA's Briefing Document, and Matt's mother was not chosen to share his RWE at the Open Public Hearing at the NurOwn AdComm.

As described below, Matt was wheelchair-bound, then he was able to stand up unassisted and take steps again. Although it defies common sense to anyone familiar with ALS, Dr. Woodcock's comment was correct, regulators were not "impressed."

But the ALS community was. People who had lived experience with ALS recognized the significance of Matt regaining function and they were astounded. Everyone with ALS that they knew in clinical trials hoped and prayed to regain some lost function but no one in those trials ever had such a strong "placebo response."

And a few months later when Matt was able to stop using a bi-pap to breathe at night, the ALS community was convinced. They didn't know anyone else who had come off NIV. They knew what it was like to struggle to breathe. They knew what it was like to huff for breaths in between sentences as their bodies strived for oxygen. And no matter how powerful the mind is, they knew a placebo effect couldn't help a weakened diaphragm expel CO2.

Matt received his 7th and final dose of NurOwn via Right to Try in 2020. In 2021 and 2022 people in EAP received up to 6 more doses. Nearly mirroring the dose-dependent response that Matt Bellina experienced, the NurOwn Petitioners also began experiencing unprecedented changes. This was unexpected as many had significant gaps in dosing of 1-2 years between the trial and EAP and then another 9 months between the two rounds of EAP.

Only 6 people in EAP received NurOwn in the Phase 3 trial (shortly after diagnosis) and at least 3 more doses in EAP – matching Matt Bellina's 6 doses, albeit not consecutive. They include NurOwn Petitioners Matt Klingenberg, Josh Smith, Roberto Muggli and Eric Stevens and two other people. Their survival data are astounding.

Because Matt Bellina's unprecedented "n of 1" improvement in function was also demonstrated by many of the people in the "n of 10" EAP, that evidence too should carry the day and be part of the substantial evidence that justifies approving NurOwn with a Phase 4 post-marketing study.

Dr. Woodcock explained that RCTs are fit for purpose for large populations but not fit for rare diseases. The smaller the size of the study arms, the more likely bias toward the null hypothesis occurs, which means an increased chance of not finding a treatment effect even if a product is effective. Dr. Woodcock lamented:

> *"That's very sad, because it's some of our most needy populations who don't have any treatments, and yet, the designs that we currently use make it much less likely that we'll find an effect when there is one… It's a math issue, it's not ideological, it's mathematical."*

Although Dr. Woodcock did not specifically mention heterogeneity, the same mathematical issue arises. While ALS affects approximately 32,000 Americans, its heterogeneity compounds the problems of finding efficacy signals in a diverse and poorly understood trial population.

As Dr. Hande Ozdinler of Northwestern so aptly stated in her Public Comment to the AdComm, if we can improve the health of a small population of ALS patients, that in itself is an achievement.

> *"ALS is a very heterogenous and rare disease. Therefore, finding a drug or a treatment strategy that would yield positive results on a broad population is very challenging…. It is very possible that one solution that is good for one patient may not be effective for the other. I think our goal should not be to find the one magical drug or solution that is going to cure them all (the science shows us that this in fact may not be possible)…. We should not expect all patients to respond in the same way. If we can improve the health of a small population of ALS patients, that in itself is an achievement….. In my opinion, the glass is half full, it is not half empty… We should not let the patients who benefit from the treatment pay the price of our unfounded expectation that all or a majority should benefit from the treatment before a treatment is approved….. What scientific or moral obligation do we have to deny the patients from having access to the treatment that improves their condition? Again, not every patient, but some patients will improve. Why not help those "some patients"?. The "all or none" approach, especially for rare and heterogeneous diseases is not suitable."*

She closed by saying: *"One may be a small number, but it that one is your loved one, it means the world to you."*

That is precisely why Petitioners submit that some must be enough in this 100% terminal and heterogeneous rare disease. Some subgroups must be enough. Some improvement in respiratory function must be enough. And certainly, some people extending survival must be enough. When the "n of 1" is your loved one and a stem cell therapy helps them live longer or live better, that "n of 1" is all that matters.

FACTUAL BACKGROUND

A. Subjective ALSFRS-R is the Patient-Reported Bounded Scale Used for ALS Clinical Trial Endpoints

As Dr. Prasad has succinctly summarized, FDA approved drugs should help Americans "live longer or live better." To assess whether a drug meets that goal, trial endpoints are often based on objective biomarkers or clinical outcome assessments ("COA") measuring changes in how trial participants "feel, function or survive."

According to the BEST glossary, COAs can be objective such as neurological tests documented by a neurologist or performance-based outcomes documented by a clinician. Examples in neurodegenerative diseases include a timed 6-minute walk test, grip strength tests, or forced vital capacity testing of respiratory function. In contrast, COAs also can be subjective, like bounded functional scales where patients or caregivers report changes.

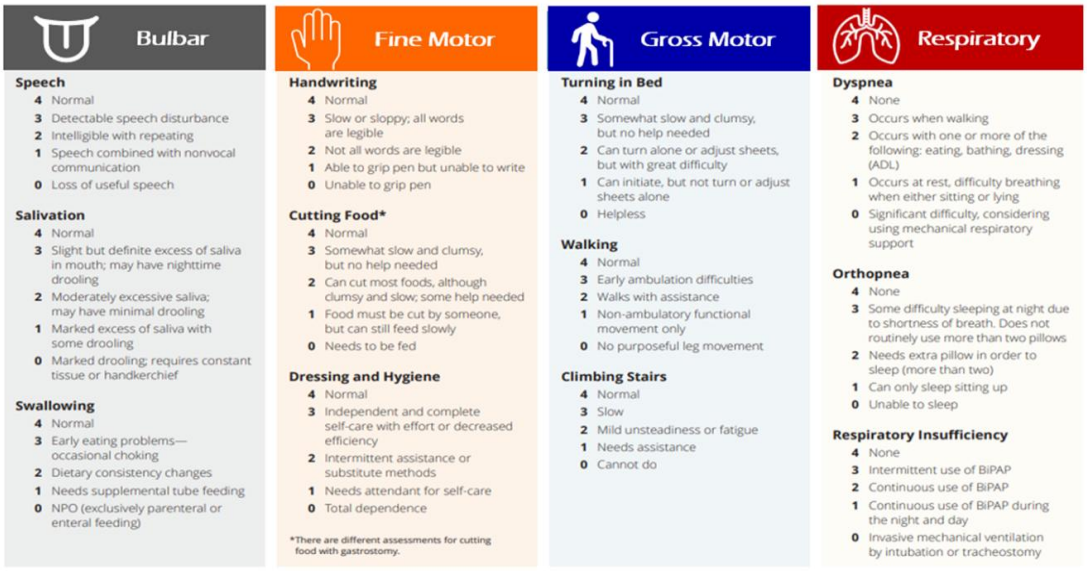
Like many of the 7,000 rare diseases, sporadic ALS lacks validated, objective biomarkers for diagnosis or tracking disease progression. Unlike cancer, where a biopsy can confirm pathology in a tumor, it is not feasible to biopsy the millions of diseased upper and lower motor neurons to assess ALS-related damage and progression. Unlike cancer, where CT or MRI scans can monitor tumor size, no standard imaging can directly measure shrinking motor neurons or reinnervating dendrites. Unlike cardiology, where an echocardiogram evaluates heart function, no radiological test assesses glial cell dysfunction in ALS. And unlike cancer, where lab work can detect specific cancer antigens, no validated labs are currently available to measure ALS progression. Thus, in ALS, it is much more difficult to accurately and reliably measure how trial participants "feel, function or survive."

First, survival data is almost non-existent in ALS trials. Because the median trach-free lifespan in ALS is 30 months, and because there are no disease-modifying treatments, few patients would agree to stay on placebo for that length of time to assess survival. And with ALS trials lasting just 24-48 weeks, drug sponsors can't collect enough longitudinal data to assess changes in survival. One reliable way to assess survival is with long-term OLEs or EAPs that can collect data on hundreds, or with Phase 4 post-marketing studies that can collect data on thousands.

Second, drug sponsors can't assess changes in how participants "feel" as there are no validated COAs measuring changes in symptoms that characterize ALS like fasciculations, spasticity, cramping or clonus. As such, in ALS, clinical trials endpoints are based on changes in function – most often as measured by the ALS Functional Rating Scale – Revised ("ALSFRS-R").

Changes in ALS function are assessed by a subjective COA that is a bounded scale called the ALSFRS-R,[53] which was designed by Yale neurologist, Jesse Cedarbaum. It is a 12-question, 48-point scale that assesses function across four domains: gross motor, fine motor, bulbar and respiratory function. Nearly all US trials currently use changes in the ALSFRS-R total score for trial endpoints. Given the heterogeneity of ALS and the fact that some drugs target specific function some trials use sub-domains as secondary endpoints. But if the trial doesn't meet its primary endpoint on the TOTAL ALSFRS-R score, then there is a statistical multiplicity penalty assessed on the secondary endpoints. For example, two S1R Agonists, Nuedexta and Prilenia's Pridopidine, didn't meet primary endpoints based on total ALSFRS-R score but they did show efficacy on bulbar and respiratory domains.

Graphic - ALSFRS-R scale



Bulbar

Speech
- 4 Normal
- 3 Detectable speech disturbance
- 2 Intelligible with repeating
- 1 Speech combined with nonvocal communication
- 0 Loss of useful speech

Salivation
- 4 Normal
- 3 Slight but definite excess of saliva in mouth; may have nighttime drooling
- 2 Moderately excessive saliva; may have minimal drooling
- 1 Marked excess of saliva with some drooling
- 0 Marked drooling; requires constant tissue or handkerchief

Swallowing
- 4 Normal
- 3 Early eating problems—occasional choking
- 2 Dietary consistency changes
- 1 Needs supplemental tube feeding
- 0 NPO (exclusively parenteral or enteral feeding)

Fine Motor

Handwriting
- 4 Normal
- 3 Slow or sloppy; all words are legible
- 2 Not all words are legible
- 1 Able to grip pen but unable to write
- 0 Unable to grip pen

Cutting Food*
- 4 Normal
- 3 Somewhat slow and clumsy, but no help needed
- 2 Can cut most foods, although clumsy and slow; some help needed
- 1 Food must be cut by someone, but can still feed slowly
- 0 Needs to be fed

Dressing and Hygiene
- 4 Normal
- 3 Independent and complete self-care with effort or decreased efficiency
- 2 Intermittent assistance or substitute methods
- 1 Needs attendant for self-care
- 0 Total dependence

*There are different assessments for cutting food with gastrostomy.

Gross Motor

Turning in Bed
- 4 Normal
- 3 Somewhat slow and clumsy, but no help needed
- 2 Can turn alone or adjust sheets, but with great difficulty
- 1 Can initiate, but not turn or adjust sheets alone
- 0 Helpless

Walking
- 4 Normal
- 3 Early ambulation difficulties
- 2 Walks with assistance
- 1 Non-ambulatory functional movement only
- 0 No purposeful leg movement

Climbing Stairs
- 4 Normal
- 3 Slow
- 2 Mild unsteadiness or fatigue
- 1 Needs assistance
- 0 Cannot do

Respiratory

Dyspnea
- 4 None
- 3 Occurs when walking
- 2 Occurs with one or more of the following: eating, bathing, dressing (ADL)
- 1 Occurs at rest, difficulty breathing when either sitting or lying
- 0 Significant difficulty, considering using mechanical respiratory support

Orthopnea
- 4 None
- 3 Some difficulty sleeping at night due to shortness of breath. Does not routinely use more than two pillows
- 2 Needs extra pillow in order to sleep (more than two)
- 1 Can only sleep sitting up
- 0 Unable to sleep

Respiratory Insufficiency
- 4 None
- 3 Intermittent use of BiPAP
- 2 Continuous use of BiPAP
- 1 Continuous use of BiPAP during the night and day
- 0 Invasive mechanical ventilation by intubation or tracheostomy

B. Limitations in the ALSFRS-R are Impacting Trial Endpoints and Drug Approvals

Unfortunately, the subjective ALSFRS-R scale has weaknesses – as do many bounded scales used in rare diseases. According to a 2022 article published in Neurology by Orla Hardiman, one of the top ALS researchers in the UK, these limitations can impact trial outcomes:

> *"The ALSFRS-r is the primary outcome measure utilised in clinical trials and research in ALS. This scale is limited by **floor and ceiling effects** within subscales, such that **clinically meaningful changes for subjects are often missed**, impacting upon the evaluation of new drugs and treatments."*

[53] Dr. Cedarbaum is a neurologist & clinical trial specialist with 30+ yrs of drug development experience in academia, biotech & pharma designing trials from pre-clinical stages to Phase 3 trials. He serves on the NINDS ALS Common Data Elements Project & fNIH Neuroscience Biomarkers Consortium Steering Committee. He also sits on the Scientific Advisory Board of the Michael J. Fox Foundation-sponsored PPMI Biomarker Initiative.

This study was published a year before the NurOwn AdComm. Indeed, since the NurOwn Phase 3 trial began in 2017, many peer-reviewed studies have discussed how those weaknesses in the ALSFRS-R impact trial endpoints. The author of many of those papers is Dr. Cedarbaum himself.

Below are some of the common critiques of the ALSFRS-R, many of which are discussed in the webinar titled *"Measuring ALS"* by Jeremy Shefner of Barrow Neurological.

- Total ALSFRS-R score is invalid at ordinal level (this is the level used for trial primary endpoints), whereas sub-scale domains are valid at the interval level.
- One point loss is not equal in different domains nor at the top and bottom of the same question in one domain.
- Issues with the ALSFRS-R -- including floor & effects, and multi-dimensionality -- could challenge its continued utility as a primary outcome measure in ALS clinical trials.
- Scale doesn't accurately measure respiratory decline; it declines more slowly than other domains
- Ignoring the multidimensional structure of the ALSFRS-R total score could have "negative consequences" for ALS clinical trials.

(See Exhibits for a list of those papers). One review characterized the ALSFRS-R as *"old friend who has overstayed their welcome."* That review expressed concerns that:

> *"The ALSFRS-R total score may be insensitive to detecting treatment benefit when a treatment affects only some of its subscales, or benefits subscales in varying degrees, resulting in potentially higher false negative rates and an increased risk of missing important treatment clues."*

At the recent 4th Annual ALS Drug Development Summit on May 12 – 14 the theme was: *"Rethink Transformative ALS Targets, Seek Translational Biomarkers & Propel More Clinical Approvals."* With that focus in mind, one of the NurOwn PIs from the Healey Center at MassGen, Dr. James Berry, presented on *'Improving Disease Scoring Systems in ALS: Addressing Heterogeneity & Decline Rates to More Accurately Interrogate Drug Efficacy in Patient Subgroups.'* In it, he discussed:

- Overviewing current ALS-FRS scoring systems & their limitations in both clinical trials & routine care, and why current scores may not adequately reflect all patients' experience
- Understanding ALS heterogeneity to explore the key factors contributing to ALS diverse progression rates and how heterogeneity can be accounted for in clinical scoring systems
- Innovative approaches to scoring ALS progression (improving scoring and patient stratification)
- Utilizing biomarkers to enhance scoring systems
- Utilizing the power of AI and machine learning to identify patterns of progression that are missed by traditional scores
- Exploring implications of improved scoring on ALS trial design (adjusting for disease onset and progression speed), regulatory acceptance and approval processes

Similarly, Michael Robinson is a physician living with ALS and a former executive at AbbVie. He pointed out some of those flaws in a review that concluded: *"several items of the ALSFRS-R were considered to inaccurately reflect the abilities of patients with ALS."* In his Public Comment at the NurOwn AdComm, he reiterated his concerns about the scale:

> *"There are several issues that pose challenging to the interpretation of the data from this phase 3 trial. Namely, the floor effect of the ALSFRS-R…. The scale has also been criticized for important psychometric limitations such as multi-dimensionality, non-linearity, poor construct validity, and potential floor and ceiling effects.*
>
> *The floor effect occurs when the scale of measurement is not able to capture progression at the bottom of the scale. The floor effects are of particular interest when interpreting the data from the MSC-NTF trial. Patients with more advanced disease are more likely to have at least one ALSFRS-R item scoring a zero and creating floor effects that are not able to adequately detect progression…. In summary, there were real floor effects encountered, particularly in the more advanced patients that scored less than or equal to 25 at baseline.*
>
> *This makes it much more difficult to detect treatment differences as there is no further worsening possible on items that score a zero at baseline. If you remove the patients with at least one item scoring zero – and hence eliminate potential floor effect impact – the primary outcome most likely becomes positive."*

Additionally, the FDA has tacitly acknowledged that the ALSFRS-R is an issue because it created a public-private partnership with the Critical Path Institute ("CPI") to study the issues with Clinical Outcome Assessments in ALS. At the Initial Public Discussion, Collin Hovinga, the VP of CPI's Rare & Orphan Disease programs admitted: *"We really need new clinical outcome assessments."*

Graphic - C-Path's Discussion regarding Clinical Outcome Assessments in ALS

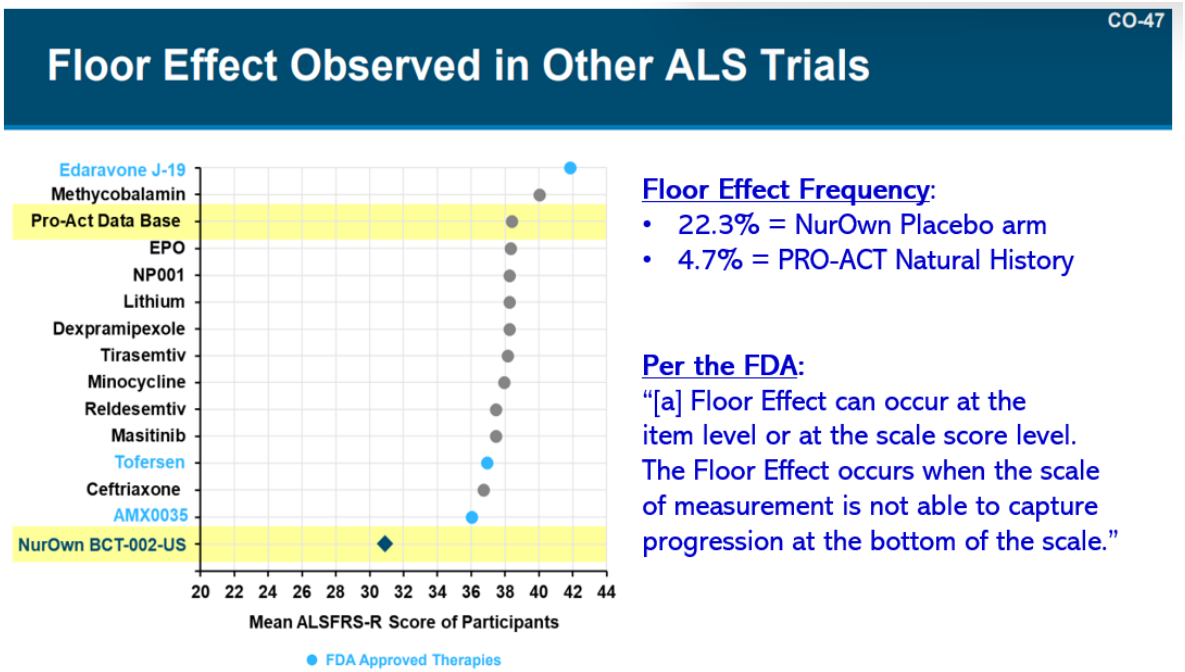
1. **<u>Floor Effect is the Scale's Inability to Measure Changes once an ALSFRS-R Sub-domain Score is Zero, Making it Falsely Appear as if People are Stabilizing.</u>**

Dr. Ardalan Minokadeh is the younger brother of Petitioner Dr. Shahriar Minokadeh. In Dr. Minokadeh's Public Comment, he illustrated the real life impact of the floor effect:

> *"An example of the Floor Effect can be found in the three Fine Motor Skill questions that relate to: (1) handwriting; (2) ability to groom oneself and take care of daily hygiene; and (3) ability to cut food and feed oneself with utensils. If you are unable to do these three tasks, you get 0/12 possible points. However, as I can attest from my brother's own ALS, there are still many things you can do with your hands and upper limbs. You can type, text, operate a mouse, gaming device, remote control, hold a urinal bottle, push a call button for a caregiver and most importantly, operate a wheelchair joystick. You can still hold a child in your arms. All of these are very clinically meaningful. But once you have a "0" in the above three questions, the ALSFRS doesn't measure when you continue to decline and can no longer do these clinically meaningful tasks."*

The lower the total ALSFRS-R score, the more likely people are to have zeroes in some of those sub-domains; and thus, the lower a participant's total score, the more likely a trial's endpoints will be affected by the Floor Effect. In the NurOwn trial, the baseline ALSFRS-R score was much lower than other ALS trials and 25% of people had advanced ALS.

<u>Graphic</u> - Baseline Scores and Floor Effect in Other ALS Trials



2. Non-Dominant Hand Onset Creates a Ceiling Effect that Can "Mislead" Clinicians about Progression in the Fine Motor Skills Domain.

Measurement of upper limb function is critical for tracking clinical severity in ALS. In approximately two-thirds of people with ALS, symptom onset starts in the limbs.[54] When someone has onset in the non-dominant hand, it can impact trial outcomes.

In the earlier referenced study[55] by Leonard van den Berg, he reported that arm onset appeared much more likely to be associated with LMN involvement and that onset was distributed nearly equally (16%) in the right and left arm.

Graphic - Limb Onset by UMN and LMN Subtypes

Site of onset	N	Bulbar	%	R Arm	%	L Arm	%	R Leg	%	L Leg	%	Trunk	%	Focal onset (%)
ALS	254	55	21.7%	41	16.1%	39	15.4%	38	15.0%	40	15.7%	3	1.2%	~85%
LMN phenotype	100	0	0.0%	21	21.0%	14	14.0%	11	11.0%	18	18.0%	6	6.0%	~70%
UMN phenotype	116	16	13.8%	3	2.6%	2	1.7%	20	17.2%	40	34.5%	0	0.0%	~70%

In the arms, ALS often manifests as weakness and loss of hand dexterity making it difficult to clip nails, snap fingers, pick up tools or open a beer can. In athletes like Kade Simons, his first symptom was a slowing in his bat speed; in Justin Rogers, it impacted his ability to make a shot on goal; both Eric Stevens and Josh Smith started dropping tools at work.

If someone has non-dominant hand onset, following is how it affects the ALSFRS-R scores on the 3 questions in the fine motor skills domain when someone is early in progression:

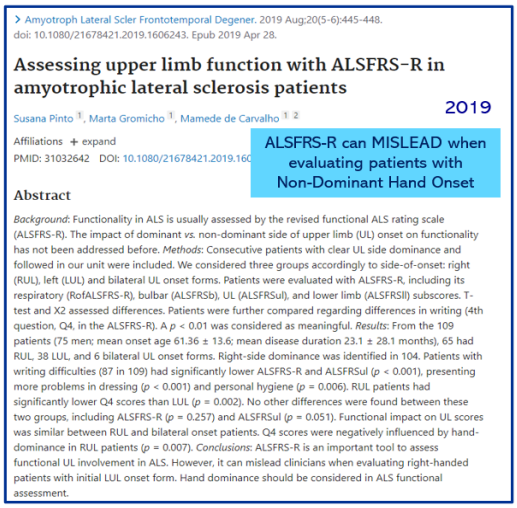
- **Handwriting:** not affected until loss of function moves to dominant hand
- **Cutting food and using utensils:** minimally affected as most tasks = dominant hand
- **Hygiene/Dressing:** dressing is somewhat impacted as things like tying shoes, pulling up pants, and fastening buttons, belts and bras do require the use of both hands. Hygiene minimally affected as most hygiene= dominant hand

In essence, in the people who have non-dominant hand onset, the ALSFRS-R fine motor skills domain doesn't accurately reflect progression – capturing neither changes in the speed of decline nor possible improvement in the non-dominant hand. As such, most changes aren't captured until the ALS spreads to the dominant hand. Indeed, in a survey, people in the ALS community expressed concern that if their dominant hand was unaffected, but the non-dominant hand was affected, the scale would fail to

[54] Wijesekera LC, Leigh PN. Amyotrophic lateral sclerosis. Orphanet J Rare Dis. 2009;4:3. doi: 10.1186/1750-1172-4-3
[55] Walhout, R., Verstraete, E., van den Heuvel, M. P., Veldink, J. H., & van den Berg, L. H. (2018). Patterns of symptom development in patients with motor neuron disease. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 19(1-2), 21–28.

capture progression.[56] Only two studies discuss this impact of non-dominant hand onset; one from China in 2017 and one from Portugal in 2019.

Graphic - Studies re Non-Dominant Hand Onset Misleading Clinicians



> Amyotroph Lateral Scler Frontotemporal Degener. 2019 Aug;20(5-6):445-448.
doi: 10.1080/21678421.2019.1606243. Epub 2019 Apr 28.

Assessing upper limb function with ALSFRS-R in amyotrophic lateral sclerosis patients

2019

Susana Pinto [1], Marta Gromicho [1], Mamede de Carvalho [1 2]

Affiliations + expand

PMID: 31032642 DOI: 10.1080/21678421.2019.160

ALSFRS-R can MISLEAD when evaluating patients with Non-Dominant Hand Onset

Abstract

Background: Functionality in ALS is usually assessed by the revised functional ALS rating scale (ALSFRS-R). The impact of dominant *vs.* non-dominant side of upper limb (UL) onset on functionality has not been addressed before. *Methods*: Consecutive patients with clear UL side dominance and followed in our unit were included. We considered three groups accordingly to side-of-onset: right (RUL), left (LUL) and bilateral UL onset forms. Patients were evaluated with ALSFRS-R, including its respiratory (RofALSFRS-R), bulbar (ALSFRSb), UL (ALSFRSul), and lower limb (ALSFRSll) subscores. T-test and X2 assessed differences. Patients were further compared regarding differences in writing (4th question, Q4, in the ALSFRS-R). A $p < 0.01$ was considered as meaningful. *Results*: From the 109 patients (75 men; mean onset age 61.36 ± 13.6; mean disease duration 23.1 ± 28.1 months), 65 had RUL, 38 LUL, and 6 bilateral UL onset forms. Right-side dominance was identified in 104. Patients with writing difficulties (87 in 109) had significantly lower ALSFRS-R and ALSFRSul ($p < 0.001$), presenting more problems in dressing ($p < 0.001$) and personal hygiene ($p = 0.006$). RUL patients had significantly lower Q4 scores than LUL ($p = 0.002$). No other differences were found between these two groups, including ALSFRS-R ($p = 0.257$) and ALSFRSul ($p = 0.051$). Functional impact on UL scores was similar between RUL and bilateral onset patients. Q4 scores were negatively influenced by hand-dominance in RUL patients ($p = 0.007$). *Conclusions*: ALSFRS-R is an important tool to assess functional UL involvement in ALS. However, it can mislead clinicians when evaluating right-handed patients with initial LUL onset form. Hand dominance should be considered in ALS functional assessment.

Review > J Clin Neurosci. 2017 Dec;46:17-20. doi: 10.1016/j.jocn.2017.08.036. Epub 2017 Sep 5.

Measuring the validation of assessing the non-dominant-hand function by ALSFRS-r in Chinese ALS patients

2017

Fangfang Hu [1], Jiaoting Jin [1], Rui Jia [1], Li Xiang [2], Huaguang Qi [3], Xing Zhao [1], Jingxia Dang [4]

Affiliations + expand

PMID: 28887079 DOI: 1

ALSFRS-R limited in assessing function in Non-Dominant Hand. Score higher in non-dominant hand patients, especially in handwriting, cutting food & handling utensils

Abstract

ALSFRS-r is a widely accepted rating scale for measuring the global function of Amyotrophic Lateral Sclerosis (ALS) patients, but we found some limitations of ALSFRS-r in assessing the function of non-dominant hand in Chinese ALS patients. We reviewed 95 ALS patients who expressed upper-limb symptoms at first visit and analyzed the ALSFRS-r score and subscale. In both upper limb involved patients, the ALSFRS-r had no difference between dominant-hand and non-dominant-hand onset groups (39.15±5.55 vs 38.0±5.91, p=0.477). But in only one upper limb involved patients, the ALSFRS-r score in non-dominant-hand onset patients was higher than dominant-hand onset patients (43.94±3.44 vs 40.87±4.42, p<0.05), especially in item of handwriting, cutting food and handing utensils (3.56±0.89 vs 2.2±1.27 p=0.001, 3.44±1.03 vs 1.8±1.21 p=0.000). When the item of cutting food and handing utensils was replaced by using food bowl and chopsticks to assess the function of non-dominant-hand, the modified ALSFRS-r score was significantly lower than original ALSFRS-r (43.94±3.44 vs 42.88±3.07 p=0.001), the progression rate was slower (0.81±0.63 vs 0.64±0.63, p=0.001). So, for Chinese ALS patients, using food bowl and chopsticks should replace the item of cutting food and handling utensils to assess the non-dominant-hand function, especially in non-dominant-hand onset patients.

The 2019 study titled *"Assessing upper limb function with ALSFRS-R in amyotrophic lateral sclerosis patients,"* evaluated upper limb function in 140 ALS patients. The study analyzed the ALSFRS-R sub-scores for handwriting, cutting food, and dressing/hygiene to assess upper limb impairment. Results showed that upper limb function declines significantly over time, and that upper limb sub-scores correlated strongly with overall disease progression, making the scale valuable for monitoring ALS trajectory. However, the authors note limitations, including the scale's reliance on patient-reported data and potential ceiling effects in early ALS. Carvalho concluded:

> *"ALSFRS-R is an important tool to assess functional UL involvement in ALS. However, **it can mislead clinicians** when evaluating right-handed patients with initial LUL onset form. **Hand dominance should be considered in ALS functional assessment**."*

Recognizing the limitations in the ALSFRS-R scoring system, Chinese researchers found that the ALSFRS-r score in non-dominant-hand onset patients was 3.07 points higher than dominant-hand onset patients (43.94 vs 40.87) ($p<0.05$).[57]

- Handwriting = 1.36 point difference (3.56 vs 2.2)
- Cutting food and handling utensils = 1.64 point difference (3.44 vs 1.8)

A three-point delta is massive in ALS when a one-point loss of function is clinically meaningful.

[56] Boyce, D., Robinson, M., Cedarbaum, J. M., Shank, L. M., McDermott, C. J., & van Eijk, R. P. A. (2023). A qualitative evaluation of the revised amyotrophic lateral sclerosis functional rating scale (ALSFRS-R) by the patient community: A web-based cross-sectional survey. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 24(3-4), 272–280.

[57] Wang, Y.-C., Bohannon, R. W., Kapellusch, J., & Garg, A. (2017). Validation of the non-dominant hand as a measure of functional reserve in healthy adults. Journal of Clinical Neuroscience, 46, 17–20.

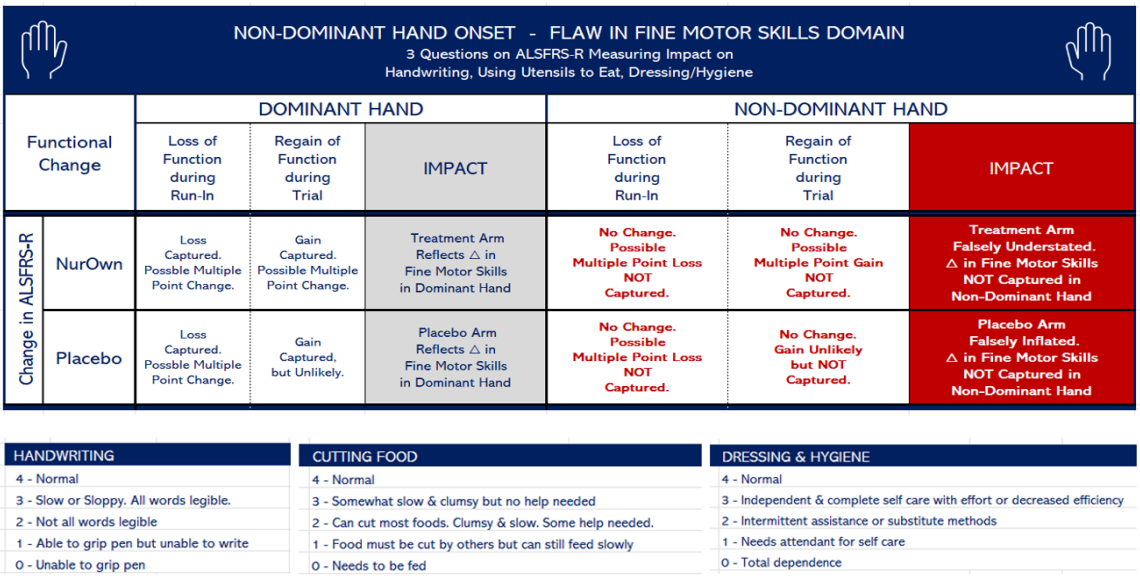
Yet as best as Petitioners can ascertain, the non-dominant hand ceiling impact on trial outcomes has never been reported in any investigational trial; and at least in the US, it appears no investigational trial designs or natural history studies have contemplated measuring the impact of non-dominant hand onset.

To adequately assess the impact of non-dominant hand onset, the clinical trial notes must first document which hand is the non-dominant hand and in Petitioners' collective experience, not all ALS clinics or clinical trials collect this information. Further, the clinical notes must reflect the scores in each domain and not just an overall score. Thankfully trial participants who concurrently participate in the ALS-TDI Precision Medicine program are able to access a *"personalized portal where you can view your own data and monitor changes in your symptoms."* [58] Many people in the NurOwn trial tracked their ALSFRS-R score on the ALS-TDI app.

3. Ceiling Effect in Participants with Non-dominant Hand Onset Likely Impacted the NurOwn Trial Outcome – especially in the Pre-specified Subgroups of ALSFRS-R ≥35.

The NDH Ceiling Effect has the largest impact on the scores on people and therapies with the most profound changes – like NurOwn and Tofersen.[59] The NDH ceiling effect cannot be fixed by randomization. And tragically it has a two-fold impact on trial results: a treatment's effect is falsely understated and the placebo arm is falsely inflated when people are early in ALS progression.

Graphic - Impact of Non-Dominant Hand Onset on Clinical Trial Outcomes



[58] The ALS Research Collaborative (ARC) is an evolution of ALS-TDI's Precision Medicine Program (PMP) – the longest-running natural history study in ALS.

[59] Petitioners suspect this ceiling effect may have impacted the ALSFRS-R score of the fast-progressing A5V-SOD1 population in the Tofersen VALOR trial, which also didn't meet its endpoints in the 28-week timeframe.

In the NurOwn trial, multiple Petitioners had non-dominant hand onset and baseline scores of 35 or above. This is the perfect storm for the ceiling effect. The magnitude of many of their profound changes likely were not captured during the 28-week NurOwn trial. Thus, it logically follows that their ALSFRS-R scores likely contributed to the pre-specified sub-group ≥35 ALSFRS-R underperforming in NurOwn arm in comparison to the changes they experienced in ADLs in the real world. But this impact is primarily seen for those earlier in ALS progression as once ALS symptoms spread to the dominant hand, the ALSFRS-R accurately picks up those changes.

As an example, Nicole Cimbura's husband Mike received NurOwn in 2015, and his story is featured in the documentary, "*For Love and Life: No Ordinary Campaign.*" In one of her Public Comments, Nicole shared:

> *"My husband Mike was in the treatment group and a responder; not only did NurOwn halt Mike's progression for a time, but he regained function. He could wash his hair and face once again, write with his dominant hand…."*

Attached to that Public Comment is the transcript of her testimony at the PFDD meeting in 2021:

> *"He was a participant in the NurOwn Phase 2 Trial at MAYO Clinic. When the trial was unblinded, it confirmed what we had suspected all along -- that he was 1 of 36 people in the treatment arm who received NurOwn. Sadly, the phase 2 trial was only one dose. But that one dose had a profound impact on Mike. When he awoke the next morning after his intrathecal treatment, Mike felt movement in his hand.*
>
> *I was surprised when he asked for a pen and a piece of paper to try and jot down a note. For over a month, Mike hadn't been able to grasp anything with his left hand that wasn't rather large. But he wanted to try. In a tearful moment of awe, we watched as he was able to write a simple note to our three kids: "Love Dad." The handwriting was shaky, but we were forever grateful for this improvement in his hand. This note was such a treasure to our family that each of my kids have etched it permanently onto their bodies."*

During Congressional calls, Nicole holds up the paper showing Mike's message to their kids. NurOwn restored his ability to write a few sloppily scribbled, but legible words. Thus, his Handwriting score increased from 0 to 3. Because this improvement was in Mike's dominant hand, the ALSFRS-R scale picked up the change. If it had been in his non-dominant hand, that 3-point delta on one single question would have been missed.

The Petitioners are aware of several people in the Phase 3 trial who confirmed they were in the NurOwn arm, reported stabilization or improvement in function, and also had non-dominant hand onset.[60] However, many people did not keep track of their ALSFRS-R scores outside the trial and even among those who did, they often only have the total score and not the domain scores.

[60] They have publicly disclosed this information; and/or they or their family members provided authorization to disclose their unblinding status.

Thus, unless Brainstorm allows the trial sites to release participants' ALSFRS-R scores, we have no way to determine how much the NDH onset may have impacted each individual's score. But we do know that Petitioners Matt Klingenberg, Eric Stevens, Josh Simth and Justin Rogers all had NDH onset as did 4 others in the NurOwn treatment arm who had NDH onset and baseline scores ≥35. For all 9 people, their loss of NDH function in the run-in period was not captured and then when they regained function that was not captured either. This would impact both the primary endpoint of change in slope and secondary endpoints of 100% improvement and change from baseline.

Similarly, Petitioners are aware of 5 people in the placebo arm who had NDH onset and all had baseline scores above 35. Those people likely appeared as if they stabilized when in fact, the ALSFRS-R just wasn't capturing the loss of function in their non-dominant hand. And Petitioners are also aware of others with NDH onset but their unblinding status is not yet known.

C. Understanding Trial Endpoints: What Constitutes a "Clinically Meaningful" Change in ALS Decline?

When asked what kind of improvement constitutes a "clinically meaningful" change to someone with ALS, Dr. Merit Cudkowicz stated:[61]

> *"**Any period of improvement** for the patient **is meaningful** because progression can often be rapid and fatal. So, the **longer we can keep a patient from deteriorating, the better chance we have to increase life expectancy**. The goal is to keep the patient ambulatory and **off a respirator**, so if we can delay this, it is surely meaningful to the patient."*

The minimal clinically important difference (MCID) refers to the smallest change in a clinical outcome measure that is considered meaningful to patients, clinicians, or researchers – indicating a significant improvement or deterioration in a patient's condition. The MCID is often used to interpret the clinical significance of results, beyond just statistical significance, to ensure that changes are relevant in real-world practice.

Determining MCID can be difficult, particularly in rare diseases in which effect sizes may not be precise because of small samples and further complicated by disease heterogeneity. [62] MCID can help interpret the clinical significance of Patient Reported Outcome measures when traditional endpoints are challenging to measure. In this review,[63] the authors focus on MCID in spinal cord injury studies,

[61] BioNap. (2016, November 28). Interview with neurologist and ALS KOL sheds light on Brainstorm's potential with NurOwn. Yahoo Finance.
[62] Berger, M. L., Dreyer, N., Anderson, F., Towse, A., Sedrakyan, A., & Normand, S. L. (2012). Prospective observational studies to assess comparative effectiveness: The ISPOR good research practices task force report. Value in Health, 15(2), 217–230.
[63] Faber, K. J., & Beaton, D. (2014). Challenges for defining minimal clinically important difference (MCID) after spinal cord injury. Spinal Cord, 53(2), 84–91.

highlighting limitations such as heterogeneity in patient cohorts, confounding variables (e.g., comorbidities), and the distinction between MCID and minimal detectable difference (MDD). It notes that MCID must exceed MDD to be valid but they acknowledge that it is challenging to define in SCI due to diverse functional outcomes.

These issues are analogous to rare disease research – as in ALS – where small, heterogeneous populations complicate MCID application. Another review warns of the risk of misclassifying patients as "non-responders" if MCID thresholds are not context-specific.[64] Notably, expert opinions often complement the determination of what is an (MCID) by providing context for interpreting limited data.[65]

1. People with ALS on What is Clinically Meaningful

What constitutes a "clinically meaningful" change? To people battling ALS, every point matters. One point matters. Every lost function was clinically meaningful. Every preserved function is clinically meaningful. And the further you are in progression, the more meaningful those remaining points of function become as they reflect the ability to remain independent.

The 2019 ALS Guidance Document states that effectiveness should be established by the *"demonstration of a treatment effect (e.g., less decline, stabilization, improvement) on function in daily activities."* But the ALSFRS-R doesn't assess impact on all ADLs. At the 2021 hearing before the Energy & Commerce Health subcommittee, Chair Anna Eshoo asked how the FDA defines a "clinically meaningful incremental benefit?" CDER Director Patrizia Cavazzoni said they defer to patients:

> **"***The perspective of the patient is very important to us because what we hear from the patients really guides us as to what they view as a meaningful incremental gains and what we have heard from people suffering from ALS, for instance, is that improvement in symptoms and improvement in quality of life is very important…. Their experiences, perspectives and priorities are a critical aspect of drug development. PFDD enables delivery of therapeutics that have a meaningful impact on people's QOL and targets what they consider the most important aspect of their diseases."*

Tweets from petitioner Jamie Rose Berry explain what one point means on the ALS scale:

> *"When your life expectancy is measured in months weeks or even days, every point matters. One point means I can write notes on my daughter's lunch napkin. One point means I can enjoy taco night with my family. One point is the difference between having a hard time breathing and not being able to breathe, at all.*

[64] Bloom, D. A., Kaplan, D. J., Mojica, E., Strauss, E. J., & Gonzalez-Lomas, G. (2021). The minimal clinically important difference: A review of clinical significance. The American Journal of Sports Medicine, 50(14), 4004–4014.
[65] Schulz, A., Ajayi, T., Specchio, N., de Los Reyes, E., Gissen, P., Ballon, D., … Kohlschütter, A. (2018). Study of intraventricular cerliponase alfa for CLN2 disease. New England Journal of Medicine, 378(20), 1898–1907.

"Explaining why #everypointmatters is difficult for me to do. I can't grasp having to justify the value of 1pt. Our lives are greater than 48pts. We're real people & we're suffering. The value of 1pt is immeasurable w/ a disease of this caliber. Video

Patty Manhardt described what one point would mean to her:

"If I can gain one point back in my ALSFRS score, I might actually be able to hold my new grandson. If I had one point back on my ALSFRS score, I might be able to brace to transfer myself and my daughter and son would not have to pick me up. If I had one more point in my ALSFRS score, I could use the bathroom on my own. I could go on and on with examples…. I would be so happy with one more point."

Dr. Ajay Sampat a neurologist and faculty member at UC Davis, shared what 1 point means:

"The ALSFRS-R scoring scale, which was used to assess the primary and secondary endpoints in the phase 3 trial, is a subjective and imperfect one, flawed by elements such as the ceiling and floor effect. Despite this, many individuals in the trials have experienced increases on this scale in the presence of debamestrocel. This is unheard of in the ALS world. A single point increase on this scale could make the difference between holding my son and not, independently turning in bed or struggling all night, going to the restroom unassisted or requiring a caregiver, and breathing independently or with the assistance of a device. A single point change on the ALSFRS-score is clinically meaningful, and any small gain of function, or a small loss of function is critically important to someone who is living with ALS.

So, when I, as a patient and as a neurologist, hear about increases in the ALSFRS-R score, it is not something to take lightly. There are no therapies that halt or reverse symptom progression, so a potential reversal of symptoms, even in a few people living with ALS, even if minor, is a huge achievement that should not be overlooked.

Attorney Mike Harrington commented on X:

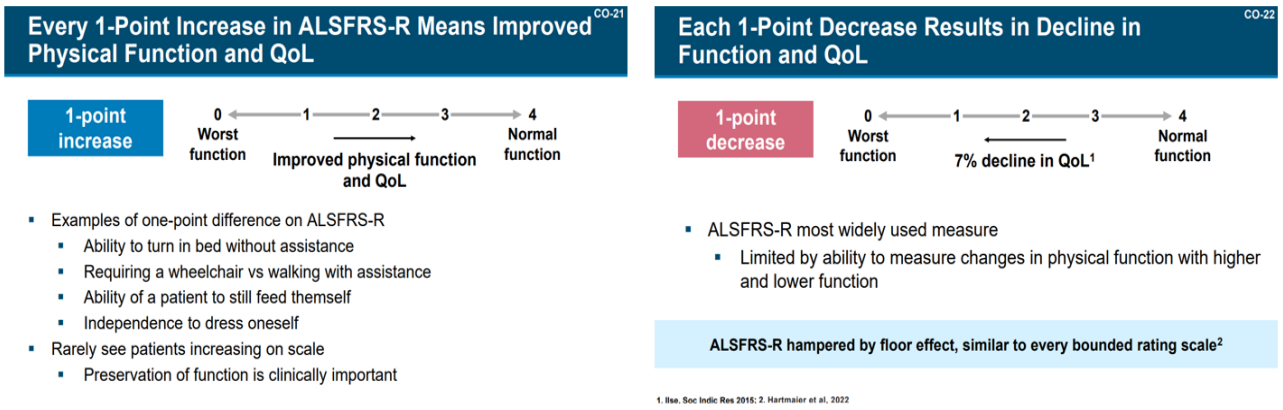
"One finger. For years I've relied on my right index finger for typing, reaching, grabbing... the last one with any real function. Now I can feel it fading as well. ALS is relentless…. the only finger ALS deserves is another one I can't use."

The loss of use of function of one last finger is zero points on the ALSFRS-R. But because it's a person's last remnant of hand function, the loss of this is more clinically meaningful because it's the last thread of one's independence.

2. Clinicians on What is Clinically Meaningful

As the FDA has acknowledged, what is clinically meaningful to a person with ALS and what is clinically meaningful to a neurologist or regulator can be quite different. At the AdComm, Dr. Windebank addressed what constitutes a clinically meaningful change in his patients and emphasized that even a single 1-point change could have profound impact on one's quality of life. (Sponsor's Presentation CO-21, 22). Quantifying this, every 1-point loss of function equates to a 7% decline in the Quality of Life. This MCID addresses the changes on NurOwn's secondary endpoint.

Graphic - Clinical Meaningfulness of One Point Change on ALSFRS-R



ALS specialists were surveyed and asked what change in the ALSFRS-R slope is "clinically meaningful?" In 2010, Dr. Merit Cudkowicz of MassGen and Jeremy Shefner of Barrow Neurological Institute published the results of this survey given to 65 NEALS clinicians and researchers. Using a seven-point scale, where 1='not at all clinically meaningful', 4='somewhat clinically meaningful', and 7='very clinically meaningful,' they were asked to rate the clinical relevance of changes in decline on the ALSFRS-R slope. This addresses the changes on NurOwn's primary endpoint.

Over 90% of those ALS specialists agreed that:[66]

- 20% change in slope = "somewhat clinically meaningful" (score of 4 or higher).
- 50% change in decline = "very clinically meaningful" (score of 7).

According to the PRO-ACT database of people in placebo arms of ALS trials, the average slope of decline is 1.02 points per month.[67] For simplicity of this example, assume the average slope of decline is 1 point per month. A "very clinically meaningful" change means progression would slow to half a point per month. Not regaining function. Not halting lethal progression. Simply slowing loss of function would be "very clinically meaningful" based on the NEALS survey.

[66] Castrillo-Viguera, C., Grasso, D. L., Simpson, E., Shefner, J., & Cudkowicz, M. E. (2010). Clinical significance in the change of decline in ALSFRS-R. Amyotrophic Lateral Sclerosis, 11(1-2), 178–180.
[67] Gomeni, R., & Fava, M. (2014). Amyotrophic lateral sclerosis disease progression model. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 15(Suppl 1), 119–120.

An associate neurologist at Temple University, Christina Martin Schaff, MD, submitted a Public Comment that gives real-life context on what is "clinically meaningful" to her patients:

> *"The regulatory standard for approval is whether or not there is substantial evidence that there is an intending "clinically meaningful" effect.* ***In a population where you have been given a diagnosis of an inevitably fatal disease, doesn't the slowed progression of disease meet that criteria? If someone can feed themselves for even months longer, isn't that meaningful? If someone can remain ventilator-free for a few months longer than without the medication, isn't that meaningful?***

3. Understanding NurOwn's Primary Endpoint of -1.25 point Change in Slope

Assume again the average slope of decline is 1 point per month. The primary endpoint in the NurOwn trial was a high target of -1.25 points per month. That equates to a **125% change** in slope for the average progressor. The average progressor had to REGAIN function to be characterized as a "responder."

To illustrate the high threshold of this endpoint, consider this simple analogy. Assume one of the new GLP-1 drugs had a trial endpoint that participants would average 125 lbs lost annually (regardless of the baseline characteristics and BMI). At the end of the year, the mean weight loss was 85 pounds. The trial would have failed to meet its hypothesized responder endpoint, but the people who lost 85 pounds would be ecstatic "non-responders."

Apparently there was some discussion between Brainstorm and the FDA about the use of the "Change in Slope" as the Primary Endpoint. At page 16, the FDA's Briefing Document says:

> *"Change in "slope" of ALSFRS-R is of unclear clinical significance and therefore would not be suitable as the primary efficacy endpoint in a study intended to provide primary evidence of effectiveness in support of a marketing application. As discussed earlier, modeling ALS progression as a linear function based on change in ALSFRS-R over time is inaccurate, because short intervals of plateau or even improvement are not uncommon. Moreover, an acceptable clinical outcome measure should reflect whether a patient feels or functions better or survives longer."*

Although Petitioners disagree with this assertion, given the FDA's position, it's then logically incongruent to take a multiplicity penalty on the trial's secondary endpoints. And this is all the more reason to utilize Dr. Lee-Jen Wei's "Totality of the Evidence" methodology, which is much more appropriate for capturing clinically meaningful and statistically significant changes across multiple endpoints and multiple bounded scale domains at multiple points in time in rare diseases like cancer and ALS.

Additionally, the statement about linearity is not accurate. First the FDA relied on data from n = 30 Belgium study[68] and ignored Answer ALS natural history study with n=861 which shows that progression is relatively linear.[69]

Top ALS neurologists from the UK, Australia and US, including Catherine Lomen-Hurst from UCSF and Jeremy Shefner from Barrow also said "in an individual with ALS, the disease advances at a relatively constant rate." [70] Indeed, Jeremy Shefner is one of the country's top neurologists and a specialist in ALS clinical trial design. In a webinar for Everything ALS two months before the NurOwn AdComm, Dr. Shefner said:

> *"One other criticism that people have sort of raised about the ALSFRS is that it may not be linear, meaning that the drop over time may not be a straight line. Certainly that is true early in the disease and probably later in the disease, but during the period of time that most people are in clinical trials, it's very linear. So I grabbed three studies just to show you that the decline in both the placebo group and the treated group almost exactly fall on a straight line. So from the point of view of statistical analysis, it's important if something drops in a linear fashion or not, and the ALSFRS-R is pretty linear."*

Graphic - Dr. Jeremy Shefner Explaining that ALSFRS-R Slope is Linear

[68] Swinnen, B., & Robberecht, W. (2014). The phenotypic variability of amyotrophic lateral sclerosis. Nature Reviews Neurology, 10(11), 661–670.
[69] The Answer ALS Research Collaborative. (2022). Answer ALS, a large-scale resource for sporadic and familial ALS combining clinical and multi-omics data from iPSC lines. Nature Neuroscience, 25(2), 226–237.
[70] Simon, N. G., Turner, M. R., Vucic, S., Al-Chalabi, A., Shefner, J., Lomen-Hoerth, C., & Kiernan, M. C. (2014). Quantifying disease progression in amyotrophic lateral sclerosis. Annals of Neurology, 76(5), 643–657.

D. NurOwn's Phase 3A Trial Design – in the US

From 2017 to 2020, Brainstorm completed its 28-week Phase 3a trial. There were 189 trial participants; 95 received 3 doses of NurOwn and 94 were on placebo. The Phase 3 data, supplement and erratum were published in Muscle & Nerve. We incorporate by reference all of Brainstorm's filings, including Briefing documents, the presentation and testimony – including all private communications and meetings.

1. NurOwn Trial - Genetics

Of the 189 trial participants, 124 agreed to undergo genetic testing for 31 pre-specified ALS-related genes and 4 SNPs. Following are the results presented by Dr. Merit Cudkowicz at the 2022 MDA Clinical & Scientific Conference.[71]

Anecdotally, Petitioners are aware of people with the C9 mutation who were in the NurOwn arm and believe they were "responders." Because of the extremely small sample size, no conclusions can be drawn about whether particular phenotypes will respond to NurOwn. However, Petitioners hope those C9 carriers will share their patient experiences and real-world data in support of this Petition.

Petitioners are also aware of several people in the trial who had Variants of Uncertain Significance (VUS) of genes such as MAPT, PSEN1, SETX and TARDBP. The prevalence of those with VUS are not reflected in the yellow highlights below.

Graphic - Genes & SNPs Tested in NurOwn Trial

Gene/SNP (#, % with positive risk allele)				
ANG	CX3CR1	MAPT	SOD1 (1, 0.8%)	UNC13A gene
ANXA11	FUS (1, 0.8%)	OPTN (1, 0.8%)	SQSTM1	VAPB
ARHGEF28	GRN	PFN1	TARDBP (1, 0.8%)	VCP
C9orf72 (3, 2.4%)	HNRNPA1	PSEN1	TBK1 (1, 0.8%)	UNC13A (77, 62%)
CDH13	HNRNPA2B1	PSEN2 (1, 0.8%)	TMEM106B	CAMTA1 (59, 48%)
CHGB	KIF5A	SETX	TREM2	MOBP (112, 90%)
CHMP2B	KIFAP3	SLC11A2	UBQLN2	ZNF12B (53, 43%)

In addition to collecting genetic biomarker data, the Phase 3 trial also collected CSF biomarker data on all trial participants at 7 times throughout the trial, measuring changes in dozens of biomarkers. To the best of our knowledge, this is the first ALS therapy in history that has collected CSF biomarker data at

[71] Cudkowicz, M. (2022, March 16). Relationship UNC13A single-nucleotide polymorphisms to clinical outcomes in NurOwn Phase 3 ALS clinical trial [Conference presentation]. 2022 MDA Clinical & Scientific Conference, Nashville, TN, United States.

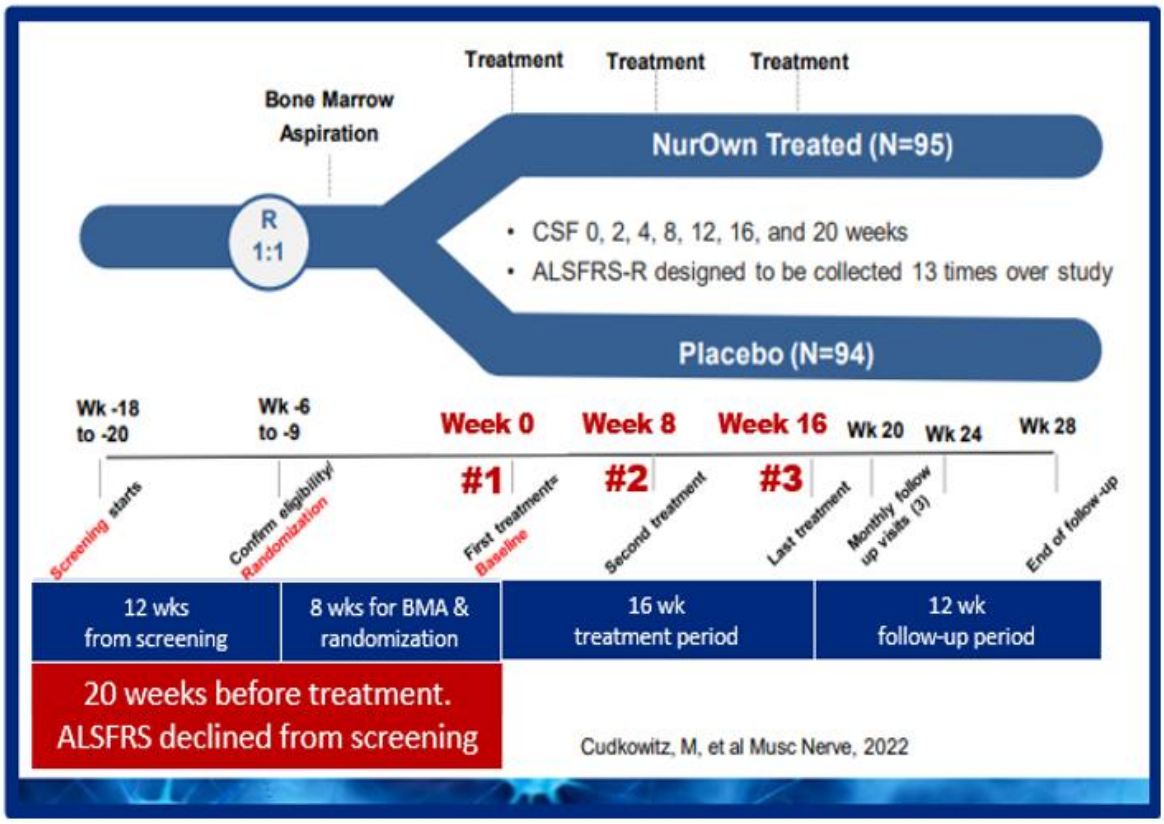
multiple points in time throughout the trial. The biomarker data and supplement were published in Muscle & Nerve in April 2024 -- after the NurOwn AdComm.

2. NurOwn Trial Design and Qualifications

Some of the relevant trial qualifications at screening were as follows:

- 24 months from symptom onset
- ALSFRS-R of 25+
- 65% SVC & No Breathing Devices
- No Feeding Tube
- Cannot have only bulbar symptoms
- Must decline 3 points in the 12-week screening

Graphic - NurOwn Phase 3a Trial Design



In the 20 weeks that passed from screening to baseline dosing, all trial participants declined by a minimum of 3 points on the ALSFRS-R. Even though the minimum ALSFRS -R was 25 at screening, some people were far below that at baseline dosing. Just over 30 people had baseline scores ≤ 25. The lowest baseline score was 16.[72] Overall, the average baseline ALSFRS-R in the NurOwn Phase 3 trial was just 31 -- much lower than baseline in other ALS clinical trials.

E. NurOwn's Phase 3A Trial Results - Totality of the Evidence Supports Approval

NurOwn works on some people with ALS. Just as the Oncology Center of Excellence doesn't expect a drug to work the same on Stage 1 and Stage 4 cancer, Petitioners submit that it makes no common sense to expect a stem cell therapy to work the same on early and late stage ALS. In a 100% fatal and heterogeneous disease, Petitioners believe some should be enough.

In his Public Comment, Kevin Keenan, MD, a UC Davis neurologist addressed the efficacy signal:

> *"The fact that benefit was most notable in those early in their disease course is uniquely compelling rather than discouraging since earlier interventions have higher chances of modifying the disease course in many neurological diseases."*

The Totality of the Evidence demonstrates NurOwn's efficacy. Moreover, NurOwn met statistical significance on both primary and secondary endpoints in various subgroups earlier in ALS progression. The Totality of the Evidence includes various subgroup analyses from the 28-week trial and biomarker data. But the Totality of the Evidence now also includes new EAP data and other long-term data spanning over 400 weeks, including new progression data, new time-to-event data, and most importantly, new survival data.

1. FDA's Position - NurOwn Trial Didn't Meet Primary or Secondary Endpoints

At the AdComm, the FDA's Presentation outlined the reasons it didn't believe the BLA met the efficacy threshold for approval.

- Double-blind, RCT failed to meet primary or secondary endpoints
- Subgroup analyses are exploratory
- Biomarkers don't show clear association between validated biomarker and clinical benefit
- Survival data are limited and unfavorable

The evidence below addresses the FDA's concerns.

[72] Some trial participants delayed getting feeding tubes or using non-invasive ventilation in order to qualify for the trial but began using them in the time between screening and dosing, or after the start of the trial.

2. Totality of Evidence - NurOwn Works on Some

At the AdComm, NurOwn's statistical data was presented by Dr. Lee-Jen Wei, PhD,[73] a globally renowned biostatistician who is recognized for his work in designing and analyzing clinical trial outcomes in oncology and rare diseases. Dr. Wei opined that the "Totality of the Evidence" supports the conclusion that NurOwn works and meets the statutory threshold of "substantial evidence."

Dr. Wei explained that, in 1984, he and his colleagues innovated a way to analyze multiple trial endpoints temporally – across multiple time points in a trial – rather than just at one time point based only on one primary endpoint. Using this approach allows regulators to assess how robust and consistent the data are in a particular prespecified subgroup. Dr. Wei opined that this should ease the concern that NurOwn's treatment effect is just due to pure chance.

As lay people who are dying of ALS, the NurOwn Petitioners remind regulators that they received NurOwn doses at weeks 0, 8 and 16. Thus – from a patient's perspective – of course we want to see a therapy's impact on how we function the entire time we are taking it, not just at week 28 – which was 12 weeks after our last dose (in an every 8-week dosing schedule).

Thus this Totality of the Evidence methodology for rare disease trials is not just gold standard science by one of the world's most renowned biostatisticians, it is also just common sense to those of us whose motor neurons are dying each and every week plotted on this graph.

In the 2023 JAMA review titled *"Using a Clinically Interpretable End Point Composed of Multiple Outcomes to Evaluate Totality of Treatment Effect in Comparative Oncology Studies,"* Dr. Lee Jen Wei and colleagues proposed a novel statistical approach to assess treatment effects in oncology and rare disease trials. The study introduces a composite endpoint that simultaneously considers recurrence, progression, and survival times, creating cumulative event count curves for individual patients. This method provides a more clinically meaningful assessment of treatment benefits compared to traditional hazard ratios, which may oversimplify complex outcomes in heterogeneous rare diseases.

Dr. Wei illustrates its application in a hypothetical oncology trial, showing how it captures the "totality of treatment effect" by integrating multiple endpoints, thus supporting personalized medicine[74] by identifying patient-specific benefits. The approach is particularly valuable for rare cancers, where small sample sizes and heterogeneous outcomes challenge conventional analyses. This work aligns with FDA's flexible evidence standards and enhances the interpretation of small-cohort trials.

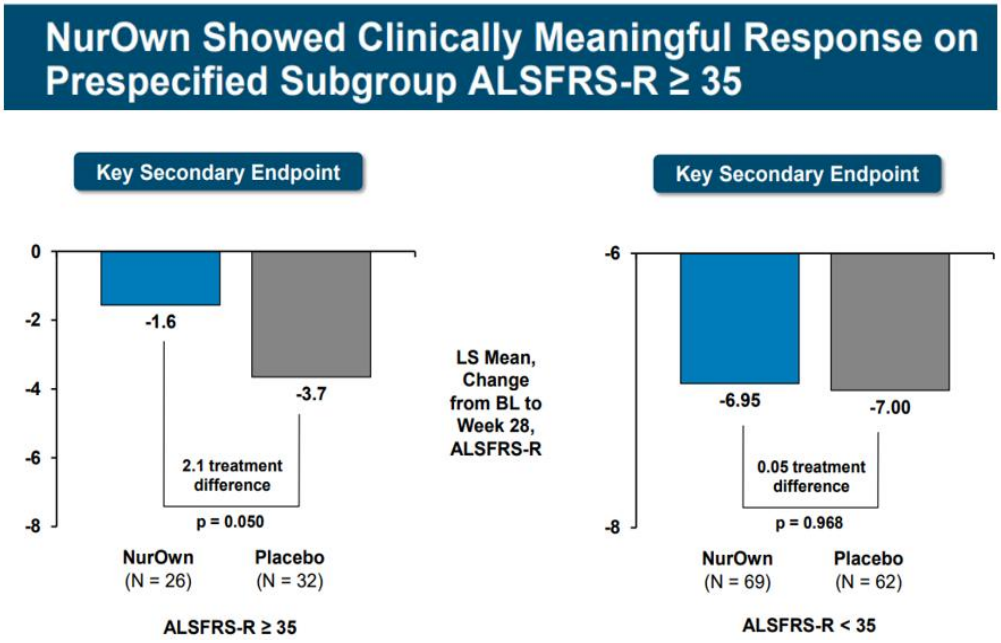
[73] Dr. Wei is a Professor of Statistics at Harvard and a Wilks Memorial Award winner. He has served as a key advisor to the FDA for over three decades. Dr. Wei has served on AdComms and advised the FDA on novel trial designs, including adaptive and Bayesian approaches, which are crucial for rare diseases and molecularly targeted oncology and rare disease therapies. His expertise in handling "time-to-event" endpoints has influenced oncology trial designs submitted for FDA review. Dr. Wei's methodologies extend to rare diseases, where small sample sizes necessitate innovative approaches like Bayesian modeling and RWE integration. He also contributed to Guidance Documents including the 2019 *"Demonstrating Substantial Evidence of Effectiveness,"* which emphasizes the "totality of the evidence" approach.

[74] Dr. Wei's research on personalized medicine focuses on developing statistical methods to identify patient subgroups that benefit most from specific treatments, particularly in oncology and rare diseases. His work quantifies treatment effects to support precision medicine, moving beyond average population effects to individualized outcomes.

a. NurOwn Met Pre-specified Secondary Endpoint ALSFRS-R ≥35

NurOwn worked on those early in progression with ALSFRS-R ≥35. This is analogous to those with Stage 1 cancer. The secondary endpoint compared how many points of function the people in the NurOwn arm lost compared to the people in the placebo arm – in just 28 weeks. In those with ALSFRS-R ≥35, the secondary endpoint showed that people in the NurOwn arm lost 2.1 points less function than those in the placebo arm (Sponsor's Presentation pg CO-33,34). As demonstrated by the patient perspective on MCID above, even one point is clinically meaningful.

Graphic - NurOwn's Impact on Early Progression Subgroup of ALSFRS-R ≥35



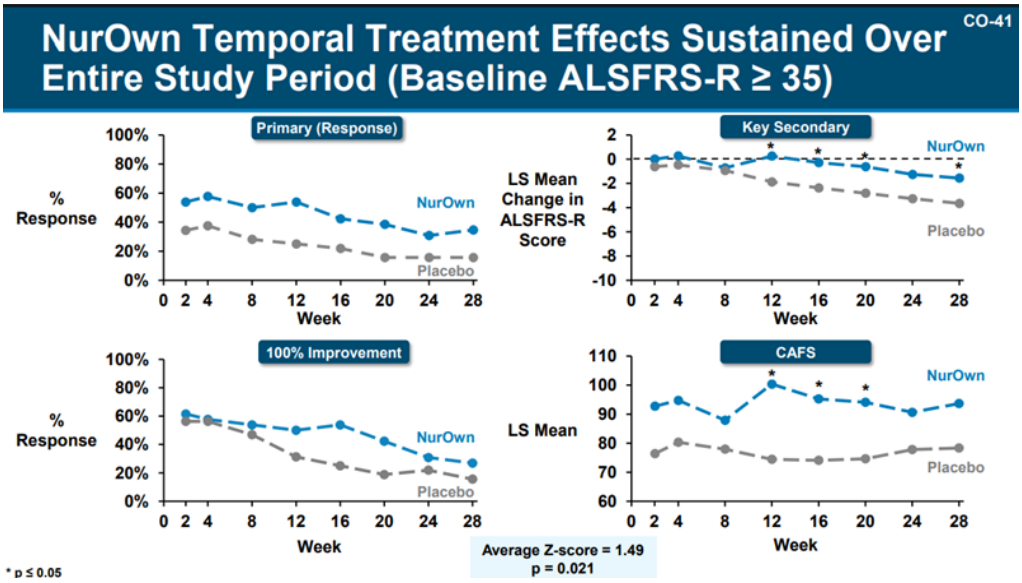
b. Totality of Evidence Demonstrated a Clinically Meaningful and Consistent Impact in the Early Progression Subgroup of ALSFRS-R ≥35

Using the "Totality of the Evidence" methodology commonly used in rare cancer trials, Dr. Lee-Jen Wei analyzed multiple endpoints at multiple times throughout the NurOwn trial to come up with a composite probability of NurOwn's efficacy in the subgroup of early progressors with ALSFRS-R scores ≥35 . (Sponsor's Presentation pg CO-41,42 and Sponsor's Brief pgs 27-28). The p-value assessing the multiple endpoints was 0.021.

c. Statistically Significant Temporal Treatment Effect Over Multiple Endpoints

The Totality of the Evidence – looking at multiple endpoints across the entire trial duration – demonstrates a consistent, clinically meaningful and statistically significant impact in the subgroup of ALSFRS-R ≥35.

Graphic - Totality of the Evidence: Multiple Endpoints in Subgroup of ALSFRS-R ≥35



On the top left hand quadrant is the curve connecting the response rate observed at a set of prespecified time points – temporally throughout the trial. The higher the curve, the better therapy's efficacy. As demonstrated above, the NurOwn blue line plots uniformly above the gray placebo line. At an early time point in the trial, the NurOwn arm separates and maintains that separation consistently over time. The delta between two curves is about a 19-20% difference in response rate. (Sponsor's Slide CO-41).

On the right quadrant is the change from baseline score over time. The treatment differences were observed after week eight – which importantly was Dose #2. That difference again was sustained over the entire study period. The same pattern is observed after the other clinical endpoints, especially for CAFS which is an outcome combining function and survival together. From this plot, you can again see the separation between two curves favoring NurOwn in all four quadrants.

During the AdComm, Dr. Wei explained how to statistically quantify these positive curves – over time and across the four clinical endpoints– simultaneously. It is a simple statistical procedure by combining standardized treatment estimates, which is simply the treatment effect divided by the Z score. If

there's no differences between treatment and control , the chance of observing these consistent positive patterns from four outcomes is only 2.1%.

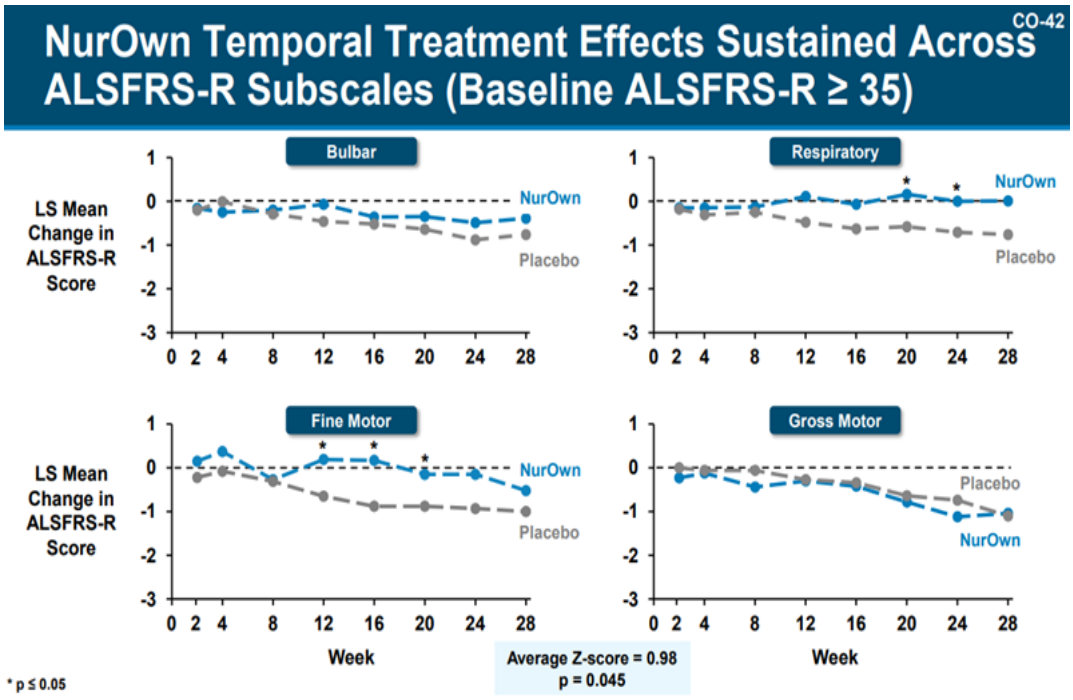
Dr. Wei concluded that this quantification suggests a positive global treatment effect in a much broader sense compared with the fixed-time analysis with the single outcome at 28 weeks. This method has been utilized, combining information from multiple outcomes, quantitatively, especially for rare disease clinical studies.

d. Statistically Significant Temporal Treatment Effect Over Multiple ALSFRS-R Domains

Dr. Wei also used this same "Totality of the Evidence" methodology to examine the treatment response across multiple subdomains on the ALSFRS-R, instead of focusing on the total score. Recall that multiple neurologists in multiple papers and presentations have criticized the ALSFRS-R's accuracy in assessing efficacy based on the total score alone.

In all categories except for the gross motor, the NurOwn curves are always above the gray curve. This suggests NurOwn appears to be effective, again, in a much broader sense than by using a single total score analysis. The p-value for the Totality of the Evidence across all four sub-domains was 0.045. If there was no difference between NurOwn and placebo, the chance of observing these consistent positive patterns from four outcomes is less than 5%.

Graphic - Totality of the Evidence:- Multiple Domains in Subgroup of ALSFRS-R ≥35



At the AdComm, Dr. Wei also shared that the positive treatment effect was also observed across other subgroups including a subgroup at the defined median of the baseline ALSFRS score which was 32. (AdComm 2:22:47).

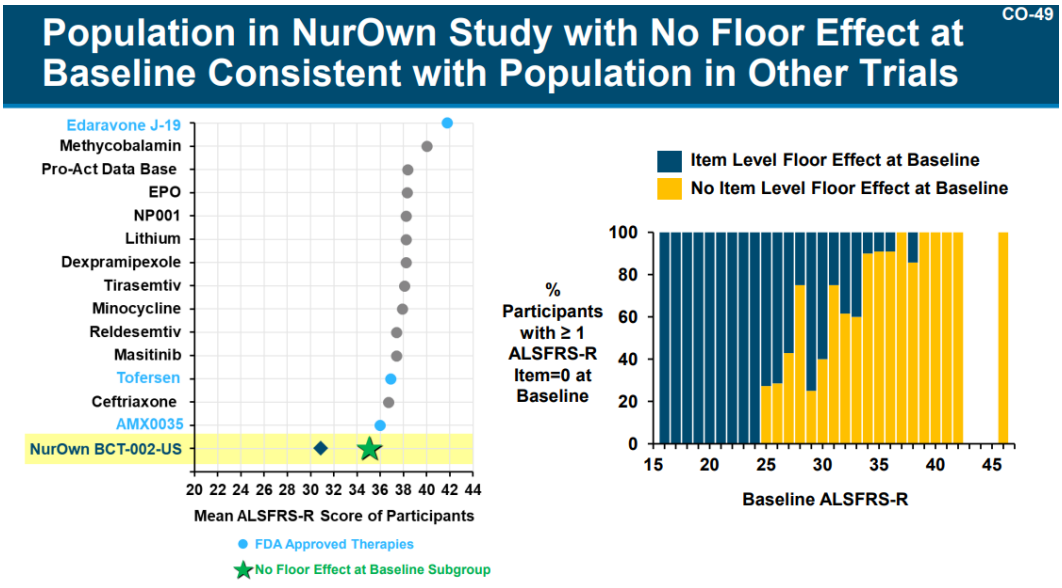
e. NurOwn Met Endpoints for Subgroup of People Earlier in Progression – Those without a Floor Effect

The Floor Effect distorted the NurOwn trial endpoints for the entire trial population. But when looking at the subgroup of the 106 participants earlier in progression – without a floor effect – NurOwn met statistical significance on both Primary and Secondary endpoints.

As discussed above, a limitation in the ALSFRS-R scale is its ability to measure ongoing decline once a trial participant has a zero in any of the twelve questions – especially those related to gross and fine motor skills. In the NurOwn trial, 100% of participants with ALSFRS-R scores ≤ 24 at Baseline had 1 or more questions on which they scored zero (0). Additionally, the Floor Effect was more prominent in participants with lower ALSFRS-R scores at Baseline.

Demonstrating that latter point is the comparison of the data in the NurOwn trial with the PRO-ACT natural history database. In PRO-ACT, the number of placebo participants exhibiting a pattern of floor effect was only 4.7%. But in the NurOwn trial – which had a much lower average baseline – the percentage of placebo participants exhibiting a pattern of floor effect was 22.3%.

Graphic - Floor Effect Impact at Baseline ALSFRS-R Cutpoints

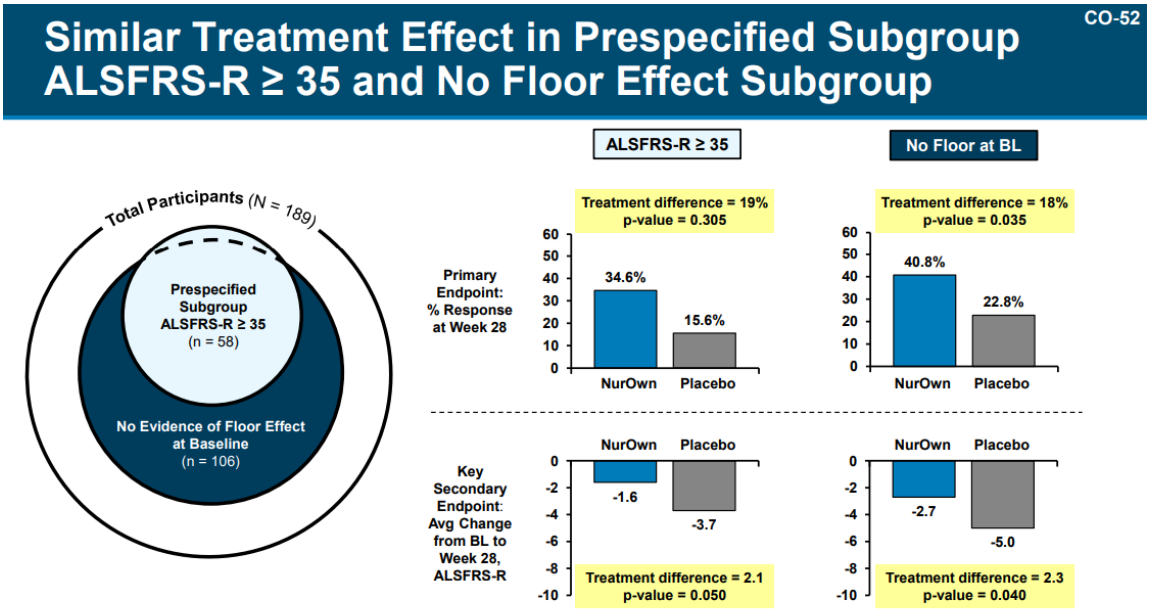


(Sponsor's Presentation pg CO-49).

When looking at the subgroup that the ALSFRS-R can accurately assess – the 106 trial participants without a Floor Effect – NurOwn met statistical significance on both the Primary and Secondary Endpoint.

- 41% met large magnitude Primary Endpoint of -1.25 point/month Change in Slope (p=0.035)
- 2.3 point delta between NurOwn and Placebo arm on Secondary Endpoint, Change from Baseline (p=0.040)

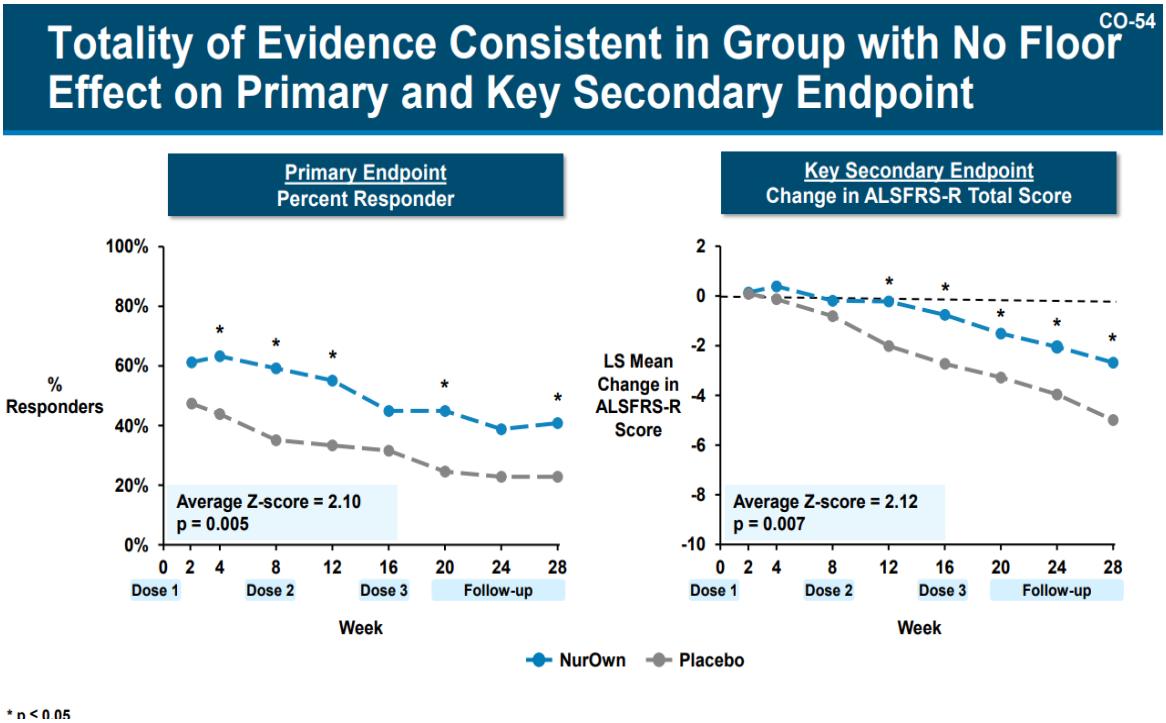
Graphic - Floor Effect Subgroup Consistent with Pre-specified ALSFRS-R ≥35 Subgroup



([Sponsor's Presentation](#) pg CO-52).

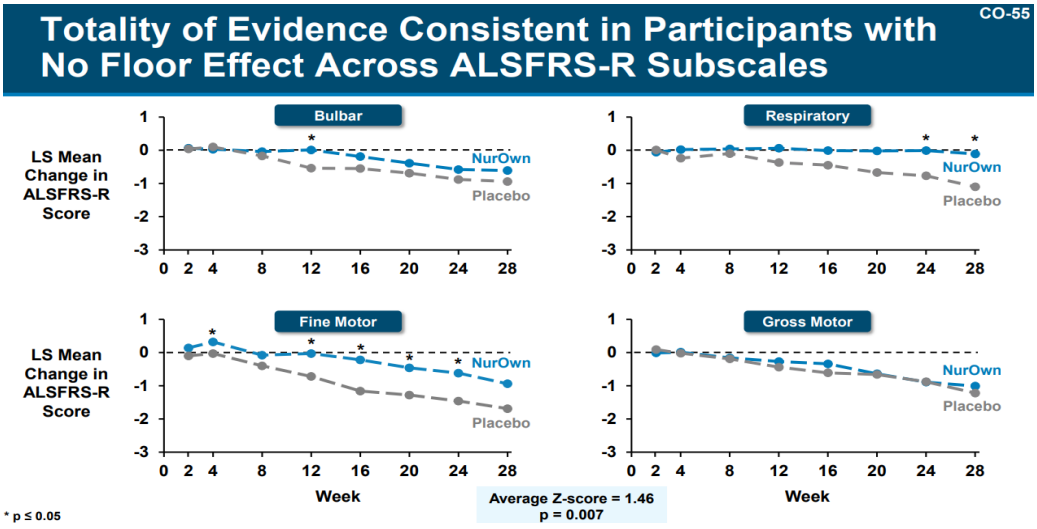
And once again applying Dr. Lee-Jen Wei's methodology commonly used in rare cancer trials, he concluded that the "Totality of the Evidence" was consistent in the subgroup with no floor effect on the Primary and key Secondary endpoints – with compelling p-values of 0.005 and 0.007 respectively.

Graphic - Totality Of Evidence in Floor Effect Subgroup Consistent Across Endpoints



([Sponsor's Presentation](#) pg CO-54). Similarly, the "Totality of Evidence" was consistent in participants with no floor effect across the four ALSFRS-R sub-domains, and again the p-value was a persuasive 0.007. ([Sponsor's Presentation](#) pg CO-55).

Graphic - Totality Of Evidence in Floor Effect Subgroup Consistent Across Domain Subscales



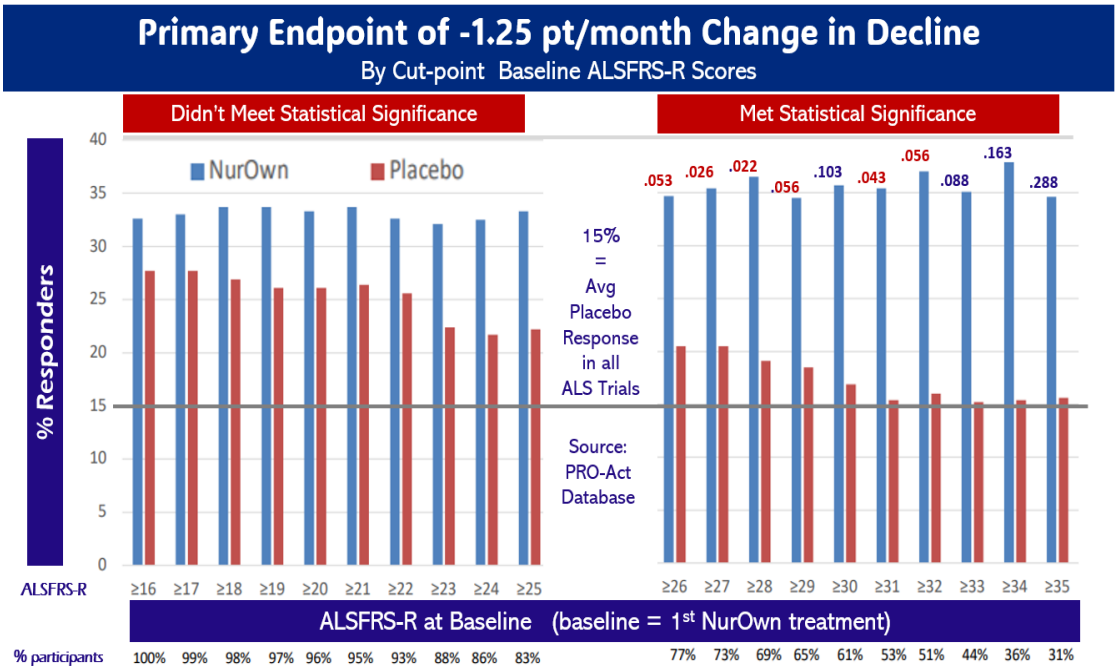
For both of these analyses, there is only a 1% likelihood that these consistent positive patterns – from multiple endpoints and multiple domains across multiple points in time – are due to mere chance.

f. Post Hoc Analysis showed that NurOwn Demonstrated a Clinically Meaningful and Consistent Impact in the Early Progression Subgroup of ALSFRS-R ≥27

Brainstorm did not seek FDA approval for people in the subgroup with an ALSFRS-R ≥27. But several people in the Phase 3 trial and EAP had scores between 27 and the pre-specified endpoint of 35 and above. And now that the trial has been unblinded, the NurOwn Petitioners have proof that NurOwn worked on us both in the trial and in EAP. **This is akin to a drug working on a Stage 1/2 rare cancer.**

NurOwn worked in the subgroup earlier in ALS progression (n=138) with an ALSFRS-R ≥27. On the massive primary endpoint, the subgroup's data met statistical significance (p=0.026) for those with baseline scores ≥27. NurOwn recipients had a 15-20% higher response rate than placebo.

Graphic - Totality Of Evidence in Floor Effect Subgroup Consistent Across Endpoints



According to Dr. Ardalan Minokadeh, MD PhD (in neuroscience), this primary endpoint graphic also illustrates some additional important points:

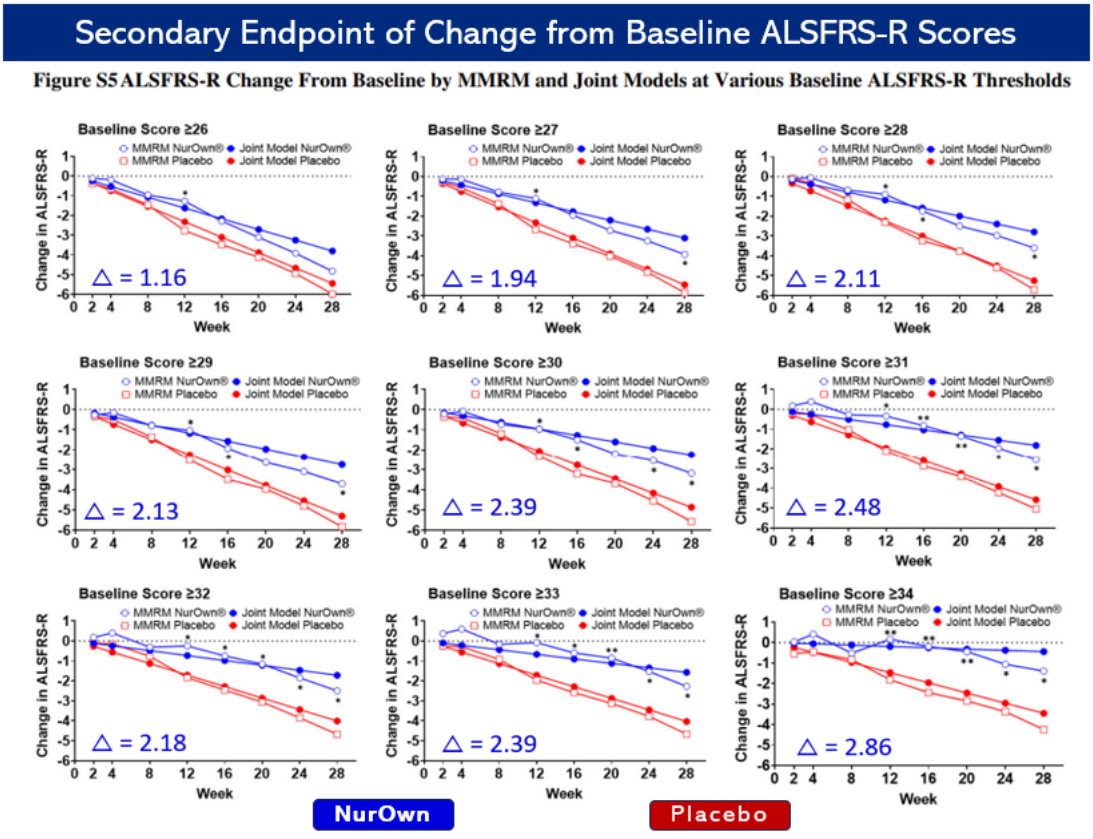
- The impact of the floor effect: as people's baseline scores decreased, the placebo response increased.
- The NurOwn treatment arm hovered at or above a 35% response rate for all subgroup cut points of ≥27, demonstrating consistency and thus reliability in the response
- The subgroup at the pre-specified primary endpoint of ≥35 was not a large enough sample size to meet statistical significance.

- But the subgroup at ≥35 demonstrated a nearly identical response with the cut points as the subgroups of ≥31, ≥32, ≥33, and ≥34.
- Once the subgroup sample size reached 100 people (at mean cut point ≥31), it was powered sufficiently to meet statistical significance (p=.046).
- The subgroup also met statistical significance at the median baseline of ≥32

The following "Efficacy Over Time Curves" illustrate the data for the secondary endpoint: change from baseline (as annotated to include the delta) from the Supplement to the Phase 3 study published in Muscle and Nerve:

- NurOwn outperforms placebo at all points in time for each cut-point baseline score ≥27
- Delta between NurOwn and placebo increases as the baseline score increases
- Floor effect impact becomes apparent ≥26

Graphic - Secondary Endpoints by Cut-point ≥ 26 to ≥35



Note: Each panel graphs the results for participants with baseline ALSFRS-R score greater than or equal to the specified threshold. MMRM: pre-specified SAP analysis, graphed with an open circle for MSC-NTF and open square for placebo. The joint model is graphed using a filled circle for MSC-NTF, open circle for placebo. For MMRM results, visits where there was a nominally significant difference between NurOwn and Placebo are marked with asterisks: * p<=0.05; and ** p<=0.01

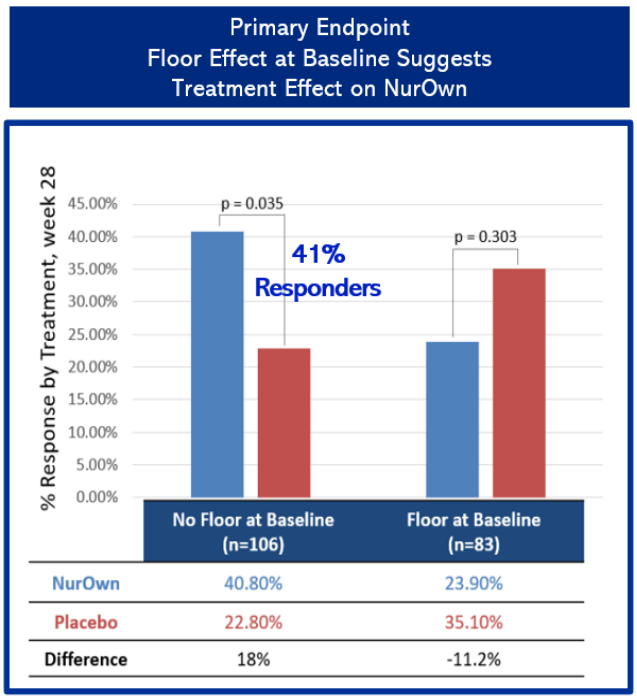
Again, this data demonstrates the logical principle that a drug is more likely to demonstrate a large magnitude response early in disease progression rather than late in disease progression. In the NurOwn trial, recall that NurOwn was dosed at weeks 0, 8 and 16. Notice that the data met statistical

significance with a 0.05 p-value, temporally, across multiple points in time for the subgroup of people with scores ≥27, which is 73% of the trial population.

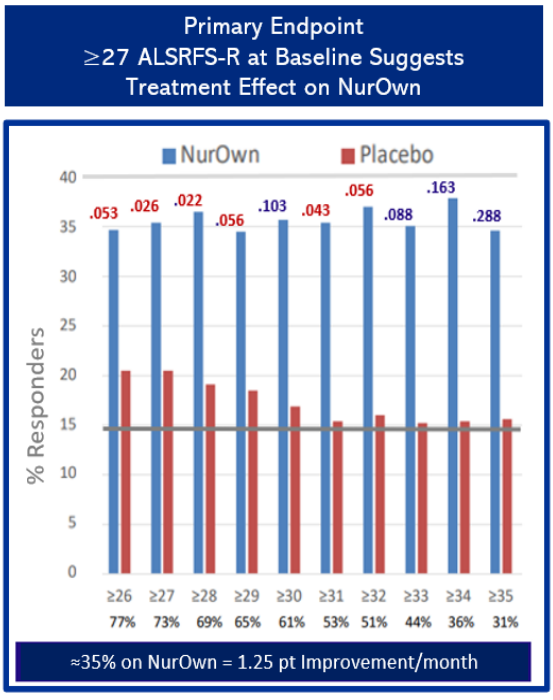
Additionally, recall that the mean baseline was 31 and that is when the statistical significance reached 0.01 p-value, not just 0.05. Also notice that week 12 appeared to be a critical week – after participants had received two doses of NurOwn. This evidences a dose-dependent response that exceeded the one-dose response in Phase 2. It also emphasizes the importance of utilizing Dr. Lee-Jen Wei's Totality of the Evidence methodology as it captures informative changes across the treatment period.

And finally, as demonstrated in the graphics below, because there is consistency in the data between the floor effect subgroup and the ≥27 subgroup, this decreases the likelihood that the post hoc results are due to pure chance.

Graphic - Primary Endpoint: No Floor Effect Subgroup and ≥ 27 Subgroup

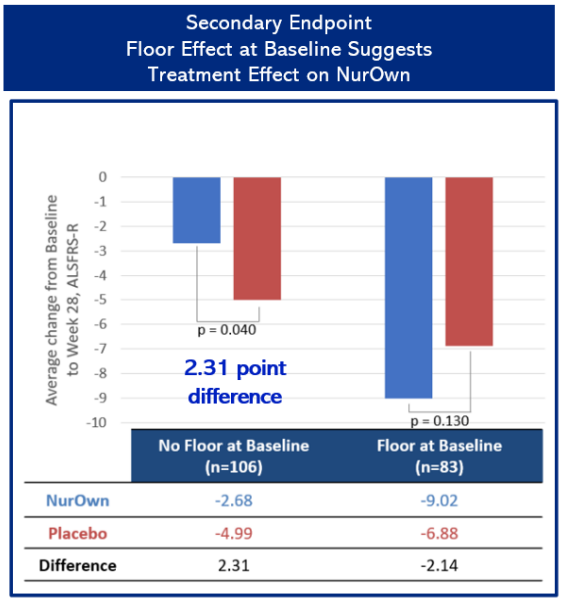


Source: Poster presented at MDA Conference (March 2023)

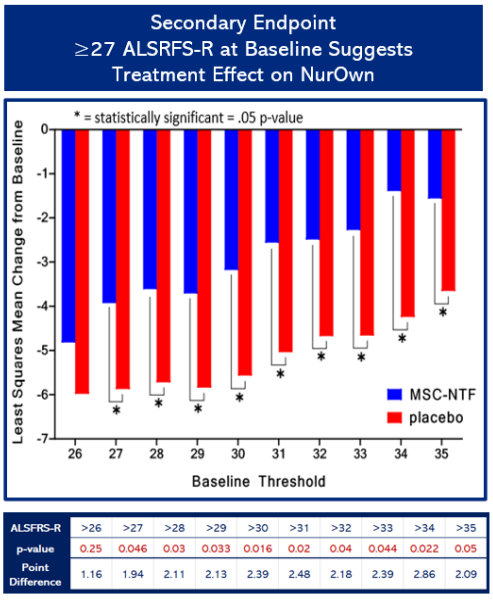


Source: Poster presented at NEALS Conference (NEALS 2022)

Graphic - Secondary Endpoint: No Floor Effect Subgroup and ≥ 27 Subgroup



Source: Poster presented at MDA Conference (March 2023)



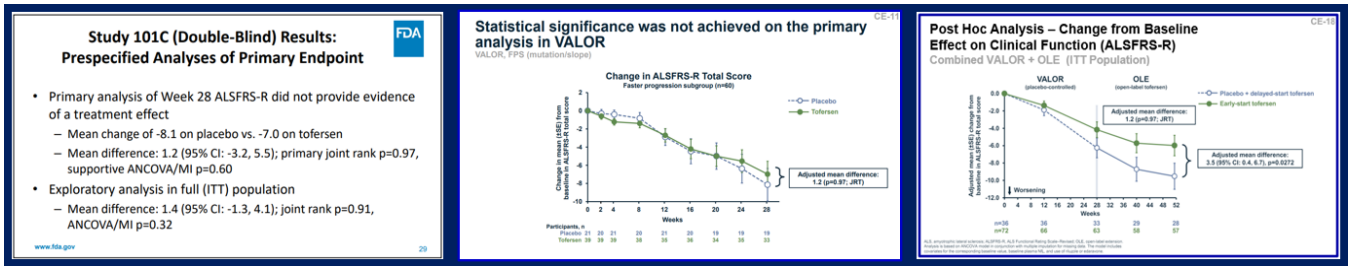
Source: Poster presented at NEALS Conference (NEALS 2022)

3. At 28 weeks, NurOwn's Results were nearly 2x Larger than Tofersen's Results

The "Change from Baseline" was an endpoint in both the NurOwn and Tofersen trials. It was the primary endpoint in the Tofersen trial and a secondary endpoint in the NurOwn trial. Both trials were the same length: 28 weeks. Tofersen did not meet its primary endpoint. NurOwn met its pre-specified secondary endpoint ≥35.

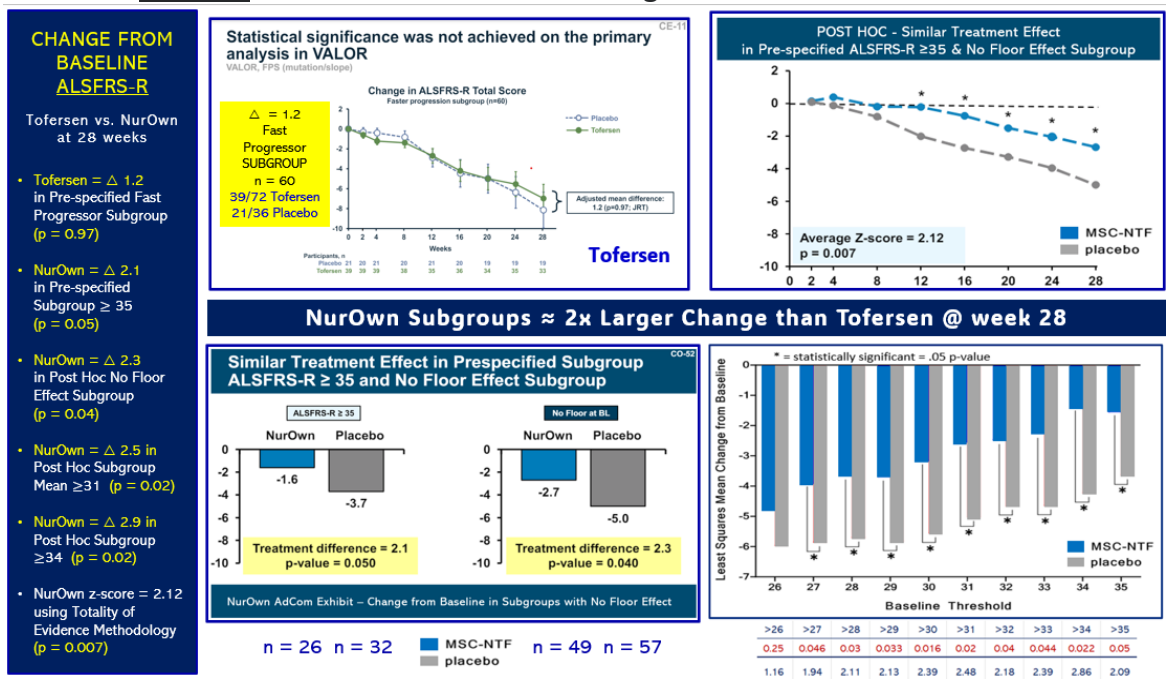
Tofersen resulted in a 1.2 point difference in the fast-progressing subgroup of 60 people; and a 1.4 point difference in the exploratory ITT population. (See Biogen Presentation pages CE-11,18; FDA's Presentation pg 29). Nonetheless, based on additional long-term data and biomarkers coupled with its failed primary endpoint, CDER appropriately exercised its regulatory flexibility and approved Tofersen.

Graphic - Tofersen Change from Baseline at 28 weeks



Now, compare the NurOwn and Tofersen results – using the same exact endpoint of "change from baseline." If a 1.2 point difference in a 60-person subgroup is clinically meaningful enough on Tofersen, then the larger 2.1 point difference in a 58-person subgroup should be clinically meaningful enough on NurOwn.

Graphic - Tofersen vs. NurOwn: Change from Baseline at 28 weeks



(Compare Biogen Presentation pgs. CE-11; Sponsor's Presentation CO-37, CO-52,CO-54 and Sponsor's Poster presented at NEALS Conference (NEALS 2022).

All the other NurOwn subgroups also outperformed Tofersen subgroups at 28 weeks:

- Tofersen = △ 1.2 in Pre-specified Fast Progressor Subgroup (n = 60, p = 0.97)
- NurOwn = △ 2.1 in Pre-specified Subgroup ≥ 35 (n = 58, p = 0.05)
- NurOwn = △ 2.3 in Post Hoc No Floor Effect Subgroup (n = 106, p = 0.04)
- NurOwn = △ 2.5 in Post Hoc Subgroup Mean ≥31 (n = 100, p = 0.02)
- NurOwn = △ 2.9 in Post Hoc Subgroup ≥34 (n = 68, p = 0.02)
- NurOwn z-score = 2.12 using Totality of Evidence Methodology (p = 0.007)

4. In the Early Progression Subgroup, the NurOwn Data Corroborated the Clinical Observations of Trial PIs, Trial Participants and their Treating Neurologists who Testified that NurOwn Halted Lethal ALS Progression.

The NurOwn trial's principal investigators and the trial participants' treating neurologists made clinical observations that NurOwn halted their patients' lethal ALS progression in a way they had never seen in their decades of clinical practice.

Recall that PIs Dr. Windebank and Dr. Brown both have 40+ years of experience treating ALS patients. At the AdComm, Dr. Windebank testified that he and other trial PIs observed that:

- Some people STABILIZED in a way that he had never seen in any other trial
- In the one to two-year interval between the trial and EAP, participants deteriorated
- People again STABILIZED when receiving NurOwn during EAP

When Dr. Windebank testified about patients' unprecedented responses during the NurOwn EAP, Petitioners Matt Klingenberg, Roberto Muggli and Kade Simons were among the people who exemplified his clinical observations. Roberto's treating neurologist was Dr. Roberto Vargas Howell, who didn't know Roberto had been participating in a clinical trial. When Roberto returned to Costa Rica, his neurologist was astounded that Roberto's ALS had not progressed beyond what he had seen 18 months previously. In her Public Comment, Roberto's wife said Dr. Vargas Howell asked, ***"What are you doing? You aren't like the other patients."***

Josh Smith's PI was Dr. Brown and his treating neurologist was Dr. Klinov. Dr. Klinov's clinical notes and his Public Comment repeatedly mention that Josh STABILIZED when on NurOwn: "***"Joshua's ALS progression halted while receiving the stem cell therapy."*** During the EAP, Dr. Brown documented Josh's moped strength as sad he was ***"strong as an ox."*** He also asked Josh for his permission to share's Josh's story during conversations with the FDA.

Lesley Krummel's trial local neurologist was Dr. Thai of University of Nebraska. Lesley's Public Comment recalled that Dr. Thai was *"in awe of how stable I was … and said something about: 'could it be the stem cells?' One of his nurses said I'm* ***'the most stable ALS patient she has ever seen!' "***

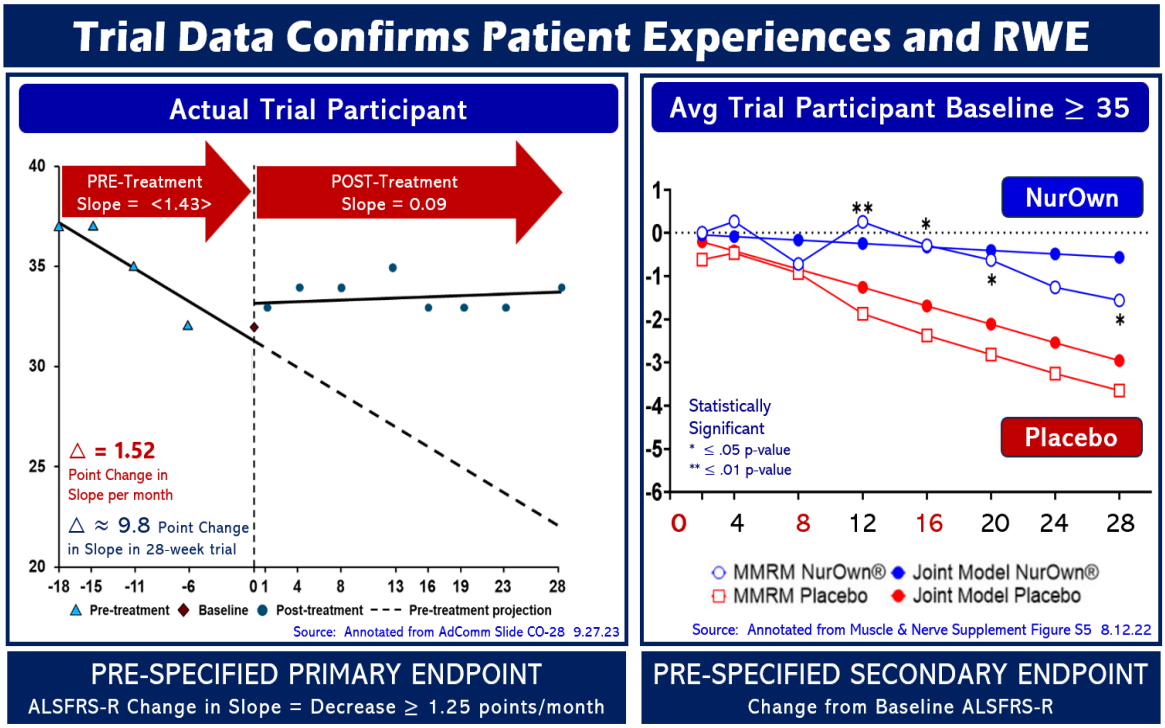
The neurologist who had the most experience with trial participants outside the trial was Synapticure's neuromuscular specialist Dr. Danielle Geraldi-Samara. Because Synapticure is a tele-neurology practice, Dr. Geraldi saw patients in multiple states across the US. Dr. Geraldi's Public Comment documented profound changes:

> *"I have been working in the ALS clinical space and in ALS multidisciplinary clinics for over 15 years…. I have seen the full breadth of clinical constellations playing out over time. What I have not seen, though, is anyone with significant functional improvement from a declining baseline;* ***I have not seen patients rise from plateaus. It does not happen in the natural course of ALS. It did happen with the introduction of NurOwn****.*

The real-world evidence could not be more striking. I have known patients nearly immobile who gained some functionality in their gait, patients with severe dysarthria become intelligible, patients who could not manage the fine motor skill needed to button or zipper, finally able to dress independently. I have patients with ***solid plateaus over the course of a year*** *and patients climb up what we have previously known to be unscalable in the disease process, the ALSFRS-r."*

The Phase 3 trial remained blinded until after the AdComm. As such, both the FDA and AdComm members characterized these unprecedented changes as "anecdotal" and disregarded them. But now that the NurOwn Petitioners have confirmation that we did receive NurOwn in the trial, we are submitting the below Phase 3 clinical trial data that further validates and vindicates our patient experiences and real-world evidence.

Graphic - NurOwn Primary & Secondary Endpoint ≥35 Demonstrating Stabilization



At 2:07:29 in the AdComm, Dr. Stacy Lindborg commented on the "n of 1" graphic on the left side showing an example of an actual responder on the primary endpoint analysis.

"Let me show you an illustration of our primary endpoint. This data on the slide is a participant from the phase three trial of a person treated with NurOwn. This participant met the criteria for clinical response for the primary endpoint….. And as you can see, there's a stable trajectory in the treatment period with a slope that is positive and near zero, or a slight increase in scores over time.

(See Sponsor's Presentation pg CO-28).

As cited earlier in this Petition, the FDA's Brief asserted that ***"short intervals of improvement are not uncommon."*** To support this assertion, the FDA:

(1) ignored ALS KOL Dr. Timothy Miller who said in the CDER Tofersen AdComm in March 2023: ***"in 2 decades of treating people living with ALS, I have not seen improvements"***[75]

(2) ignored correction from top ALS KOL Merit Cudkowicz, when asked about short-term linearity at prior CDER AdComm

(3) ignored ALS treating neurologists whose RWE in clinical notes expressed the rarity of stabilization & regaining function in ALS

(4) ignored ALS top KOLs Dr. Windebank and Dr. Brown who testified that they haven't seen this type of improvement in the 40+ year careers in treating people with ALS

To be clear, this fallacy was the most incorrect assumption at the NurOwn AdComm. And it went uncorrected by the Patient Rep and the six neurologists on the AdComm. It was as if "Groupthink" took over.[76]

ALS is relentlessly progressive. People with an ALS diagnosis do not experience a dramatic and sustained change in the trajectory of decline. People with ALS don't routinely regain function. People don't spontaneously stand up out of wheelchairs and stop using NIV like Matt Bellina did. People don't stop using walkers like Bobby Forster did. People don't start writing again like Mike Cimbura did. People don't regain 40+ points in FVC like Josh Smith did. It just doesn't happen. But it did with NurOwn.

As Commissioner Makary said in his book, Blind Spots: "Never underestimate the difficulty of changing false beliefs with facts." (pg. 83).

There is nothing more illogical than requiring patients to self-report their function on a clinical outcome assessment then doubting those same patients who self-report regaining function.

There is nothing demonstrating more hubris than neurologists who haven't treated people on NurOwn doubting the opinions of those who have. There's nothing more nonsensical than regulators telling

[75] Tofersen Presentation pg CP-3.

[76] "Groupthink is a powerful force." From the book BLIND SPOTS: Groupthink reflects a paternalism that plagues modern medicine. (pg. 102). Doctors on the frontline of medicine witnessed the remarkable arrogance of the medical establishment – ignoring data & plowing over dissent. (pg. 110). Time and time again institutions & organized medicine have kept dissenting opinions of highly credentialed doctors hush-hush, creating an illusion of consensus. (pg. 184).

dying patients that a therapy might be riskier than the 100% chance of dying. There is nothing more paternalistic than a PhD with no clinical experience telling a paralyzed patient that they couldn't possibly be trusted to know when a therapy helps them move again. There is nothing more patronizing than a bioethicist with no clinical or personal experience in ALS lecturing the mother of a NurOwn recipient about "false hope." And there is nothing more disrespectful than any person who has the audacity to tell a dying patient that they couldn't possibly understand when a therapy is helping them live.

People with ALS live with this hell every day. We know this disease better than anyone. We experience loss of function from one day to the next. We watch our friends die. That is why the ALS community has held protests, signed petitions, made documentaries, written Open Eds, spoken at hearings, cried with Congress, and pleaded at PFDD meetings for someone – anyone – to listen to their lived experience. It is why the ALS community has been understandably astounded that the FDA has not approved a stem cell therapy that is causing improvements that have never before been seen in the history of ALS. And it is why Petitioners had no choice but to file this Citizens' Petition.

F. NurOwn's Expanded Access Program Provided Dosing & Durability Data, along with Unprecedented Survival Data

The Phase 3 trial had no open label extension. However, the FDA did approve an Expanded Access Program for a small proportion of trial participants who received up to an additional 6 total doses in 2021 and 2022 (NCT04681118). Initially several Petitioners were advised that the EAP was approved for up to 20 people. Only 10 received EAP doses.[77]

On page 25 of its Briefing Document, the FDA conceded that the EAP data was not a part of its efficacy assessment:

> *"An intermediate-sized expanded access protocol (EAP), BCT-003-US, is ongoing. At the time of the BLA submission, BCT-003-US enrolled 10 subjects, all of whom had participated in the Phase 3 study, to allow continued access of MSC-NTF. The BLA contained limited information regarding BCT-003-US and did not include the study report or datasets. BCT-003-US consequently is discussed only to a limited extent in this Briefing Document…. Therefore, this Briefing Document focuses on the efficacy data from studies BCT-001-US and BCT002-US."*

There are no peer-reviewed publications summarizing the compelling EAP data and BrainStorm did not present any information about it at the FDA AdComm. But many of the EAP participants shared their life-changing stories in Public Comments to the docket and in the Open Public Hearing at the AdComm.

[77] As Commissioner Gottlieb noted in the March 2019 press release: *"Many novel therapies are being developed by small companies that may have only a single product. The supply of investigational products may only be sufficient to support the clinical research trials, and not adequate to support EA…. C**ertain biologics, such as cell & gene therapies, are particularly complex & expensive to manufacture, so the cost to the company of providing such access may be prohibitive."***

There are ample RWD and RWE from both the people in EAP and their doctors that NurOwn helped them "live longer and live better."

But today, for the first time, Petitioners are presenting new evidence of critical EAP data including compelling, long-term evidence about slowing of lethal progression, improvements in breathing, and accordingly, extension of survival. Not surprisingly, the people who received the most doses of NurOwn via EAP had the slowest progression, the largest magnitude and longest lasting improvements.

Additionally, in the Press Release issued on June 16, 2025, Brainstorm reported that, at the start of the Phase 3 trial, the 10 EAP participants were "relatively early" in their ALS progression. Following were the baseline ALSFRS-R scores at the start of the Phase 3 trial and EAP:

- 35.8 mean baseline ALSFRS-R for Phase 3 (Range: 32 – 40)
- 31.4 mean ALSFRS-R at the start of the EAP (Range: 27 – 38, with one outlier score of 13).

This is significant information as 73% of the people in the Phase 3 trial had baseline scores ≥27. And the trial met unadjusted statistical significance in that population with p-values of 0.026 and 0.046 on the primary and secondary endpoints, respectively. As such, it lends more credence to the assertion that NurOwn caused "clinically meaningful" changes in EAP participants.

In its own 2019 press release, the FDA expressed support for EAPs and tried to encourage drug sponsors to offer it more often. Former Commissioner Gottlieb stated that EAPs can be combined with evidence from clinical trials to support approval decisions:

> *"While perhaps not commonplace, Expanded Access may add to the evidence for approval…. We urge sponsors to consider EA in appropriate settings; and* ***especially after patients who are showing promise on an experimental drug complete therapy in a clinical trial setting****…. EA has been an important program, providing access to innovative therapies that can provide meaningful benefits to patients with serious diseases who lack therapeutic alternatives….* ***Information from EA has sometimes proven valuable, contributing to the overall data available about a drug that is included in the marketing application.****"*

In addition to the RWE demonstrating long-term safety, efficacy and durability in the NurOwn EAP, below is an example of the valuable new survival data. **All ten people in the NurOwn EAP lived or are still living 2x-3x longer than median trach-free survival in ALS.**

G. NurOwn's Phase 2b Trial – in the US

In 2015, Brainstorm began the Phase 2b study in the US, its first randomized controlled trial. The trial had a 3:1 placebo ratio with 36 people receiving one dose of NurOwn and 12 on placebo. There was a 12-week run-in period to observe slope, followed by a 24-week trial. The baseline score was 36, which was 5 points higher than the Phase 3 trial.

Based on the Phase 1 results in Israel, there was tremendous interest in the trial. NurOwn principal investigator Tony Windebank told HBO VICE that Mayo had only 16 slots in the Phase 2 trial but had almost 1000 people on the waiting list.

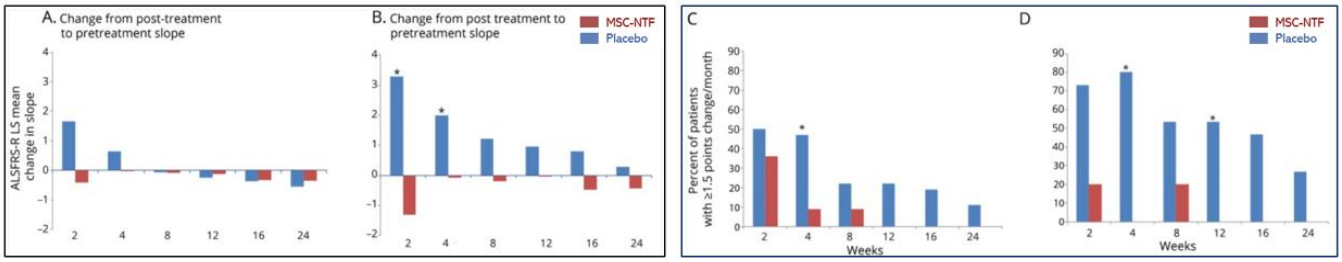
1. Statistical Results of Phase 2 Trial

Among the 48 randomized participants, 43 (89.6%) completed the trial. Of the 5 who didn't complete the trial, 3 were in the NurOwn arm and 2 in the placebo arm. Thus, there were 33 on NurOwn and 10 on placebo. The pre-specified fast progressor subgroup was defined as those who lost 2 points in the 12-week run-in period. Responders were defined as those who lost ≥1.5 pts/mo on ALSFRS-R slope improvement.

a. Overall Phase 2 Trial Results

The results of the NurOwn trial were published by Neurology. Using the ≥1.5 pt/mo responder threshold, the NurOwn arm outperformed placebo at all time points; The difference was significant at week 4 (MSC-NTF 47%, placebo 9%, p = 0.033, figure 2C). In the rapid progressors subgroup, the NurOwn arm outperformed placebo at all time points; the difference was significant at week 4 (80% vs 0%; p = 0.004) and week 12 (53% vs 0%; , p = 0.046) (See figure 2D).

Graphics - Phase 2 Trial Results



The data matched the reports of people in the trial. When asked if these "stark improvements" are common in ALS, Principal Investigator Dr. Merit Cudkowicz responded:

> *"I've been treating patients with ALS for over 25 years and we very rarely see instances of 100% improvement. Patients will ebb and flow and the disease has periods of stabilization and then rapid decline. But improvement is very rare in ALS. The trajectory is almost always downhill."*

Some fast progressors maintained 100% improvement at the end of the 24-week Phase 2 dosing trial. This is consistent with what many people in the trial said. NurOwn improved their function or halted their progression, but the effects on the ALSFRS-R washed out several weeks to several months after receiving that one single dose. Thus, with a trial not powered for efficacy and with one only dose in 36

people, it's not surprising that the NurOwn Phase 2 trial did not meet its endpoints at week 24 (6 months).

It seems nonsensical to have to posit, but what would happen to a diabetic's blood-sugar and A1C if they didn't get insulin for 6 months? Would regulators conclude that insulin didn't work?

Because the Phase 2 trial was to help determine the proper dosing schedule, Brainstorm looked at the different response rates of slow (≤0.7 pts/mo) versus fast progressors. ALS is a vastly heterogeneous disease with variable progression rates, which complicates the detection of treatment effects in clinical trials. In this 2020 webinar, Dr. Namita Goyal explained that slow progressors likely don't progress quickly enough in a short 6 month trial to enable researchers and regulators to detect any efficacy signal of a change in function. Two years before the NurOwn AdComm, a **2021 review** confirmed the rationale for excluding slow progressors: patients with a slower decline in ALSFRS-R can mask potential treatment signals within the typical 6-month trial duration.[78]

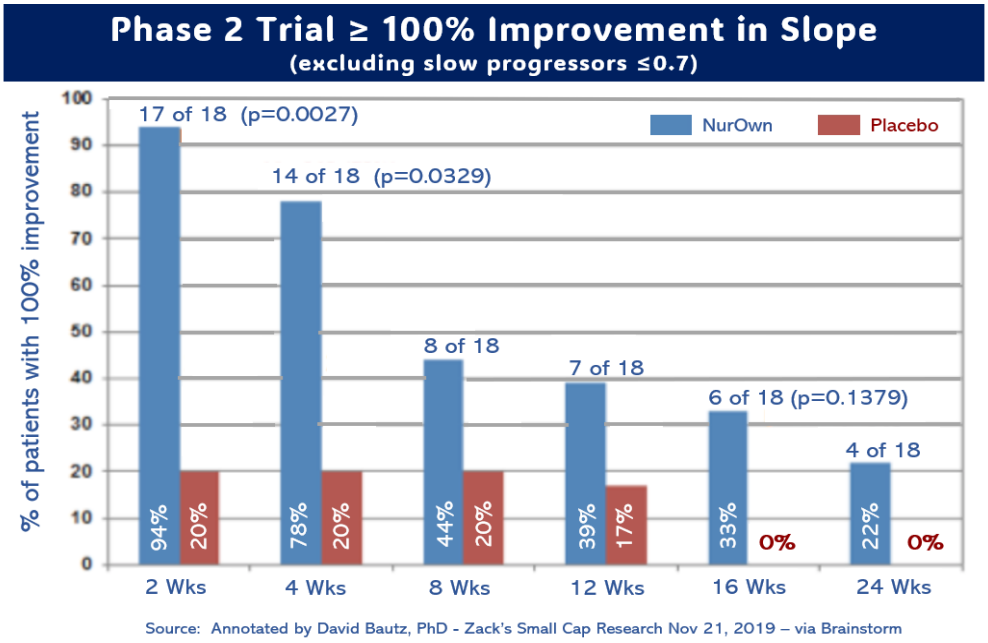
b. Results of Fast Progressors

With this in mind, below are the NurOwn Phase 2 data for fast progressors. Almost 100% of fast progressors had almost a 100% response almost immediately – at week 2. As you can see, **17 people on NurOwn but only 1 on placebo halted their progression.**

As time passed and that one dose of NurOwn washed out, some people began to decline. Again, the data are consistent with the patient reported outcomes from trial participants and their caregivers. At week 8, you can begin to see a change in durability: "only" 44% still had 8 weeks of progression-free survival with that one dose of NurOwn. **To be clear about what regulators see versus what people with ALS see when they look at this same Phase 2 data at 8 weeks: That's two months of not dying**!

Graphic - Phase 2 Trial Results ≥100% Improvement in Slope in Rapid Progressors

[78] Wong, C., Stavrou, M., Elliott, E., Gregory, J. M., … Macleod, M., Pal, S., & Chandran, S. (2021). Clinical trials in amyotrophic lateral sclerosis: A systematic review and perspective. Brain Communications, 3(4), fcab242.



By week 16, everyone on placebo had begun to decline but still one-third of the people in the NurOwn arm continued their progression-free survival. And finally at the end of the 24-week trial, one-fifth of trial participants continued to be stable. This is **nearly 6 months of progression-free survival.** **Again, this is 6 months of not dying!**

If a cancer therapy caused 6 months of progression-free survival, oncologists would be screaming from the mountain tops about the huge win. Indeed, in Exhibit A you can see 40+ cancer therapies that were approved based on ≤6 months of progression-free survival.

c. Inconsistent Acceptance of Efficacy Data of Subgroups of People with Fast Progressing ALS

The exclusion of slow progressors enhances the statistical power to enable researchers and regulators to detect differences between treatment and placebo groups – without exposing dying patients to longer placebo-controlled trials as it would take years to see a signal in slow progressors.

Because ALS is a heterogeneous disease with variable progression rates, trial results must try to focus on a population that can be more easily measured. The **2021 review** confirmed that slow progressors: can complicate or mask the detection of treatment effects in clinical trials within the typical 6-month trial duration.[79] The study's authors reviewed 125 ALS trials between 2008 and 2019. They concluded that traditional fixed-design trials (which constituted about 90% of the 125 ALS trials) often struggled to demonstrate efficacy due to this variability.

[79] Wong, C., Stavrou, M., Elliott, E., Gregory, J. M., … Macleod, M., Pal, S., & Chandran, S. (2021). Clinical trials in amyotrophic lateral sclerosis: A systematic review and perspective. Brain Communications, 3(4), fcab242.

Many people are unfamiliar with the heterogeneity of ALS and the difficulty of conducting clinical trials in a rare disease with a flawed clinical outcome assessment and without objective biomarkers. Unfortunately, the FDA reached a conclusion about the Phase 2 data without taking the above factors into account. In its Briefing Document, the FDA said:

> ***As FDA stated in the November 18, 2019, Type C Meeting Summary:***
>
> *"We interpret your Phase 2 data as evidence that your product is not effective in the treatment of ALS. Your proposal that your Phase 2 data suggest benefit for the 'rapid progressors' is most likely over-interpretation of your subgroup analyses. In subgroup analyses, the results for the 'slow progressors' could be interpreted to suggest that your product is harmful to some patients with ALS. However, such subgroup results, for both the 'rapid progressors' and the 'slow progressors', are most likely spurious and misleading, as is often the case for such subgroup analyses.*
>
> *We note that it is not clear why a product that you propose to have neuroprotective and immunomodulatory effects would be beneficial for some patients with ALS and harmful to other patients with ALS. Due to their inconsistency (i.e., opposite effects in 'rapid progressors' versus 'slow progressors'), and the unclear biological plausibility for such inconsistency, your subgroup results do not support that your product has any meaningful activity in the treatment of ALS." (Figure 16 and Figure 17).....*
>
> *Despite FDA's consistent concern about the definition of "rapid progressors," and the exploratory nature of the subgroup findings, the Applicant decided to enroll only "rapid progressors" in the Phase 3 study. For that study, the Applicant modified the definition of a "rapid progressor" to be subjects who experienced at least a 1.0-point decline in ALSFRS-R per month, on average, during the 3-month pretreatment period.*

For many reasons, Petitioners have concerns about the FDA's conclusion. First, it demonstrates a fundamental misunderstanding of this rare disease and the clinical outcome assessment tool used to measure changes in function. This exemplifies why Petitioners have been advocating for both a Rare Disease Center of Excellence and a Neurodegenerative Disease Center of Excellence.

Second, in fairness to the FDA, they cannot be expected to be experts in rare diseases like ALS. That is why there are Patient Reps who are supposed to correct inaccuracies. But the Patient Rep missed the opportunity to correct this misstatement. That is why we also agree with Dr. Makary's decision to add more patients and caregivers to AdComms. For example, both Ajay Sampat, MD and Michael Robinson, MD are physicians with ALS. Before their diagnoses, Ajay was a Professor of Neurology and Michael was a Clinical Research Physician with Eli Lilly and later, the VP of Global Therapeutic Areas at AbbVie. Both were eminently qualified personally and professionally. Neither was chosen. They would not have missed this mischaracterization of ALS trial design.

Third, at the time of the Type C meeting, the Office of Tissues and Advanced Therapies (OTAT) was headed by a neurologist Dr. Wilson Bryan. Before joining the FDA in 2000, Dr. Bryan practiced for 13

years as a neuromuscular specialist and clinical investigator. It was incumbent upon him to understand the disease, the flaws in the COA, and barriers in ALS trial designs.

Fourth, it is also disappointing that not one of the six neurologists on the AdComm offered the insights explained by neurologist Dr. Goyal on this October 2020 webinar (1:05:10). The study cited above had been available for two years. But this shouldn't be something that neurologists have to research. It's fundamental to understanding ALS and ALS clinical trials.

For example, in a blog summarizing ALS clinical trials, in August 2023 – one month before the NurOwn AdComm – neuromuscular specialist Dr. Danielle Geraldi-Samara stated: *"the research community knows that it's easier to detect a signal in fast progressors in short six-month trials."* Dr. Geraldi is a practicing ALS clinician not a researcher who specializes in clinical trial designs. Nonetheless, she knew why her slower progressing patients couldn't qualify for trials as she helped explore EAP options for them. One of the six neurologists on the AdComm should have corrected this inaccuracy about why short, six-month trials must exclude slow progressors from efficacy assessments.

Reinforcing the opinions expressed in the study and by both Dr. Goyal and Dr. Geraldi, Dr. Christina Fournier is a neurologist at Emory who is involved in designing alternative COAs like the ROADS assessment.[80] On this July 2022 webinar (42:35) with EverythingALS, she was asked how researchers deal with statistical outliers that have a slow decline over two or three years. She pointed out that it's a statistical strategy. If everyone that you enroll is progressing quickly, you can measure that treatment effect faster and in shorter trials that are less burdensome on the patients. She clarified:

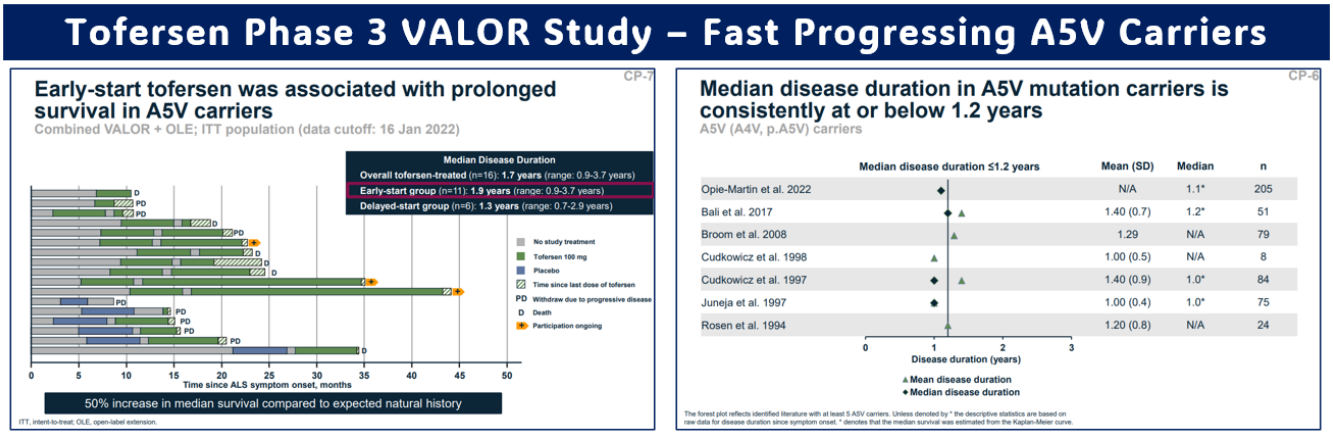
> *"In an ideal world, we would be able to just measure change faster so more people could be included, but we're just not there yet. The strategy, currently, seems to be to exclude slow progressors from the trial so that you can measure effects faster."*

Fifth, as Dr. Fournier also pointed out, MT Pharma's Edaravone and Amylyx studies excluded slow progressors. CDER was not troubled by this and nonetheless approved both. Edaravone was approved the year before Brainstorm started enrolling its Phase 3 study, with the NurOwn study design that CBER criticized.

Sixth, Biogen affirmatively included and analyzed a subgroup of 16 fast progressors (SOD1-A5V carriers) for its survival analysis of Tofersen. CDER properly assessed those data and Tofersen was approved in 2023. (See Biogen's Presentation CP-6, 7). (FDA's Tofersen Brief pg. 55-56).

[80] In this NEALS webinar, Dr. Fournier explains the ROADS clinical outcome assessment.

Graphic - Tofersen's Phase 3 Survival Data in A5V Rapid Progressors



If it's appropriate for Biogen to analyze a 16-person subgroup of fast progressors in a Phase 3 efficacy study (and we agree that it was), then it's appropriate for Brainstorm to do so in a 21-person subgroup in a Phase 2 dosing study.

Finally, the FDA's statement is highly prejudicial and not at all probative. And once a perception is established in the minds of decision makers, it is hard to un-ring the bell. How many people on the FDA's pharmacology, statistical or clinical teams were misled by this ill-informed characterization of the NurOwn data and trial design dating back a decade?

It is especially troubling because presumably PI Dr. Merit Cudkowicz explained to the FDA at the Type C meeting in 2019 just as she did to this reporter in 2016. When asked about "rapid progressors," who had an overall response rate far superior to the "slow progressors," Dr. Cudkowicz explained why slow progressors may not show a response in a short trial six-month:

> *"These are the patients that we can show a benefit in for such a short trial. It is easier to show a benefit in a population with a rapid progression compared to a patient that does not change. So, there may not be anything from a mechanism standpoint with these patients, it's just the fact that to show a difference, a patient needs to have a change in status."*

And yet, the FDA persisted in adding this mis-informed commentary to its 2023 Briefing Document, demonstrating its ongoing prejudicial impact.

H. NurOwn Phase 3 Petitioners with Real-World Evidence

1. Matt Klingenberg - Phase 3

Matt was a participant in the NurOwn Phase 3a trial at Mayo Clinic. Neurologists Anthony Windebank and Nathan Staff were the principal investigators at this trial site. Matt received 3 doses in the trial in 2019 and an additional 6 doses in the EAP. During and after the Phase 3 trial, Matt had 20 months of "progression-free survival." Four days after his fourth dose in EAP in May 2022, Matt proclaimed with excitement: ***"My body feels whole! I feel like my body is working again."***

Matt grew up in a small farming town in Iowa. In high school, he was a multi-sport athlete particularly excelling in wrestling. Throughout those early years, he sustained repeated sub-concussive hits in his athletic career.

Matt's ALS symptoms began in November 2017 with onset in his non-dominant left hand. Like many others with ALS, before his diagnosis, Matt repeatedly prayed that he had a less ominous diagnosis like brain cancer, not ALS. Ultimately, his prayers weren't answered as he was diagnosed in March 2018 in Iowa, then received a confirmatory opinion from Mayo Clinic.

Matt began the NurOwn trial shortly after diagnosis. His three trial doses of NurOwn ended in June of 2019. Only his close family knew of his ALS as his symptoms were not visibly obvious and he had not progressed. He was doing so well, the tragedy of the disease was buffered by the lack of progression news. Exemplifying this present-sense impression, on January 4, 2020, Matt's mother, Mitze, wrote to friends to share the news.

> *"Our Matthew has been diagnosed with ALS (Lou Gehrig's). He began having symptoms in late 2017, diagnosed March of 2018. It is limb onset so his hands aren't working very well - but are still working…. His progression is very slow, and for that we are grateful…. He was diagnosed at U of Iowa with a second opinion at Mayo, Rochester. He participated in a clinical trial up there last year. For a long time we didn't say anything because he was doing so well and now we're telling people for the same reason - he's doing well and it's so good to be able to say that."*

Because of NurOwn, Matt was doing so well that he continued to work as an agricultural scientist. With his master's degree in horticulture and growing up in a farming family, Matt continued that lineage by operating a 700-acre research farm for the largest American agriculture company. He spent his days inspecting corn fields. He didn't go on disability until April 2021.

Ultimately, after a year and a half without NurOwn on the anticipated dosing schedule, Matt's progression resumed. But it was cyclical. When he got NurOwn, he improved. When he didn't, he declined.

Despite the gaps in treatment,[81] each time Matt received NurOwn, he halted his ongoing paralysis, regained some function, and experienced extended slowing of his symptoms. NurOwn helps Matt live longer and live better.

During screening for the NurOwn trial in 2019, participants had to be losing 1 point per month to qualify. Yet when Matt finished both rounds of EAP, his ALSFRS-R score still remained 39 on the 48-point scale. **In the 5 years from symptom onset in 2017 until the end of EAP in 2022, Matt lost only 9 points. This equates to a loss of 0.15 points per month instead of the average of 1 point per month.** Because NurOwn slowed his progression, ultimately, **Matt has lived 91 months "trach-free" – 3x the ALS natural history.**

Matt submitted a Public Comment on the docket for the NurOwn AdComm. Others in his family are health care professionals and they too also submitted Public Comments, including his wife and his sister – both of whom have their Doctorates in Physical Therapy, as well as his mother, Mitze Klingenberg who spent 40 years working as a psychiatric nurse. All observed that NurOwn improved how Matt felt and functioned.

Matt and Mitze also spoke at the AdComm. They showed a few videos and Mitze's Public Comment also hyperlinked to multiple videos on her YouTube channel that illustrated the positive changes Matt experienced on NurOwn. Compare the videos of Matt walking up the stairs in September 2021, after doses #4-6, and then 7 months later in April 2022. Remarkably, Matt was still able to climb stairs 4+ years after symptom onset – demonstrating the durability of NurOwn treatments.

After an 8-month gap in EAP dosing, Matt's 7th dose was on May 20, 2022. Compare Matt's gait in the videos from May 19th, May 27th versus May 29th. Matt was walking heel-to-toe, which demonstrates an improvement in his drop foot. **Matt's improvement was so obvious that his 6-year-old son proclaimed: *"Dada's walking better!"***

Later that summer, after NurOwn dose #8, Matt went on vacation with his family. He was able to toss rocks off the creaky bridge with the boys and teach the kids how to putt -- nearly 5 years after symptom onset. This is not typical ALS progression! In other videos, you can see Matt:

- Raising his arms higher above his shoulders, which makes grooming oneself easier – but the ALSFRS-R remained a '2' as he continued to "need intermittent assistance"
- Bending over to pick up a leaf – but the ALSFRS-R didn't change as balance isn't assessed
- Sitting up unassisted from a lying position – but the ALSFRS-R didn't change

Exemplifying the long-term impact of NurOwn, 90 months after symptom onset, Matt still has some function. He has leg strength and can still stand to transfer. Although he can no longer lift his arms

[81] There was a 25-month gap between Matt's last trial dose and doses 4-6 in beginning in June 2021. Then again, there was an 8-month gap before he received doses 7-9 in beginning in May of 2022. He has been unable to receive any more doses of NurOwn in the last 32 months. Because there was no OLE and the drug sponsor cannot continue to manufacture the cells, in total, Matt has missed 30 doses in the every two-month dosing schedule.

overhead and is dependent on others for most ADLs, he does have some use of his fingers that enables him to maintain his independence by operating his wheelchair, a remote, and a gaming device to play with the kids, Mason, James, and Aubrey. Although he has a feeding tube to augment caloric intake, he maintains some bulbar function: he is able to eat, drink and speak – reading books to the kids, cheering them on at soccer games, and giving them fatherly wisdom. His respiratory function is declining, but he still only uses an NIV at night as needed.

Just this month, Matt saw his treating neurologist Nicholas Purcell of Avera Neurology, a neuromuscular specialist in Sioux Falls, SD who is unrelated to the NurOwn trial. In relevant part, Dr. Purcell's notes reflect Matt's decline without NurOwn since 2022.

- Continues to require assistance with almost all ADLs
- Severely limited mobility
- Able to use PWC and occasionally help with transfers due to spastic leg weakness.
- Using BiPAP each night.
- **ALSFRS-R 17. FVC 46%**

Matt's mother Mitze continues to fight for her son's life. She has repeatedly said their entire family knows NurOwn helps Matt "live longer and live better," and they feel a moral obligation to help everyone else get the same benefit that Matt was blessed to receive.

Mitze continued Matt's advocacy by submitting a Public Comment at the FDA's Listening Session: *Optimizing the FDA's Use of and Processes for Advisory Committees"* on June 13, 2024 speaking (at 1:10:55). Her topic was the "Public Perception and Understanding of Advisory Committees." Mitze also shared Matt's story at the 2025 ASCPT Conference. The session was entitled: *"Exploring Expanded Access: Balancing Patient Needs and Regulatory Considerations."* She shared Matt's story and how their real-world evidence of efficacy was disregarded at the NurOwn AdComm. She knows the AdComm members and decision-makers at the FDA didn't watch the many videos of evidence documenting Matt's improvements as their YouTube page shows only a few views – far less than the number who participated on the AdComm or were on the review team at CBER.

Matt was diagnosed with ALS at just 32 years old. He is a husband and father of three young children. Today he is 39 years old. He is fighting to squeeze more years out of life so his kids will remember their Dad when they grow up.

2. Eric Stevens – Phase 3

Eric was a participant in the NurOwn Phase 3 trial and first round of EAP at Cedars-Sinai. Initially the principal investigator was neurologist Dr. Robert Baloh. Eric then completed the second round of EAP at University of California at Irvine with neurologist and principal investigator Namita Goyal. Eric received 3 doses in the Phase 3 trial from February 2020 through June 2020, and additional doses in the EAP in 2021 and 2022.

Eric sustained multiple concussions and repeated sub-concussive hits in his athletic career. He played football and wrestled in high school then went on to play fullback in college for the CAL Bears where he was a team captain and earned the Joe Roth Award for courage and sportsmanship. In 2013, Eric was signed by the St. Louis Rams as an undrafted free agent but suffered more injuries and concussions.[82] He also experienced repeated sub-concussive impacts in a lifetime of surfing and riding motorcycles.

Eric's ALS symptoms began in March 2019 with bulbar symptoms and onset in his non-dominant left hand. Eric recounts:

> *"I was feeling kind of a weakness in my left hand. Obviously as a Firefighter you're using your hands all the time; you're picking up tools, picking up gurneys. You're constantly working with your hands. You're also working out all the time trying to stay fit. And because previously, as an athlete … Everything I've done has been working out or trying to stay fit. You're pretty in tune to your body. So you know right away when something's not working right."*

[82] Fox Sports West. (2020, March 24). Eric and Amanda Stevens are looking to axe ALS [Video]. YouTube.

Before he was a trial participant, Eric shared how it feels to NurOwn was helping some people and ALS patients can't get to it:

> *"There's something out there that's actually helping people and you can't get it. It's crazy. So I think after this appointment, we're gonna fight for that. The one guy who's getting it right now outside the trial was in a wheelchair and on a breathing machine. And since he's been getting the treatment, he's been able to stand on the wheelchair on his own; he's off the breathing machine and he's able to ride a bike.… We don't have access. You don't have access to this treatment unless you're picked for the trial and then, even then, you don't know if you're actually getting it. It's already been through phase one; it's already been through phase two so they know it's safe for use and they know that it works…. Yet we can't get to it. ALS patients can't have it.*
>
> *I don't understand why we can't have access to these treatments. I understand that research has to be done. I respect the process but when you're dealing with a terminal diagnosis, why is it the same process as a treatment for say arthritis? ALS, it's a 100% chance that you're gonna die from ALS. That's fact. I don't think anyone is expecting to find this magic cure. I think people just want hope and they want a treatment. There's no cure for HIV. There's no cure for cancer. There's excellent treatment options, and I think with these treatments that are on the horizon and almost available, the people in the ALS Community just want access."*

Ultimately, Eric was diagnosed in September 2019 and began the NurOwn trial shortly after diagnosis. Initially a fast progressor, Eric was losing almost 2 points per month on the 48-point scale, and he was on a 2-year trajectory to death or tracheostomy.[83] On the day of his first EAP injection in March 2021, Eric's baseline score was 37. At his third EAP dose, his score was 39. He had gained 2 points. Eric's PT notes in May 2021 noted an improvement after just one dose in EAP:

> *"Mr. Stevens is a 31 y.o. male who was diagnosed with ALS in August of 2019. Pt is currently participating in a NurOwn trial, which has a series of 3 injections. Pt received his first injection in March and since then,* ***pt demonstrates improvement in strength, balance, and speech. His voice sounds louder and more clear****. Pt Pt will be getting the second injection on May 25, 2021. Pt is not using an assistive device for mobility."*

And again after the second dose, his PT documented more objective improvements!

> *"Pt is participating in a NurOwn trial and received his second injection on May 25, 2021. Since his second injection, pt has* ***maintained his strength*** *since previous progress note, but has* ***improved his balance significantly****."*

[83] Eric has a mutation in the CAMTA1 gene, which is not causative but which is associated with a reduction in survival.

When he finished the second round of EAP in 2022, Eric's ALSFRS-R score still remained a 34 on the 48-point scale. NurOwn helps Eric live longer and live better. Despite gaps in treatment,[84] each time Eric received NurOwn, he halted his ongoing paralysis, regained some function, experienced improvement of his symptoms, and has benefited from "progression-free survival." Following are Eric's scores that they tracked personally during the NurOwn trial.

Graphic - Eric's Phase 3 and EAP Data[85]

Phase 3 Trial & EAP1				
Visit	Visit	ALSFRS-R	Date	Comments
P3	1	?		
P3	2	47	8-Oct-19	
P3	3	42	7-Nov-19	
P3	4	?	17-Dec-19	
P3	5	42	12-Feb-20	NurOwn #1 injection
P3	6	40	25-Feb-20	
P3	7	41	10-Mar-20	
P3	8	43	1-Apr-20	NurOwn #2 injection
P3	9	41	29-Apr-20	
P3	10	?	4-Jun-20	NurOwn #3 injection
P3	11	41	1-Jul-20	
EAP	1	38	17-Feb-21	Screening
EAP	2	37	30-Mar-21	EAP 1st injection
EAP	3	38	25-May-21	EAP 2nd injection
EAP	4	39	27-Jul-21	EAP 3rd injection
EAP	5	37	24-Aug-21	Follow-up

Eric was a fast progressor before NurOwn. He is a carrier of a CAMTA1 mutation that causes faster progression; he also had onset in two regions: upper limb and bulbar. Onset in 2 or more regions is also an indicator of faster progression. Before NurOwn, he lost 5 points in 4 months. This equates to 1.25 points per month.

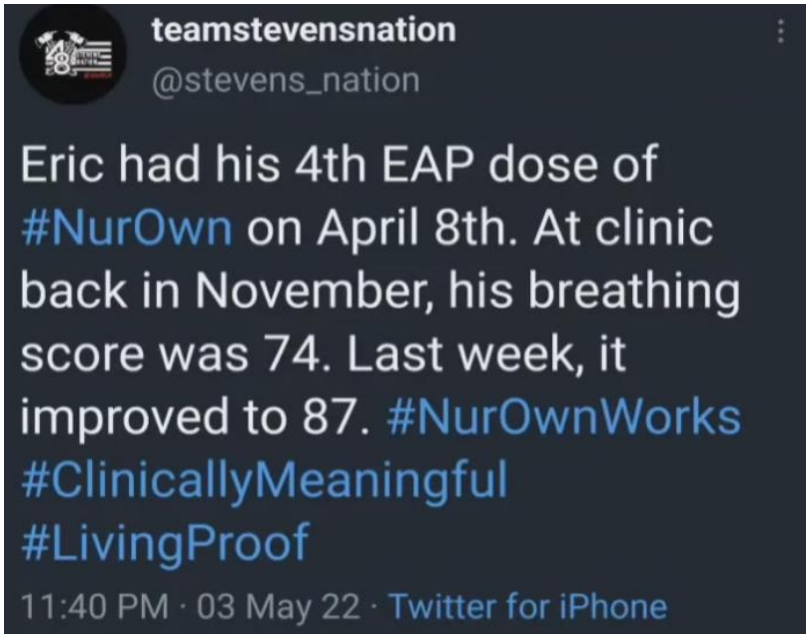
[84] His 3 trial doses of NurOwn ranged from February 2020 through June 2020. There was a 9-month gap between his last trial dose and doses 4-6 in EAP beginning in April 2021. Then again, there was a 9-month gap before he received doses 7-9 in EAP beginning in 2022. Eric has been unable to receive any more doses of NurOwn in the last 33 months. In total, Eric has missed over 20 doses in the every two-month dosing schedule.

[85] Eric's wife Amanda was the one tracking his ALSFRS-R scores. During Round #2 of EAP, she was a new first-time mom, having just given birth to Peyton. She did not track his scores during the second round of EAP.

During the NurOwn Phase 3, Eric's progression came to a near screeching halt on NurOwn. His baseline score was 42 and it stabilized at 41. He only lost 1 point from baseline in the trial. His rate of progression slowed dramatically to 0.20 points per month. In the gap between the Phase 3 and EAP, it rebounded to 0.43 per month. Then with 3 more doses in the first round of EAP, it again slowed to 0.16 per month. It has never returned to the original fast progression.

This was a large magnitude and immensely beneficial 1.05 point delta. But this classified him as a non-responder on the Primary Endpoint.

Even though he was a fast progressor and had early bulbar symptoms, Eric didn't start using a bi-pap for 38 months – this was **2.5x longer than average time-to-NIV** in ALS natural history for fast progressors. As of June 2025, **Eric has lived 75 months "trach-free" – more than 2.5x longer than ALS natural history.** Here's a post from their social media account showing Eric regained points in respiratory function on his FVC as well:



Eric's Public Comment shared both clinical and real-world evidence demonstrating that NurOwn improved how he felt and functioned:

> *"Even though I had upper limb onset, I was still able to use the dexterity of both hands to tie a bow, peel open a Reese's peanut butter cup, turn pages in a book, use the TV remote, text, bathe, shave, and eat with a fork and spoon. I was eating a normal diet. My speech remained loud and clear. NurOwn also changed my symptoms (how I felt). Each time I got NurOwn, my fasciculations decreased and I had less painful cramping."*

Eric and his wife Amanda ("Team Stevens") have been fighting for changes in FDA's policies for six years. In November 2019, the Daily Breeze published a story entitled: *"Ex-NFL star Eric Stevens battles ALS and finds hope in a new stem cell-based treatment.*" In it Eric pleaded for access:

> *"When you get a terminal illness like this, obviously a cure would be the best case scenario. But what you really want is just a chance to fight it, a chance to live. Treatment is all we ask for. There's a chance-for the first time ever, to help people with ALS…. It's there. It's right at our door. It's so close, but unfortunately 'so close' is years away, and years are something that we don't have."*

In 2020, in her "Fight for Hope" TedTalk, Amanda Stevens posited a question: *"At what point does the scientific method surpass human compassion, decency, and common sense?"* In December of 2020, Team Stevens joined in publishing a video called "PALS: Counting the Days." Although the NurOwn trial had just recently ended, Eric already suspected NurOwn had worked on him:

> *"I don't know if I got placebo or the real stuff, because as you know it's a 50-50 chance of getting the actual drug. But I felt like* ***my progression within that time slowed down****. It's pretty scary, that feeling knowing that something was potentially helping you and now you can't get to it."*

When asked what needs to change, Eric and Amanda responded about the need for a new pathway for terminal diseases so the FDA urgency matches the speed at which ALS is killing people.

> *"A way to try to fix this is through policy change and you know right now a treatment for ALS, it goes through the same FDA pathway as medicine for arthritis, for a headache -- and this is a terminal disease. And* ***even if a cure was found tomorrow, it would be years and years before Eric or any ALS patient would even see it****…. "*

Accordingly, Team Stevens' family asked the FDA to act with urgency and treat ALS the same way that it treats other diseases -- similar to how the FDA rushed the approval of AZT for HIV in 1987; a cystic fibrosis drug in 2019; or the COVID vaccine in 2021. If the FDA can use the EUA pathway for COVID, a disease that, at the time, had a 2% case fatality rate, certainly it can use its regulatory flexibility for ALS, a disease with a 100% case fatality rate.

The Stevens' fight continued not just to change the approval pathway, but this time… just to be heard. In November of 2022, Stevens Nation issued a Press Release supporting Brainstorm's efforts to seek an Advisory Committee ("AdComm") meeting as they asserted: *"the FDA's position ignores the vast evidence of efficacy and denies both the company's and patients' rights of due process."*

Eric and his wife Amanda also spoke at the AdComm's Open Public Hearing. Eric shared that he was working as a firefighter for the City of LA when he was diagnosed with ALS. In his testimony, Eric challenged the FDA and expounded on the firefighter's credo that you ***"risk a lot to save a lot."***

"As a firefighter, I took an oath to 'Protect and Serve.' I laid my life on the line every day for others. I ran into burning buildings putting others' lives before mine. As doctors, you took a similar oath to "Do No Harm.' I'm asking you to remember that oath, listen to my testimony and that of our neurologists. Then act with the same urgency as I did when I ran into a burning structure. I am not asking you to risk your life for me... like I did for others. ***I am simply asking you to not stand in the way of getting more of the drug that is helping me live.“***

Eric was diagnosed with ALS at just 28 years old – a few weeks after his wedding and honeymoon. Today, the father of two young kids, Eric knows NurOwn helps him “live longer and live better.” He is fighting for a chance to spend more time with his four-year old daughter Peyton and his one-year-old son Dean.

3. <u>Josh Smith - Phase 3</u>

Josh was a participant in the NurOwn Phase 3 trial with world-renowned neurologist Dr. Robert Brown, who was the principal investigator in both Phase 2 and Phase 3 at the University of Massachusetts Chan School of Medicine (“UMass”). Josh received 3 doses in the trial in September 2019 through January 2020, and an additional 6 doses in the EAP in 2021 and 2022.

Josh, Dr. Brown and Josh's local neurologist all believe NurOwn helps Josh live longer and live better. Josh told the FDA: ***"I am Living Proof of the success of this therapy."***

The only son of Paula and Randy Smith, Josh grew up in Brick Township, New Jersey. His life was all about football. He both played football then went on to coach kids after college. Throughout his football career, he sustained repeated sub-concussive hits. After college, he joined his Dad working in the family's construction business.

Josh's ALS symptoms began in June 2018 with onset in his non-dominant left hand. He was diagnosed in March 2019. Josh began the NurOwn trial shortly after his ALS diagnosis with his first dose in September 2019 and his last EAP dose in August 2022. Josh's three trial doses of NurOwn ended in January of 2020.

Despite gaps in treatment,[86] each time Josh received NurOwn, he halted his ongoing paralysis, regained some function, experienced slowing of his symptoms and "progression-free survival" because of NurOwn. At the start of his NurOwn dosing, Josh's baseline ALSFRS-R score was above 40 on the 48-point functional scale. When he finished both rounds of EAP, his ALSFRS-R score still remained a 34 on the 48-point scale. And it remained there for nearly one year of "progression-free survival." Because NurOwn slowed his progression, ultimately, **Josh has lived 83 months "trach-free" – nearly 2.8x the ALS natural history.**

Before NurOwn, Josh was an "average progressor." NurOwn changed that trajectory.

- Before the NurOwn trial, Josh had lost 8 points in just 9 months (0.89/month).
- During the NurOwn trial, his losses slowed to 3 points in 6 months (0.5/month).
- After receiving just 9 doses in the NurOwn trial and EAP, his overall progression slowed to approximately 7 points every 48 months (0.15/month)

[86] There was a 15-month gap between his last trial dose and doses 4-6 in EAP beginning in April 2021. Then again, there was a 10-month gap before he received doses 7-9 in EAP beginning in May of 2022. Josh has been unable to receive any more doses of NurOwn in the last 32 months. In total, Josh has missed ___ doses in the every two-month dosing schedule.

This benefit equates to only 1.75 points per year instead of the average of 12 points per year. This is a 91% slowing compared to average or an 83% slowing compared to pre-treatment slope.

In his Public Comment, Josh shared both clinical and real-world evidence of NurOwn's efficacy:

> *"NurOwn works. I stabilize when I receive it. I decline when I don't. The ALSFRS scale is how clinical trials measure function in ALS. People with ALS lose an average of 1 point a month on the ALSFRS scale. In the 4 years from June 2019 to 2023, I only lost 7 points – declining from a 40 to a 33.* ***This 7-point loss in 48 months equals 0.15 points per month****. NurOwn drastically slowed my decline….*
>
> *Confirming my own observations were the opinions of my local neurologist, Dr. Klinov. My third dose of NurOwn in EAP was July 20, 2021. I saw Dr. Klinov one week later, on July 26, 2021. He conducted muscle testing, and most of my scores remained at 5/5 or 4/5. This is an excerpt from his clinical notes:"*
>
> > *'Joshua Smith is 32 y.o. male patient with PMH of ALS. Patient was* ***diagnosed about three years ago****.* ***No significant progression*** *noted on exam…. In my opinion, there has been no progression of ALS since my last visit. If anything, there is* ***some improvement in strength*** ***in both upper extremities & proximal muscles****. There is some weakness which mildly progressed in distal muscles in both upper extremities. I strongly recommended for him to continue stem cell infusion as the patient has been generally stable.'*
>
> *"To this date, Dr. Klinov continues to believe that NurOwn works on me. I do too."*

Josh's treating neurologist, Dr. Klinov, also submitted a Public Comment with clinical data and opinions about how NurOwn impacted Josh's ALS progression, symptoms and function. For example, ***"before the trial, Joshua had difficulty ambulating and used a cane and then a walker to assist him. In April of 2021… he was able to ambulate without any assistance at all."***

Other clinical observations included:

- fasciculations nearly completely resolved
- muscle stiffness improved
- ambulation improved
- muscle strength in both his upper and lower extremities improved
- QOL improved significantly
- Respiratory function improved
- No significant progression in his symptomatology through 2022

In contrast, Dr. Klinov's Public Comment compared what happened when Josh stopped receiving NurOwn:

> ***"Joshua's ALS progression halted while receiving the stem cell therapy****….*
> *He had his last treatment in August 2022. Since then, he has lost his mobility to walk, his strength in his upper extremities have weakened to the point where he cannot raise his arms over his head. He has to have constant care at home to be bathed, dressed, etc. I can conclude that when Joshua was in the Nurown trial, the disease progression significantly slowed down and he even had some improvement, and since the infusions were halted he has declined tremendously. At this point, in my professional opinion, Nurown trial has given Joshua a quality of life that was unexpected but proved to be* ***giving him more years to enjoy life****."*

Josh's Public Comment also hyperlinked to multiple videos on the family's SmithStrong YouTube channel that demonstrated the clinically meaningful changes Josh experienced while receiving NurOwn. In one video, he was climbing into his Jeep on his tiptoes 30 months after symptom onset – something you cannot do with drop foot.

In the other videos after EAP started, Josh could still walk down slippery rock steps at a waterfall (3 years after symptom onset) and walk down steps in front of his home (4 years after symptom onset). Other videos document him cutting his own food, cutting the lawn, and throwing the ball to his dog. In one video, he is swinging on a playground swing, demonstrating retained muscle strength in both his hands and core, then he hollers out ***"How's that for NurOwn!"***

Today, Josh is still walking (shuffling), feeds himself, and refuses to sit on the wheelchair. He tells his mom that once he starts sitting in a wheelchair, he knows he won't be getting out. The time-to-event data shows that the average time until use of a wheelchair is 14 months for fast progressors and 29 months for intermediate progressors. **Josh is 84 months past symptom onset – 6x longer than time-to-wheelchair natural history.** Significantly, Josh still does not use any non-invasive ventilation to breathe!

Below is a summary of Josh's real-world data from his own notes and from clinical records – outside the trial – with Dr. Klinov and other neurologists and pulmonologists. Dr. Klinov does not use the ALSFRS-R. This was filed as an Exhibit to his Public Comment before the AdComm. And after the AdComm, Dr. Brown did confirm Josh did receive NurOwn in the trial – just as he and his mother had advocated for years.

Graphic - Josh Smith's Real-world data

JOSH SMITH - Phase 3 NurOwn Trial & EAP Participant						
ALSFRS	FVC	Date	What Happened	Doctor	Clinic	
		01/02/19	1st Neurology Appointment	Klinov	South Ocean Medical - Neurology	Diagnosis
		02/25/19	EMG		SOCH	
		03/01/19	Suggested ALS	Klinov	SOMG	
		04/03/19	Confirmed ALS	Leich	Rutgers University	
		05/13/19	NurOwn Trial Screening	Bob Brown	UMass	Screen
		05/19 - 08/19	Run-In	Bob Brown	UMass	
40		06/05/19		Sedarous	Jersey Shore ALS Clinic	
		08/20/19	Bone Marrow Aspiration	Bob Brown	UMass	
40		09/24/19	Trial Dose #1 = Baseline	Bob Brown	UMass	Dosing
39		10/28/19		Sedarous	Jersey Shore ALS Clinic	
39		11/20/19	Trial Dose #2	Bob Brown	UMass	
41		01/14/20	Trial Dose #3	Bob Brown	UMass	
41		01/20/20		Sedarous	Jersey Shore ALS Clinic	
39		07/10/20		Sedarous	Jersey Shore ALS Clinic	
	64%	08/21/20	Pre-EAP Assessment	Kamel	Ocean Pulmonary	
37		04/06/21	NurOwn Dose #1	Bob Brown	UMass	EAP #1
36		06/02/21	NurOwn Dose #2	Bob Brown	UMass	
36		07/20/21	NurOwn Dose #3	Bob Brown	UMass	
		07/20/21	Last EAP visit in Round #1	Bob Brown	UMass	
	104%	08/25/21	Post-EAP Assessment	Kamel	Ocean Pulmonary	
	87%	02/03/22	Pre-EAP Assessment	Kamel	Ocean Pulmonary	
33		05/12/22	NurOwn Dose #4	Bob Brown	UMass	EAP #2
		05/25/22		Kamel	Ocean Pulmonary	
34		06/22/22	NurOwn Dose #5	Bob Brown	UMass	
		07/14/22		Klinov	SOMG	
	86%	07/20/22		Kamel	Ocean Pulmonary	
		08/17/22	NurOwn Dose #6	Bob Brown	UMass	
		10/13/22	Neurologist	Klinov	SOMG	No NurOwn
	92%	10/24/22	Pulmonologist	Kamel	Ocean Pulmonary	
		02/07/23	ALS clinic	Heiman-Patterson	Temple ALS Clinic	
34		02/14/23	Neurologist	Geraldi-Samara	Synapticure	
34		04/20/23	Neurologist	Geraldi-Samara	Synapticure	
33		06/29/23	Neurologist	Geraldi-Samara	Synapticure	

Josh was diagnosed with ALS at just 28 years old. Today he is nearly 36 years old and still fighting for his life. Several years ago, he told a local news station: ***"If you got into a trial knowing that this drug might not work but there's a 35% chance it does work...of course you're going to take it. <u>That's common sense</u>."*** Now Josh needs the FDA to use common sense and give him access to therapy that is helping him live longer and live better**.**

4. Estate of Roberto Muggli - Phase 3 - (Dec 2, 1974 - May 2, 2023)

Roberto is represented by his widow Shelly Goettl. He was a participant in the NurOwn Phase 3a trial at Mayo Clinic with neurologists Anthony Windebank and Nathan Staff. Roberto received 3 doses in the trial and an additional 6 doses in the EAP in 2021 and 2022.

In 2017, Roberto was diagnosed by neurologist, Roberto Vargas Howell, in Costa Rica. Later, he traveled to Minnesota and the diagnosis was confirmed in May 2018 at Mayo. During the trial and after each EAP treatment, Roberto's progression halted and he regained some function. When he began the trial, Roberto's baseline ALSFRS-R score was above 40 on the 48-point functional scale. During the trial, Roberto was in the subgroup of trial participants -- earlier in ALS progression – where the clinical data met statistical significance on both the trial's primary and secondary endpoints.

Roberto's symptom onset was in his dominant right hand. During the NurOwn trial, Roberto had "zero progression" in his right hand and arm. As of September 2019, his ALS still had not progressed beyond his right arm. In an interview with a fellow trial participant, Roberto stated:

> *"There is definitely something with NurOwn. I've seen it and just the fact that **in the last 7 months, I haven't progressed** is huge. There is hope out there. I just hope that it will be approved for the current patients with ALS."*

In October of 2019 – eight months after his first trial dose -- Shelly filmed Roberto taking batting practice with the grandkids. Even with onset in his dominant hand, you can see he is still able to grip the bat and swing it repeatedly. You will also notice he has no impairment in his voice, core, or lower limbs. In May 2020, he posted the video to his private Youtube page announcing: ***"This is what ALS in remission looks like!"***

This was documentation of his **function 2.5 years after his ALS diagnosis**.

Roberto's survival data is compelling. Although he chose not to use a non-invasive bi-pap to assist with breathing and expelling CO2, he nonetheless **lived "trach-free," for 60 months – 30 months longer than ALS natural history.** And likewise, without any non-invasive ventilation for 60 months – he lived **4x longer than natural history for time-to-NIV**.

During the significant gaps when Roberto couldn't receive more NurOwn, he declined in function. Despite these gaps in treatment, each time he received NurOwn, Roberto regained some function, experienced slowing of his symptoms, as well as months of "progression-free survival" because of NurOwn.

Because he experienced NurOwn's clinically meaningful benefit during the trial, Roberto wanted more in EAP. Thus, despite living in his native Costa Rica, Roberto and Shelly flew the exhausting multi-day trip from their home in Costa Rica back to Minnesota. And even in an advanced stage, when ALS had robbed him of all upper limb function, when he received NurOwn during EAP, he regained the ability to move his fingers. While this may not seem clinically meaningful to people without ALS, it was profound for Roberto as it allowed him to operate his own wheelchair and joystick – maintaining some independence. When Roberto finished both rounds of EAP, in 2021 and 2022, his ALSFRS-R score was below the threshold that met statistical significance but NurOwn still improved his function in clinically meaningful ways.

Roberto's widow documented these and other changes in his Public Comment for the NurOwn AdComm. It hyperlinked to multiple videos on their YouTube channel and social media comments that affirmed contemporaneously, the clinically meaningful benefits that Roberto experienced -- both early in ALS progression during the trial and later in ALS progression during EAP. Roberto's widow was **not** chosen to speak at the AdComm on September 27, 2023.

Ultimately, Roberto lived 71 months both NIV-free and trach-free. That is over 4.7x longer than Time-to-NIV natural history for ALS. It is also 41 months longer (2.3x) than the natural history for median trach-free survival in ALS. NurOwn gave him that chance.

Although Roberto knew that NurOwn helped him "live longer and live better," he forecasted that he would die waiting for NurOwn to be approved. Sadly, his worst fears came true. Roberto died on May 2, 2023.

5. Estate of Kade Simons - Phase 3 - (Aug 10, 1997 - August 4, 2024)

The Estate of Kade Simons is a Petitioner represented by his mother Kandy Simons. Kade received three doses of NurOwn in Phase 3a trial at Mayo Clinic with neurologists Anthony Windebank and Nathan Staff. NurOwn worked on Kade and he could feel the impact almost immediately. But he was not one of the ten people chosen to receive additional doses via EAP.

Kade was diagnosed with juvenile-onset ALS (jALS) at just 21 years old. He was also a carrier of a variant of uncertain significance ("VUS") in the SETX gene (c.3187A>G). Kade's variant is not listed on ClinVar, but other SETX variants are associated with juvenile-onset of ALS.[87]

When his mom was pregnant with Kade, they lived in Cottonwood Canyon, Utah where his dad played for the Twins' Triple-A club, the Salt Lake City Buzz. Kade was a natural athlete from the moment he was born. He was walking by seven and half months and hitting the ball off the T by 2 years old. Kade spent his youth rolling around on the grass at minor league baseball fields where his dad played for eleven years.

Like his Dad, Kade was a multi-sport athlete. He wrestled, played wide-receiver and cornerback in football, and centerfield in baseball. Before the eighth grade, Kade had already sustained stingers and two concussions playing football. After that he focused on baseball year-round and in baseball, he excelled. In high school, Kade was on the Oklahoma state All-Star team, ranking 14th overall and 4th in Oklahoma among all outfield prospects. Ambidextrous, Kade batted left and threw right.

Kade's speed from home-to-first was considered "elite."[88] On the diamond, Kade was the lead-off hitter and known for lightning fast speed and his laid out, diving catches. But that rough and tumble

[87] Kade's SETX mutation is a variant of uncertain significance. A different variant of SETX causes ALS-4, a subtype of ALS that causes juvenile-onset. Neuropathological characterization of SETX mice revealed nuclear clearing of TDP-43, accompanied by TDP-43 cytosolic mislocalization, consistent with the hallmark pathology observed in human ALS patients.

[88] Statcast defines "elite" times as those below 4.2 seconds. Kade's college speed rivaled him with MLB players like Diamondbacks' CF Corbin Carroll (4.06), Royals' SS Bobby Witt Jr (4.05), Mariners' Ken Griffey Jr (4.10), A's LF Rickey Henderson (4.05), and Angels' CF Mike Trout (4.2).

athleticism also led Kade to multiple injuries, and dozens of broken bones, including a spontaneously fractured right humerus when he was throwing a baseball from centerfield in the spring of his freshman year. He also sustained multiple concussions and repeated sub-concussive hits throughout his career.[89]

Playing his second year of college baseball, Kade's first symptoms were on the diamond, just as it had been for Lou Gehrig. His bat speed slowed and his timed speed from home-to-first base was one-half second slower. He initially noticed onset in his dominant right hand and right leg, and by May it started to impact his speech. His initial symptom onset was in February 2018; he was diagnosed in December 2018, and then received 3 doses of NurOwn in July, September and November of 2019.

KADE SIMONS' ALSFRS SCORES IN NUROWN TRIAL				
TRIAL VISIT	DATE	DOSING WEEK	ALSFRS-R	COMMENT
	05/15/18		48	Symptom Onset - speed
	10/14/18			Italy Trip
	12/10/18			Diagnosis
1	03/19/19		36	Screening
2	04/18/19		34	Run-in
3	05/20/19		35	Run-in
4	06/12/19		33	Run-in
5	06/19/19		33	BMA
6	07/23/19	0	34	Baseline & Dose #1
7	08/08/19	2	33	
8	08/19/19	4	34	
9	09/19/19	8	33	Dose #2
10	10/16/19	12	32	
11	11/14/19	16	32	Dose #3
12	12/10/19	20	32	1 Years from Diagnosis
13	01/15/20	24	30	
14	02/17/20	28	28	Last NurOwn Trial Visit
	12/10/21		27	3 Years from Diagnosis
	03/15/23		21	Neurologist Visit

[89] Kade's autopsy showed early signs of changes consistent with CTE.

Before NurOwn, Kade was a "fast progressor." NurOwn changed that trajectory.

- Before the NurOwn trial screening, Kade had lost 14 points in just 8 months (1.75/month).
- During the NurOwn trial, his losses slowed to 3 points in 6 months (0.5/month).
- After receiving just 3 doses in the NurOwn trial, his overall progression slowed to approximately 1 point every 6 months (0.16/month) – a 91% slowing versus before NurOwn.

While not "progression-free survival," this marked slowing in lethal progression was life-changing.

Kade could tell immediately that NurOwn was working. Kandy's Public Comment hyperlinked to two videos where Kade commented on how he had regained function after just one NurOwn injection. In the first video in June 2019 – the day after his first dose -- he spoke about how his toes were "popping up," meaning his foot drop was improving. In the second video a few weeks later, he spoke about having to adjust to the increased strength in his previously weakening legs. Neither of those improvements resulted in any change in his ALSFRS-R score of '3' as he still had "early ambulation difficulties."

Kandy's Public Comment and testimony also shared other ways that NurOwn improved how Kade felt and functioned.

NurOwn Improved How He Functioned:

- Legs were stronger
- Able to climb stairs to his bedroom
- More balance when standing
- Able to effortlessly cross one leg over the other
- All gross and fine motor movements required less effort
- Foot drop improved with "toes popping up easier"
- Speech improved, and his words were easier to enunciate
- Grasped utensils and could direct them to his mouth without missing
- Texting was easier and writing remained legible

NurOwn Improved How He Felt (nothing on ALSFRS-R measuring symptoms)

- Muscle twitching stopped immediately after injection
- Significantly less spasticity
- Less clonus & cramping
- Full body improvements
- More ROM, loose & limber
- "Everything felt better"

Kade and his family weren't the only ones to witness these improvements. Kade was seeing a physical therapist, John Carey, who specialized in treating collegiate and professional athletes. John didn't know Kade had participated in a clinical trial. But when Kade returned in August 2019, John remarked that Kade's entire body was more stretchable, had more ROM and less spasticity.

Perhaps most importantly, NurOwn made a significant difference in Kade's respiratory function. Up until the day of his death, Kade didn't need a bi-pap to breathe. He slept lying flat on his back (4/4 points on the ALSFRS-R).

NurOwn didn't only impact Kade's phrenic nerve and diaphragm function, it unexpectedly improved his lung function. Kade had been a lifetime asthmatic, in and out of ERs since he was one-year-old. He regularly used albuterol and nebulizers. He needed albuterol so often that he kept it in his gym bag and in the dugout. But after receiving three doses of NurOwn in 2019, he seldom needed his albuterol again. Over the ensuing 5 years until his death in 2024, Kandy estimates Kade only needed his albuterol a total of 5 times. NurOwn's plausible mechanism of action also had a profound systemic biological impact on his asthma too.[90]

On September 28, 2021, Kade had his first and only visit with Dr. Frank Sorhage, a pulmonologist at the Holy Cross ALS Center of Excellence. Dr. Sorhage has 30 years of experience in critical care and has treated hundreds, if not thousands, of people with ALS. Upon assessing Kade's breathing function, Dr. Sorhage proclaimed:

> ***"Are you sure you have ALS? Your breathing is not typical for someone who's had ALS for 3 years."***

Ultimately, Kade decided he didn't want to attend a multi-disciplinary clinic. He didn't want to go to be reminded how fast he was dying. He was an athlete who knew his body. He didn't want a doctor to tell him what he already knew. He wanted a neurologist to give him the only thing that would make a significant difference in how he felt and functioned. If he couldn't get more NurOwn, he didn't want anything else.

But Dr. Sorhage was right. Kade lived 78 months without using NIV. This is **over 5x longer than the Time-to-NIV natural history for fast progressors.**

[90] MSCs are known to suppress excessive immune responses by modulating both innate and adaptive immunity. They can inhibit T-cell proliferation, reduce Th2 cytokine production (e.g., IL-4, IL-5, IL-13), and promote regulatory T cells (Tregs), which dampen inflammation. NurOwn's MSCs secrete growth factors that may also reduce airway inflammation by stabilizing endothelial barriers, reducing vascular permeability, and inhibiting pro-inflammatory cytokine production. HGF, secreted by NurOwn's MSCs, has been shown to inhibit fibrosis and promote tissue repair in lung injury models. MSCs secrete paracrine factors that may stabilize airway smooth muscle tone. For example, HGF and VEGF can modulate calcium signaling in smooth muscle cells, potentially reducing contractility. By reducing smooth muscle hyperresponsiveness, NurOwn could decrease the frequency or severity of bronchospasm, mimicking or complementing albuterol's broncho-dilatory effect. By reducing vagal-mediated bronchoconstriction, NurOwn could decrease airway hyperresponsiveness, reducing the need for albuterol to counteract parasympathetic-driven bronchospasm. Although NurOwn is administered intrathecally, MSCs and their secreted factors can enter systemic circulation or influence peripheral tissues via paracrine signaling. Systemic reduction of inflammatory mediators could decrease airway inflammation and eosinophil or neutrophil infiltration, stabilizing asthma symptoms and reducing reliance on albuterol for acute relief. This unintended impact is more evidence of the "plausible mechanism of action" of these mesenchymal stem cells supercharged with neurotrophic factors.

Despite the massive amount of evidence that NurOwn worked on Kade, Kandy Simons was only given 3 minutes to speak at the AdComm to advocate for her son's life. Kandy closed by pleading with the FDA.

> *"Four years ago, Kade gave his body to advance ALS science. It would be inhumane to now deny Kade's access to this drug because the FDA approval process didn't act as quickly as ALS is killing him… No mother should have to watch their child die when we believe a treatment is available to help him live a life worth living."*

Inhumane it was. Three months after this plea, Kade learned he did indeed receive NurOwn – just as he and his family had believed from his very first injection. Tragically, Kade died waiting for more NurOwn -- just six days before his 27th birthday.

Kade lived 78 months both NIV-free and trach-free. That is over 5x longer than Time-to-NIV natural history for fast progressors. It is also 48 months longer (2.5x) than the natural history for median trach-free survival in ALS. NurOwn gave him that chance.

Up until the AdComm, the day Kade was diagnosed with ALS was the worst day in Kandy's life. But the day of the AdComm was the second worst day. When she told Kade the news about the negative AdComm vote, Kandy saw the light go out in his twinkling blue eyes. He knew at that moment that he was never going to get NurOwn. After that, emotionally, Kade was ready to die.

Kandy did everything she could to keep Kade alive, but the FDA didn't do all it could.

So instead, Kade asked his Mom to arrange Medical Assistance in Dying (MAiD). A mother was forced to help her 26-year-old son make arrangements to end his life because the FDA wouldn't give him the therapy that he KNEW extended his life.

Under MAiD law, there are multiple requirements. One is that you must sign yourself attesting that this is your choice. But Kade couldn't sign his name so he held a Sharpie in his mouth to sign the "X." He also needed two witnesses to sign so Kade chose his Aunt Kathy and his Granny Kathy. But Kade didn't want them to feel the guilt of attesting to his suicide.

So, with wisdom far beyond his years, and in an ode to Lou Gehrig's speech, Kade typed this message using his eye gaze:

*"I have fought this for as long as I can. I am never comfortable or able to sleep well, and **I feel like I am buried alive all the time**. It's no way for my parents or my brother to live – and not for me either. Just be happy that I can painlessly choose where and when I want to end my life and also be happy that we all get to say goodbye to each other because very few people get that luxury in life. I will be with you guys always, and in a blink of an eye, we will all be together in a way better place. We are all good and loving people and will all go to the same place in the end. I'll get to meet Grandpa Jim and Grandpa Bill, Brucie and Memaw Kat, and many other people. Like it says in Shogun: 'We live and we die. It's what we do in the middle that counts.' I lived every day like it was my last. I got to do and see more than most people do in ten lifetimes. **I am the luckiest kid in the world**."*

6. Lesley Krummel - Phase 3

Petitioner Lesley Krummel was a participant in the NurOwn in Phase 3a trial at Cedars-Sinai with PI Bob Baloh. She received 3 doses of NurOwn in 2019, with the last dose on July 17, 2019.

In August 2017, Lesley's first symptoms were weakness in her right leg and foot during her body pump class; she felt fatigued, experienced balance issues and fasciculations. It did not progress to her upper limbs until long after the NurOwn trial ended. She was diagnosed with ALS on May 15, 2018 and got a confirmatory opinion at Mayo in August 2018. With trial enrollment at Mayo booked, Lesley chose a different trial site with more capacity: she flew back and forth from Iowa to Los Angeles over 15 times to participate in the trial and screening.

Like the people in EAP, NurOwn halted Lesley's ongoing paralysis and she regained some function as well as years of slowing of her symptoms. In her Public Comment, Lesley told the FDA:

*"I have been telling anyone who would listen that **my symptoms did not progress at all for a year**… Right before Covid hit, **I actually was stronger than before I started the trial**. In January 2020 – six months after my last trial injection – I visited my local ALS clinic at UNMC in Omaha, Nebraska. They were in awe of how stable I was. Dr. Thai even thought my legs seemed stronger than before I was in the trial. He had a big smile on his face and said something about: **'could it be the stem cells?'** One of the nurses said I'm **'the most stable ALS patient she has ever seen!' "***

Lesley was diagnosed with ALS by Dr. Thaisetthawatkul ("Dr. Thai") at University of Nebraska Medical Center (UNMC) on May 15, 2018. While she doesn't have her scores from the trial, she does have real-world data from her medical records from UNMC before and after the NurOwn trial. They corroborate what Dr. Thai's team was observing, and what she was feeling. The ALSFRS-R scores substantiated her belief that she received NurOwn in the trial and that it worked on her.

Months after the AdComm, the trial team at Cedars-Sinai confirmed that Lesley had been right all along. Lesley did receive NurOwn in the trial. That makes these clinical records attached to her Public Comment even more probative now.

Because of NurOwn, Lesley had over **12 months of progression-free survival**. On September 27, 2023, the date of the NurOwn AdComm, it was exactly 4 years from her last appointment in the NurOwn trial and just over 6 years (73 months) after symptom onset – and her ALSFRS-R was still 31/48!

Most people lose an average of 1 point a month; and to qualify for the NurOwn trial, she too had to lose 3 points during the 12 week run-in phase. And yet, with only 3 doses of NurOwn and her last dose in July 2019, **she averaged only .23 points lost per month – which equates to approximately 75% slower progression**. This demonstrates NurOwn's durability.

Graphic - Lesley Krummel's Real-world data

ALSFRS	FVC	Date	Type of Appointment	Doctor	Clinic
		15-May-18	ALS Diagnosis	Thaisetthawatkul	U Nebraska MC
	83%	Jun-18	Neuro Appt	Thaisetthawatkul	U Nebraska MC
46	77%	25-Jul-18	Neuro Appt	Thaisetthawatkul	U Nebraska MC
		Aug-18	Second Opinion	Martinez-Thompson	Mayo Clinic
46	73%	19-Sep-18	Neuro Appt	Thaisetthawatkul	U Nebraska MC
		Nov-18 to Feb-19	Trial Screening & run-in	Lewis	Cedars Sinai
		12-Feb-19	Last run-in visit	Lewis	Cedars Sinai
		19-Feb-19	Bone Marrow Aspiration	Lewis	Cedars Sinai
		27-Mar-19	Trial Dose #1	Lewis	Cedars Sinai
		21-May-19	Trial Dose #2	Lewis	Cedars Sinai
		17-Jul-19	Trial Dose #3	Lewis	Cedars Sinai
	80%	24-Jul-19	Neuro Appt	Thaisetthawatkul	U Nebraska MC
		27-Sep-19	Last trial visit	Lewis	Cedars Sinai
46	73%	22-Jan-20	Neuro Appt	Thaisetthawatkul	U Nebraska MC
	79%	24-Feb-21	Neuro Appt	Thaisetthawatkul	U Nebraska MC
39	77%	25-Aug-21	Neuro Appt	Thaisetthawatkul	U Nebraska MC
39		23-Feb-22	Neuro Appt	Thaisetthawatkul	U Nebraska MC
	75%	22-Jun-22	Neuro Appt	Thaisetthawatkul	U Nebraska MC
	77%	26-Oct-22	Neuro Appt	Thaisetthawatkul	U Nebraska MC
35		22-Feb-23	Neuro Appt	Thaisetthawatkul	U Nebraska MC
		03-May-23	Multi-disciplinary care	Martinez-Thompson	Mayo Clinic
31		05-May-23	Telehealth Neuro Appt	Faber	Synapticure

NurOwn improved not only how Lesley felt and functioned, but it also extended her survival. Ultimately, **Lesley has lived 94 months "trach-free" – over 3x the median ALS natural history**. To this day in June 2025, Lesley does not use a bi-pap to breathe. This is over **6x longer than the 15-month ALS natural history of Time-to-NIV.**

Lesley's Public Comment documented how she was still able to enjoy life, travel, take cruises, attend KC Chiefs' games and it allowed this grandmother to spend meaningful time making memories with her family. Her data aligns with her lived experiences. All demonstrate that NurOwn helps her "live longer and live better."

Lesley closed her Public Comment with this plea to use common sense when looking only at the statistics versus listening to the real life experiences:

> *"I pray every day that I will be given a chance to continue to receive Nurown. Please listen to the evidence from ALL the people who improved when they received 6 doses in Expanded Access…. Listen to the people who improved when they received it in 2015 with just 1 dose… Listen to the Navy pilot who benefited when he received 7 doses through the VA… And listen to people like me who are beating the odds of a 2-5 year prognosis. <u>All of us can't be wrong</u>."*

Lesley is 1 of 5 unrelated people in her small Iowa farm town of 769 people[91] who have been diagnosed with ALS in the past 10 years. All were lifelong residents: four women and one man, all who were diagnosed near the average age of onset. Four of them lived within a few blocks of each other. Four had limb onset; one had bulbar onset. All died within a few years of diagnosis – all but Lesley – who's now 7 years post-diagnosis and still not using any NIV to breathe!

[91] The population of Lesley's town is 769 according to 2020 Census data. Lesley has no known genetic risk factors but exposures to pesticides/ herbicides are associated with an increased risk of ALS. Farms in the area produce corn and soybeans.

7. Estate of Justin Rogers - Phase 3 - (Jan 15, 1984 - June 15, 2023)

Petitioner, the Estate of Justin Rogers, is represented by his wife Stacy Rogers. Justin was a participant in the NurOwn Phase 3 trial at Cedars-Sinai in Los Angeles and the trial PI confirmed that he received 3 doses of NurOwn. Justin died on June 15, 2023 at 39 years old.

Just four years earlier, Justin had his first symptoms of ALS in April 2019, with concurrent bulbar and limb onset. He had trouble opening a beer can in his non-dominant left hand, and he started missing clear shots on goal when playing hockey. His speech was slurred. He had mild dyspnea when giving presentations at work, but not when playing hockey or jogging. His diagnosing neurologist documented pseudobulbar affect symptoms occurring as well.

> *"Pseudobulbar affect seems to be happening. He has always been the tender one but this is more than normal. Awkward moments will make him laugh when he does not mean to, and funny moments he will be laughing even harder. He cries more than normal and has trouble controlling it."*

Initially seeing Dr. Robert Neel, a neuromuscular specialist at the ALS Center of Excellence at the University of Cincinnati, Justin was quickly diagnosed in July 2019 -- at just 35 years old. He documented UMN and LMN signs in his bulbar and cervical with UMN only in the lumbar region.

Only one month post-symptom onset and Justin already had *"**significant denervation, positive waves, fibrillations and fasciculations**"* in his left upper extremity but also the right arm and leg. His tongue showed involvement and his speech was mixed flaccid/spastic dysarthria. He diagnosed Justin with *"definite ALS"* with *"**very abrupt and acute**"* **onset**.

By his one-year appointment in 2020, Dr. Neel was concerned about how much Justin had progressed over the past year– so much so that he began the discussions about DNI/DNR and upcoming milestones before hospice.

> *"Have discussed the course of ALS, the average life expectancy and problems associated with the disease. He is progressing faster than I would like and if the speed continues this way **with bulbar function, he likely would have less than 12 months of life left. Somewhere between 6-12 months**."*

But Justin beat those odds. When he was diagnosed Justin's ALSFRS-R score was 46/48 – losing 1 point for early speech and breathing impairments. When he started the trial, it had dropped to 40/48. His last dose of NurOwn was in June 2020 and his last trial visit, he celebrated by drinking a Guiness beer at his favorite Irish pub across from the hospital. After his last NurOwn dose had washed out, Justin's progression resumed. By the inaugural Lou Gehrig Day in 2021, Justin's score had dropped to 20/48. Then in 2023, Stacy and Varen watched helplessly as his score dropped to 6/48 and his once muscular body wasted away.

You can compare Justin's progression and bulbar impairment by watching these videos:

- 2020 - Justin's Prayer -
- May 2020 - "Local man shares battle with ALS in midst of pandemic" (WKRC)
- June 2021 - "What do I have to lose?" (WKRC)
- July 2021 - "Girl honors father on Cincinnati Reds' first Lou Gehrig Day" (WXIX)

Even though he had bulbar onset and early dyspnea at his diagnosis at his July 2019 appointment, Justin didn't start using NIV at night until May 2021.[92] And even when he got COVID and was in the ICU in 2022, he didn't get trached. Stacy shared this scare:

> *"On Feb. 4th he was taken by ambulance to UC, where he was admitted to the ICU for several days. At one point his doctor told me to prepare for the fact that he may not come home. I'm not sure anyone can prepare for that. Miraculously, the infection didn't result in pneumonia and after a few days of monoclonal antibodies and steroids he was able to return home. The following two weeks were really hard but he made it through!*

Justin's neurologist was concerned he wouldn't live to see Christmas in 2020. And then his ICU doctor warned that he might not make it to Valentine's Day in 2022. He proved both of them wrong. Instead, with just 3 doses of NurOwn, Justin survived, trach-free, until June 2023.

When Justin was first diagnosed, Stacy compared the option of the ominous paralysis and suffocating death, versus the prospect of trying an unproven therapy:

> *"The bright spot is that we got him into a clinical trial. Even though there's only a 50% chance that he'll get the NurOwn treatment, I'll take 50% over zip any minute of any day. I understand that even if he gets the treatment, at the end of the trial, it could be stripped from him and everybody else who's in the trial… All they're asking is '**give me the right to try this treatment'. He's not asking for a cure. Neither am I. I'm just asking for a shot**."*

Justin would have loved an opportunity to get more doses of NurOwn. But without an open label extension[93] or an FDA accelerated approval, he was never to get that chance. Justin worried that the slow FDA approval process would take away his chance at getting more NurOwn and making more memories with his family: ***"Depending on how long this takes … I could, in the next 12 months, I could die waiting for this to become available to me."***

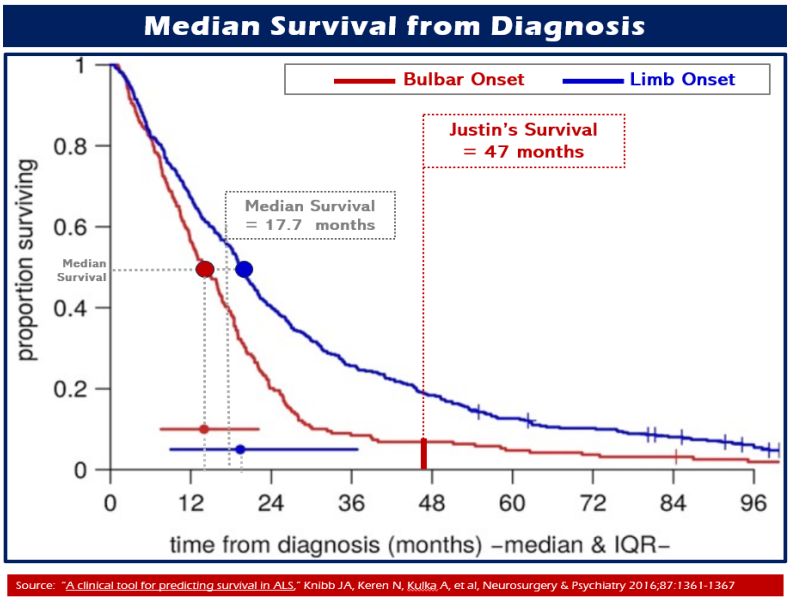
---

[92] You can see Justin's progression by comparing his June 2021 interview for Lou Gehrig's Day with his interview in June 2020.

[93] While all people want the option to continue on OLE, the fiscal reality of rare disease drug development is that many therapies are developed by start-up pharmaceutical companies without a revenue stream from other products on the market. The fiscal constraints are exacerbated in personalized gene and cell therapies because the cost of manufacturing is much higher than small molecule, off-the-shelf products.

Tragically, that is precisely what happened. Ultimately, Justin lived just over 4 years (50 months) from symptom onset and 47 months from diagnosis. On its face that seems aligned with the oft-repeated 3 - 5 years average ALS lifespan. But that is nowhere close to the median for people with bulbar onset like Justin.

Graphic - Justin Rogers' Bulbar Survival versus Median Survival from Diagnosis



In his video, Justin's Prayer, Justin shared the ominous advice that most neurologists share with their ALS patients: "start working on your bucket list." So, Justin did just that. He focused on *"trying to make the best of what I can while I can."* He came out of his office two days after his diagnosis and said: *"Let's get to living!"*

While Justin's lifespan may not have been extended as long as other people in the NurOwn Phase 3 trial, those extra years were beyond clinically meaningful as they allowed Justin to make memories with his family. This story on FOXNews, entitled "A Father's Final Gift," reflects on Justin's remaining time with Varen.

Stacy also shared many of the blessings of time that NurOwn gave to Justin and their family:

- 3 more years of Father's Days.
- 3 more years of Christmas and birthdays. This may not seem like a huge deal, but every gift Varen unwrapped from her Dad felt like it might be the last one.
- Getting Varen her first puppy so she wouldn't feel so alone when he was gone.
- Varen's last Daddy/Daughter dance in June 2022 where he was still able to stand and slow dance. COVID took 2 years and we were afraid he wouldn't get another chance, but he did!
- Two trips to Hawaii with us and his brothers.
- Watched Varen perform in the production of "Annie" (she was the lead orphan) with a professional children's theater.
- Took Varen to see her dream musical production of Hamilton- twice!
- 2 years of homeschooling Varen during COVID
- Attending Varen's graduation from elementary school, the only graduation he would ever attend
- Trip to Paris that he had promised Varen when she graduated from high school

Sports were a huge part of Justin's life and because of NurOwn, they continued to be. With family and friends, Justin attended numerous Reds and FC Cincinnati games including the inaugural Lou Gehrig's Day in MLB where Varen's sign caught the attention of the Reds' players, and Justin got to meet his favorite player Joey Votto. He also "met" his childhood hockey idol Jeremy Roenick (via video call) and was still able to speak clearly enough to talk to him. They formed a friendship that helped lift Justin's spirit for years.

Most importantly, NurOwn gave Justin more time to be a Hockey Dad. You can hear and see Justin's passion for hockey in the video Justin's Prayer where he fondly recounts memories of growing up playing hockey with his own Dad and brothers. And you can see it at his funeral when friends and family came dressed in hockey jerseys, left messages on pucks, and walked out of his services with a stick salute. Justin passed on that love and that legacy to Varen. When his ALS became more advanced, the only reason he left the house was to watch Varen play hockey. This kind of clinically meaningful moment isn't measured by the ALSFRS-R.

NurOwn gave Justin more time to do the things he loved most with the people he loved most.

When he was interviewed in May of 2020 in the midst of the pandemic, Justin said quarantine has given him time to see the urgency and flexibility with which the FDA was responding to COVID and the discrepancies in how it was responding to ALS:

> *"I understand ALS is not a pandemic. It's not killing millions of people like cancer. But the fact is, there are legitimate treatments for saving lives. We know they exist. But I can't have them because the FDA won't approve them and give them to me. This is a terminal illness. What do I have to lose? Give it to me. If I die, so what. I was going to die anyway."*

For ALS Awareness Month two years later in May of 2022, Stacy shared a video showing what Justin's fasciculations looked like and included the following plea:

> *"ALS introduced our family to the F word: fasciculations. They're extreme muscle twitches caused by the disruption of signals from the nerves to the muscles. They're also an external, visual reminder of the absolute war raging in my husband's body. He doesn't deserve this. No one does. That's why we can't give up fighting for treatments and for regulatory flexibility from the FDA. Please keep fighting with us."*

ALS is on the rise. It is killing far too many young people and no one understands why. Sadly, both Justin and a high school teammate, Eric Von Schaumberg,[94] were diagnosed with ALS. Justin was born in a Chicago suburb where he played football, baseball and hockey. No one knows why two athletes from the same graduating class of 2001 both got ALS (2 of 500) when, according to the now-defunct

[94] Eric was diagnosed with ALS at just 29 years old, on June 19, 2013. Like Justin, he had bulbar onset and received a tracheostomy in March of 2016 – living approximately 33 months "trach-free" from diagnosis. Like Justin, Eric was a high school athlete playing both football and baseball for Schaumburg High School. His mantra was: *"Live like you are dying!"* Eric died on June 18, 2023.

National ALS Registry, the national incidence is less than 2 per 100,000. They both died waiting in 2023 – at just 39 years old – decades earlier than the disease's natural history.

I. Real-world Evidence from NurOwn Phase 2 Recipients - 2015

Just as in Phase 3, multiple people in the Phase 2 trial reported that NurOwn halted their progression and in some ways, restored function, albeit temporarily. They reported differing times of durability before they started feeling the wash-out. This is completely consistent with the phase 2 trial results discussed above. In the three examples below, Terri Saenz halted her overall progression for about 4 months; Mike Cimbura for about 2-3 months; and Bobby Forster for about 2 months.

Unlike cancer trials, when the NurOwn trial ended, none of the 36 people in the treatment arm could get more of the drug that was helping them live. And the 12 people in the placebo arm never got a chance to get NurOwn at all.

1. Petitioner Terri Pickering Saenz

Petitioner Terri Pickering Saenz was a participant in the NurOwn Phase 2 trial with Principal Investigator Dr. Nathan Staff at Mayo. She received 1 dose of NurOwn in July 2015. The trial was unblinded in 2016 and Dr Staff sent a letter confirming that she received NurOwn. In the unblinding letter, Dr. Staff also shared: *"You may already know that the results of the Brainstorm NurOwn study were favorable."*

Terri, like many other Phase 2 participants, is adamant that NurOwn worked on her. Like the people in Phase 3 and EAP, NurOwn halted Terri's ongoing paralysis and she had years of slowing of her symptoms.



In her Public Comment to the NurOwn AdComm, Terri shared details about her progression after NurOwn Her ALSFRS-R score stabilized during the trial in the low 40s and 17 months later in October 2016, her score was still 39. She was only losing about 1 point every 4 months instead of the average of 1 point every month. In the 15 months after that, her progression returned to normal in both upper and lower limbs. But thankfully, her breathing and swallowing have progressed much more slowly. This is surprising as slurred speech was one of her first symptoms in 2014. At the time of the AdComm, she could still speak and people understood her. Almost 9 years after diagnosis, Terri only used a bipap to breathe at night.

Terri was diagnosed with ALS at the age 47, on January 8, 2015:

> *"My symptoms began in March 2014 with muscle twitching all over my body. Later that summer I noticed my non-dominant left hand, arm and shoulder were weaker. It was hard to open packages. I began choking on my almond snacks… My legs and my breathing were weaker. While running a 5K in October, I noticed I didn't have any "gas in the tank". I was having trouble pushing myself to go quicker and unable to breathe properly. Around the holidays, my slurred speech began to be more noticeable and that led me to seek medical care."*

With bulbar and respiratory onset accompanied by onset in other regions, the natural history indicates Terri should have been a fast progressor. But after the Phase 2 NurOwn trial, she wasn't.

Terri's one and only dose of NurOwn was on July 3, 2015. When she began the trial, Terri was earlier in progression than the average phase 2 participant. She was in the trial just six months after diagnosis, whereas the average in the trial was nine months. The baseline score in the trial was 38, and Terri's was 43. Just before the holidays, she started to feel NurOwn wash out and her progression ensued. Then, in the first 9 months of 2016, her score again stabilized at 39. Her breathing, speech and swallowing remained stable. Five months of progression-free survival followed by 9 months of progression free-survival!

As 2017 and 2018 came and went, Terri progressed from a cane to a rolling walker. Her upper limbs were most progressed, and she needed assistance to lift utensils to her mouth. But her breathing, speech and swallowing remained stable.

In 2019 and 2020, Terri began using a power wheelchair, but she could still transfer by walking with assistance. She used that power wheelchair to "lead" her son during the Mother-Son dance at his wedding. And just as before, for those two years, Terri's breathing, speech and swallowing remained stable.

With the passing of two more years through 2022, Terri's progression was more noticeable. Her upper body weakened and she needed assistance to eat. She had a slight decline in breathing, speech and swallowing, but still was not using any NIV to breathe – almost 9 years after symptom onset and eight years after diagnosis . And because of this blessing of strong respiratory function, she and her family were still taking their annual trip to Mackinac Island.

Since the AdComm, Terri continues to celebrate life's blessings. She was here as her youngest son brought his first child into the world. She danced again at a wedding; this time with her oldest son.[95]

One decade after she received NurOwn at Mayo, we believe Terri Saenz is the only remaining survivor from the Phase 2 trial. Terri's NurOwn journey is notable for several reasons:

- Living Trach-free 125 months post-diagnosis - 6.9x 4.6x longer than median TFS
- Living Trach-free 134 months post-symptom onset - 4.6x longer than median TFS
- Bulbar and respiratory onset with upper limb onset which usually typifies a "fast progressor"
- Yet her breathing, speech and swallowing remained stable for approximately 7 years
- 15 months of significantly slowed progression, down to 1 point lost every 4 months
- 4 months of progression-free-survival after dosing

But life has gotten harder since the NurOwn AdComm. For all those years, Terri's breathing, speech and swallowing remained stable. Now they are not. There are consequences to the FDA's Type II error.

In May, for ALS Awareness Month, Terri "celebrated" by spending a week in the ICU with pancreatitis. Don't ever let anyone tell you ALS isn't painful. And her husband Jeff was by her side. On May 22nd, Jeff updated all her friends on social media about Terri's ICU admission:

> *"All settled in at UofM. Hasn't been a fun day. Started with another CT scan at St. Joe, definitely not enough people to handle an ALS patient transferring to the table. Got her all prepped and took an ambulance ride to UofM. Unfortunately, the best thing for her safety, and wear and tear on her body, was getting put in a bed. Remember she has been full-time in her wheelchair for the past 6+ years. Communication has been very difficult trying to get her eye gaze working adequately…. One of the hardest things I've ever had to deal with."*

Living a decade with ALS, Terri is already beating the odds. She is not only living but she is still trach-free. But she cannot continue to wait for yet another Phase 3 trial. With NurOwn she could continue to take the family's annual trips to Mackinac Island.

Terri closed her AdComm Public Comment with this question and photos from the family's 2016 trip to Mackinac: *"I was so filled with hope after Nurown changed how I felt and functioned. But I wonder… What if I had continued to get Nurown in 2016?* Today I still have hope that the FDA can End ALS.

[95] Never doubt the impact of a few extra years of life. Not only did Terri get to dance the Mother-Son dance at her son's wedding, so too did Kathy Poirier, who also received NurOwn during the Phase 3 trial.

2. Phase 2 NurOwn Trial Participants who Stabilized and Improved

a. Mike Cimbura Improved but Died Waiting for FDA

Nicole Cimbura is an ALS widow. Before his ALS diagnosis, her husband Mike was an elite cyclist. Bicycle.com tells the story not only his ALS, but of Mike's elite athleticism and thrill for constant motion.

> *"If cycling -- a sport synonymous with movement, exertion, and exhilaration -- had its polar opposite in a disease, it would be ALS."*

Mike began road racing in college at UCSB. When he moved to Lakeland Colorado, Mike and his brother John started their own team and picked up a few sponsors. In between being a dad and working as an accountant, Mike trained about 30 hours a week and managed to squeeze in two to three races each week from March through September.

During the off-season he was just as dedicated. He'd pick up John up at 5 on Saturday mornings to snowshoe up nearby Loveland Pass. They'd spend two and a half hours climbing through thigh-deep snow, then snowboard back down, and do it again, and again. Mike's work ethic paid off, especially on the hills. Mike's teammate said: *"regardless of how in shape I was, I could never outclimb Mike."*

Mike had a passion for life, a massive amount of energy, and an all-in, zero-fear riding style. His brother John, a Cat 2 on the team, talked about Mike's need for constant motion: "*To sit still and not do something physically active, I think just drove him nuts."*

So, when ALS came for him in 2014, Mike knew something was wrong. The first neurologist said Mike was too young, too fit, and too healthy to have ALS. Nicole prayed for cancer. Something they could beat. One day, the athlete who used to snowshoe through waist-deep snow and compete in the "Death Ride" over Loveland Pass, that same athlete couldn't walk up a flight of stairs. The man who thrived on constant motion told Nicole: ***"I feel like every day more of me is dying … my body feels like it's changing."***

As an elite athlete, Mike knew his body. He knew when he was dying before the neurologist did. And when he was the 9th person to receive NurOwn in the phase 2 trial at Mayo with Dr. Windebank, Mike knew NurOwn had worked on him.

Nicole has repeatedly shared her husband's compelling story privately with both the FDA and with Congress, and publicly with the media. Mike and Nicole Cimbura's story was part of the documentary, *"For Love and Life: No Ordinary Campaign."*

> *"Back in 2015 there was no fighting ALS. We were following the most promising study going on and that was Brainstorm's NurOwn trial. Within 24 hours of Mike getting NurOwn, we saw results. We saw gains continue probably for about the next 12 to 14 days. Being able to stand up without my assistance, being able to just have the independence, washing your own hair again. We immediately reached out to the company and the FDA, saying* ***"look this has worked,' we're seeing something."***

On Congressional calls with Mitze Klingenberg and Kandy Simons, Nicole has repeatedly shared their real-world evidence about how much Mike improved in the ensuing weeks after receiving that one precious dose of NurOwn. In July 2015, Mike was doing so well that he was able to walk – without a walker – at the Garden of the Gods. This was something he could not do before receiving NurOwn.

But without an OLE, Mike couldn't get more NurOwn.

Frustrated with our regulatory system, Nicole became a legislative advocate. She launched the IAM ALS Legislative team and spawned the idea for a bi-partisan Congressional ALS Caucus. Nicole teamed up with Deb Bellina to change regulatory policy and made repeated trips to the FDA and Capitol Hill. In 2021, she authored a WSJ OpEd entitled: *"A Slow FDA Is Denying ALS Patients Their Only Hope."*

She and Mike also fought for President Trump's Right to Try law and attended the bill signing with Matt Bellina's family.

Graphic - Right to Try Bill Signing with Matt Bellina and Nicole Cimbura

Nicole was persistent in telling everyone that NurOwn worked on Mike. Notably, Mike could feel the impact of NurOwn within 24 hours -- just as Kade Simons had reported. In one of her Public Comments to the FDA's 2023 AdComm, Nicole attached the transcript of the zoom testimony at the private PFDD Listening session in 2021 where she shared with former CBER officials, Dr. Wilson Bryan, Dr. Celia Witten and Dr. Peter Marks:

> *"He was a participant in the NurOwn Phase 2 Trial at MAYO Clinic. Sadly, the phase 2 trial was only one dose. But that one dose had a profound impact on Mike. When he awoke the next morning after his intrathecal treatment, Mike felt movement in his hand. I was surprised when he asked for a pen and a piece of paper to try and jot down a note. For over a month, Mike hadn't been able to grasp anything with his left hand that wasn't rather large. But he wanted to try. In a tearful moment of awe, we watched as he was able to write a simple note to our three kids: "Love Dad." The handwriting was shaky, but we were forever grateful for this improvement in his hand. This note was such a treasure to our family."*

When Mike regained the ability to write again, he wrote his three kids a second note: "always remember I love you." Nothing could be more clinically meaningful. Today all three now-adult children have Mike's last words tattooed on their bodies.

Nicole and her family lived the hell that every family with ALS endures. The Cimbura family watched Mike suffer, going from an elite endurance cyclist, runner and avid skier to someone who couldn't move a single muscle in his body. ALS transformed the man with an impressive VO2 max into one who couldn't breathe without a ventilator.

Compounding that suffering, Nicole and Mike Cimbura endured the disrespect and medical paternalism when the FDA and the scientific community dismissed Mike's improvements as anecdotal and a placebo effect. They wouldn't believe NurOwn improved how Mike felt and functioned. They couldn't believe that someone with ALS could regain function. They dismissed the real-world data and evidence as anecdotal story and unreliable "n of 1."

And then the Cimburas endured the ultimate inhumanity that resulted from a Type II error. They watched Mike die when they knew a cell therapy could help him live.

Despite CBER leadership being personally aware of Mike's unprecedented improvements and having communicated with Nicole repeatedly over the years, Nicole was not chosen to speak at the NurOwn AdComm. No one else from the Phase 2 NurOwn trial was chosen to speak either. And CBER still refused even when an ALS advocate wrote to the FDA before the CTGT AdComm, raising concerns about the lottery system not choosing people to speak – like Nicole Cimbura and Deb Bellina – who had probative and unprecedented real-world evidence. (See Exhibits). Thus, Nicole was not allowed to publicly share her story of the real-life implications of a fatal Type II error.

b. Bobby Forster Improved

Bobby Forster shared his story on his YouTube channel. He was diagnosed with ALS at 25 years old, in September 2014, just four months after symptom onset. Bobby participated in the NurOwn Phase 2 trial, and when the trial was unblinded, he confirmed that he received NurOwn.

In August 2019 -- trached and living with ALS for five years --Bobby shared how NurOwn had worked:

> *"In the fall of 2015, I participated in the phase 2 clinical trial for Brainstorm's NurOwn.* ***After two weeks of treatment, I went from barely able to stand for more than ten seconds, to being able to walk with a walker, to being able to walk unassisted. I also saw significant improvements in my forced vital capacity and speech****…. I am so disgusted & ashamed with myself for not being able to get NurOwn approved by the FDA. Please, I am begging you to not make another person suffer unnecessarily anymore."*

Four years later and understandably frustrated, Bobby had to use a Tobii to speak at an ALS-TDI fundraiser event.

*"I am not going to be a happy go lucky ALS patient as you all know me to be. I am really tired of ALS. I am so f***ng sick and tired of seeing my friends die from this disease, when **I know that a treatment exists that can reverse my symptoms**. Carol O'Keefe Hamilton, over three and a half years ago, I remember video chatting with you when **I was walking after receiving NurOwn**. After the treatment wore off, I remember all I could think about was if it worked for anyone else? And what if I continued taking it? I got the first answer when the trial was over and the answer was 'yes'."*

Bobby started a change.org petition that asked Brainstorm to pursue Accelerated Approval with the FDA. It collected 169,711 signatures. In his request, he told the world that NurOwn improved his ability to walk and breathe. He said his improvements continued for a month, then he plateaued for a month before he began declining again. That was over **two months of "progression-free survival."**

*"Unfortunately, the company that makes NurOwn, Brainstorm, is hesitant to pursue accelerated approval of this treatment with the FDA and has opted to conduct a **Phase III trial which could delay approval for another 5 years**. Without accelerated **approval thousands of ALS patients could die over the next several years waiting for the traditional process for approval** to be completed…. This treatment has now been in multiple trials both in the US and Israel. It has been shown to be effective and has no significant side effects. It is time for all ALS patients to gain access to this ground- breaking treatment."*

Tragically Bobby died on June 12, 2023 at just 34 years old. He died waiting for NurOwn. But his caregiver continued his fight to get NurOwn approved for his friends who were still fighting ALS. She filed a Public Comment at the NurOwn AdComm repeating Bobby's testimony. She closed by saying:

"Bobby never stopped from trying to make a difference.
My hope is that even in death we continue to remember his testimony."

Her Public Comment described Bobby as a "rapid progressor" but a "super responder." One decade ago, Bobby was yet another "n of 1" responder who the regulatory community didn't believe. Bobby died waiting when he could no longer get the cell therapy that was helping him live.

c. Phase 2 Placebo

Petitioner Justin Rogers' high school classmate, Eric Schaumberger, was also in the NurOwn Phase 2 trial at UMass with Bob Brown. Sadly, he was one of twelve in the placebo arm and without an OLE, he never received NurOwn. In his blog, Eric said:

"Unfortunately, the FDA (and other countries' equivalents) move too damn cautiously for my liking, forcing companies to do long, drawn out trials at each step. I get it. I get the macro perspective….That doesn't make it any easier on us 'micro' individual patients who are dying."

J. Matt Bellina Regained Function after receiving NurOwn via the Right to Try Law.

"We want to focus the agency on cures and meaningful treatments. We believe in the letter and the spirit of Right to Try."
-Commissioner Marty Makary
(FOXNews - May 8, 2025)

We do too. In 2018, "Right to Try" became law. Named after Navy pilot Matt Bellina, it was only fitting that Matt was one of the first people to benefit from it. This was possible only because the tiny start-up pharma company, Brainstorm Cell and the VA, covered the cost of manufacturing and administering NurOwn.

POLITICS

STAT+

Prominent 'right-to-try' advocate is getting treatment under the new law

By Nicholas Florko Feb. 5, 2019 Reprints

President Trump and several patient advocates, including Matt Bellina, at the bill signing for the federal "right-to-try" law.
ALEX WONG/GETTY IMAGES

WASHINGTON — One of the namesakes of the federal "right-to-try" law confirmed Tuesday that he gained access to an experimental treatment thanks to the new law.

Matt Bellina, who has ALS, thanked the drug company BrainStorm for providing the treatment on Facebook.

From December 2018 through 2020, Matt Bellina received 7 doses of NurOwn via Right to Try; of which 6 were consecutive doses at two-month dosing intervals. The seventh was received 9 months after the initial 6 doses. Matt is the only person in the US who received six consecutive doses. But sadly, after his seventh dose, Matt couldn't get more. It's now been nearly 5 years since his last dose of the stem cell therapy that is helping him live.

Matt Bellina's results via Right to Try are not mentioned in the FDA Briefing Document. They are, however, publicly available and were provided by the Bellinas to the FDA during multiple PFDD meetings. Thus, his RWD/RWE and PROs constitute new supporting evidence of efficacy and it should be considered by the FDA.

Matt has released clinical data from his VA medical records in his blog and on social media. In February 2019, Matt posted on Facebook:

> *"I have been given a gift. Many of you read last June that Brainstorm would be treating me with the experimental treatment of Nurown under the new federal Right to Try law…. Only one month after my first round of treatment, I have improvement in the clinical strength of my right deltoid and my left bicep. My forced vital lung capacity is 23% higher & I am seeing subjective improvement in my speech & swallowing. I no longer need a bi pap at night. Due to increased core strength & coordination, I am now able to pull myself up to standing. Because this is an investigational therapy we don't know what tomorrow will bring but for now, we are feeling incredibly blessed."*

On NurOwn, Matt's ALSFRS-R score increased by 6 points on the 48-point scale and he stopped using a non-invasive ventilator to breathe at night. In May 2019, Matt again posted videos on Facebook demonstrating a profound increase in function and added this commentary:

> *"What is remarkable is that I was not able to get out of my chair on my own before NurOwn. After my second treatment I was able to pull up to standing using both my legs and my arms.* ***Since the third treatment I am able to stand from my chair without the aid of my arms. I have not been able to do this for over 2 years*** *and it feels great. We all need to push the FDA to approve this treatment. It is simply unacceptable that I am the only one receiving this treatment outside of the trial. All pALS deserve this chance."*

In 2020, other rare disease advocates were still sharing Matt's hopeful story:

> *"On the morning of December 27th, 2018, American Airlines flight 1776 flew from Boston to Philadelphia with a small, temperature-controlled box containing my personal mesenchymal stem cells in the form of the treatment known as NurOwn….* ***Within two weeks, I felt the overwhelming urge to stand up out of my wheelchair, so my family propped me up against the kitchen counter and I stood****!*
>
> *Since then, I have had six injections and I have regained the ability to stand on my own without assistance. My lung capacity is 37% higher than it was before my first injection, so I* ***no longer need the assistance of a breathing machine****. I have* ***gained enough mobility in my arms to scratch my face and even take my glasses off****. All of these are improvements from where I was before the treatment."*

Matt's objective and unprecedented improvement in FVC was shared in the Emergent Facts section above.

Anyone with ALS experience knows that Matt's response is not typical in ALS. Matt's real-world data is critical, not only because of his profound improvement, but also because of many unique factors that are illustrative as supporting evidence:

- Only person in the US to receive 6 consecutive doses
- Matt's baseline score of 21 was 6 points below the data that met statistical significance in the Phase 3 trial
- Matt was a slow progressor and this population was excluded from the NurOwn trial

Petitioners acknowledge that Matt is an "n of 1" – but not the only "n of 1." Matt has a squadron of people who, individually, are also an "n of 1." Combined there is power in numbers. Matt's results are synthesized in this table below.

Graphic - Matt Bellina's Real-world Data

Matt Bellina's Real World Data on NurOwn					
DOSE #	DATE	ALSFRS-R	FVC	Elliptical Distance	COMMENT
	11/19/18			1.81	40 minutes
	11/19/29	21			Run-in score
1	12/27/18	21	70%		NurOwn Dose #1
	01/25/19	23	82%		
2	02/12/19		82%		NurOwn Dose #2
	03/08/19		73%		
	03/15/19	26		3.11	40 minutes
3	04/18/19				NurOwn Dose #3
	05/17/19	27	66%		
	05/30/19			4.41	40 minutes
4	07/18/19		85%		NurOwn Dose #4
	08/07/19			5.84	60 minutes
	08/23/19	27			
5	09/18/19				NurOwn Dose #5
	11/01/19	27	76%		
6	11/21/19				NurOwn Dose #6
	12/02/19			6.11	60 minutes
	12/20/19	26	78%		
	02/00/20				Hospitalized - Pneumonia
	03/27/20	25			
	07/31/20	24			
7	08/12/20				NurOwn Dose #7
	10/02/20	24			

Matt so believed in NurOwn's efficacy that he also co-authored a press release asking the FDA for an AdComm so veterans' voices could be heard:

> *"Veterans with ALS have a unique stake in the fight for a NurOwn AdComm. We sacrificed our lives for every citizen's right of due process. It is the antithesis of all we fought for if we, now, were denied that same right."*

Although the FDA had actual knowledge of Matt's unprecedented improvements, his mother Deb Bellina was not chosen to speak at the FDA AdComm. Matt got this terminal disease from serving our country and the FDA's lottery process didn't give him an opportunity to be heard. A patient advocate wrote to the FDA in advance of the AdComm to alert them of this inequity (See Exhibits). Nonetheless, the FDA refused to allow the Bellinas to testify during the Open Public Hearing. No veterans with ALS were chosen to speak despite comprising approximately 1 in 6 people afflicted with ALS.

So instead, Deb Bellina went to the media. Just before the FDA's AdComm on NurOwn, Deb authored an OpEd with Fox News:

> *"Mothers of children with ALS are helplessly watching our children wither away under the burden of this disease. For those who have seen the benefits of this treatment, every day that passes without a decision is like a slow death unto itself."*

The night before the AdComm, Deb Bellina and Paula Smith were on Cincinnati affiliate WLWT sharing their story about fighting for their sons' lives. Deb spoke about the blessing and tragedy of being in this fight with Matt for over a decade:

> *"I've watched a lot of people die over and over and over again, and every time that happens, I think how different it could have been and how different it can be."*

Even worse than denying the Bellinas a chance to tell Matt's story at the AdComm, the FDA also failed to discuss or believe his real-world evidence. Matt Bellina's results are not even mentioned in the FDA Briefing Document.

Consider this irony. The Navy entrusted Matt with a $50 million aircraft and the lives of fellow crew members, but the FDA didn't trust him to know if a drug was helping him live.

As a Navy pilot, Matt had to inspect his plane before every flight to ensure it would function properly. His pre-flight checklist was outlined in Naval Air Training and Operating Procedures Standardization Flight Manual, Navy model EA-6B Aircraft ("NATOPS").[96] For example, the Navy entrusted Matt to be responsible for:

- Inspecting critical weapon systems, such as the AGM-88 HARM (High-speed Anti-Radiation Missile), a tactical, air-to-surface anti-radiation missile, was a key responsibility for Matt. (NATOPS III-7-6). Matt was required to be knowledgeable not only about his aircraft, but also about the weapon systems that complemented it. This depth of knowledge highlights Matt's ability to understand complex systems and their interactions.

[96] Naval Air Systems Command. (n.d.). Naval Air Training and Operating Procedures Standardization flight manual, Navy model EA-6B aircraft. U.S. Navy.

- Closely inspecting the aircraft's struts and landing gear, noting that if the anti-skid drive cap lacks all four rivets, the aircraft will experience anti-skid system failure during landing rollout. (NATOPS III-7-9). The consequence of missing even a single rivet could result in system failure. The Navy entrusted Matt to maintain an exceptional level of attention to detail, even for seemingly minor components, in a manner demanded by few professions.

- Conducting a 29-step ejection seat preflight inspection. (NATOPS III-7-11). Failure to perform this inspection correctly would result in the certain death of both the pilot and crew in the event of a catastrophic aircraft failure. The Navy aircrew relied on his judgment when inspecting a system designed to save their lives when there is no time to think.

- Memorizing 28 "boldface" emergency procedures for each phase of flight. (NATOPS V-12-1). As Pilot-in-Command, he was required to diagnose and execute over two dozen emergency procedures from memory without reference aids. The Navy, Matt, and his crew depended on his training, critical thinking, quick reaction, and level-headedness during emergencies, as their lives hinged on his abilities.

This begs the question: if Matt can be trusted to execute missions in a $50 million aircraft and to diagnose complex, interconnected systems; inspect both mundane and critical components; and execute multi-step emergency procedures from memory to save lives, **why didn't the prior FDA trust him to know if a therapy caused him to regain function in his own paralyzed body?**

K. Veterans with ALS who couldn't get Access to NurOwn

Veterans are dying of ALS at an alarmingly high rate. One in six people (16%) with ALS are veterans. Since 9/11, our country has lost three times more servicemembers to ALS than were killed in Iraq and Afghanistan combined.[97] Yet veterans often learn of ALS clinical trials too late to qualify. That was the case for NurOwn. Of the 189 people in the trial, at least 31 should have been veterans. Of the 100+ NurOwn Phase 3 trial participants that Petitioners know, we are aware of only two who were veterans.[98]

1. Petitioner Nick Warack

Petitioner Nick Warack had symptom onset and was diagnosed with ALS in July 2020 at age 37 – just as the NurOwn Phase 3 trial was ending. Nick's symptoms began with upper body fasciculations, followed by a subtle left foot drop.

As a "slow progressor," Nick's current ALSFRS-R score is 32. He has averaged about 0.54 points per month in loss of function. Due to his slow progression and delayed diagnosis, Nick does not qualify for clinical trials of investigational drugs, which typically require participants to be within 24 months of symptom onset.

Like Matt Bellina, Nick served as a Naval aviator, flying the P-3 Orion. Commissioned as a Naval Officer in 2006, he earned his wings in 2008 and rose to the rank of Lieutenant Commander. He served as a flight instructor and mission commander, and was captain of the U.S. Navy Select XV Rugby Team, earning a selection to the All-Military XV.

Operationally, Nick was stationed at Patrol Squadron 47, Marine Corps Base Hawaii, Kaneohe. As a Mission commander, Nick and his squadron conducted anti-submarine warfare and reconnaissance in support of the Fifth and Seventh Fleets, and operations in the Horn of Africa. While in Iraq from 2009 to 2010, his squadron's operations office was located adjacent to burn pits. He was also stationed at Camp Lemonnier in Djibouti. Nick received two Air Medals (Strike Flight) for combat missions and served as Mission Commander for a search-and-rescue operation that saved 68 lives adrift at sea. He was honorably discharged from active duty on August 28, 2014, and later served in the Selected Reserve until 2017.

---

[97] Mulholland, C. (2021, October 28). ALS is killing veterans. Military Times. https://www.militarytimes.com/opinion/commentary/2021/10/28/als-is-killing-veterans/

[98] Although 1 in 6 people with ALS is a veteran, Petitioners believe veterans are underrepresented in promising clinical trials. For example, Petitioners are only aware of two veterans who participated in the 189-person NurOwn trial: one man served 7 years in the US Navy as a machinist on a nuclear submarine; and Chuck Harkins, who served 15 years and retired as a staff sergeant in the US Army.

Nick's wife, Jamie, was also a naval aviator, combat veteran, and Weapons and Tactics (“Top Gun”) instructor. After they resigned their commissions, both Nick and Jamie thought they had their whole lives ahead of them. Soon thereafter they had four children, and Nick attended law school and began practicing technology and intellectual property law at an AMLAW Top 50 firm.

Now, because of his ALS diagnosis, Nick no longer flies, plays rugby, practices law, or runs in the yard with his family. Though his speech and breathing remain entirely untouched, and he retains useful arm and hand function, Nick is in a power wheelchair full-time.

Nick petitions for himself and other veterans, understanding that NurOwn is not a cure. For Nick, it’s a chance to continue squeezing his daughter’s hand when she’s frightened, to keep cheering on his kids, and to tell his wife, “thank you” for her continued service, now as a caregiver. For all veterans with ALS, Nick petitions to stop a horrible disease that slowly kills our nations’ war fighters long after they’ve left the battlefield.

Like many service members with ALS, Nick receives treatment through the Department of Veterans Affairs (VA) system. Unfortunately, many Veterans Integrated Service Networks (VISNs) lack an ALS Center of Excellence, leaving veterans unaware of clinical trials until they no longer qualify – typically two years post-symptom onset. This was the case for Navy aviators Matt Bellina and Nick Warack.

These men launched aircraft off carriers, sheltered on bases under missile fire, and executed missions in hostile areas, only to return home to find decision makers too conservative to save their lives, and clinical trials too restrictive to even try.

Veterans with ALS face at least three significant challenges. First (as noted) many veterans, like Nick, are excluded from clinical trials due to delayed diagnoses or lack of trial information from the VA. Second, during their service, veterans are often exposed to environmental hazards and Superfund related toxins – leading to ALS being a presumptive “service-connected” disease. Third and most tragically, when they return home, they are denied access to the most promising drugs in the medical arsenal.

In a painful irony, veterans like Nick, who faced significant risks to serve and save lives, are denied therapies like NurOwn, which failed to gain approval partly due to safety concerns. Nick frequently asks his Congressional representatives, *"How can veterans serve and save lives in the face of great risk, yet we cannot overcome a perceived slight risk to save our own?"*

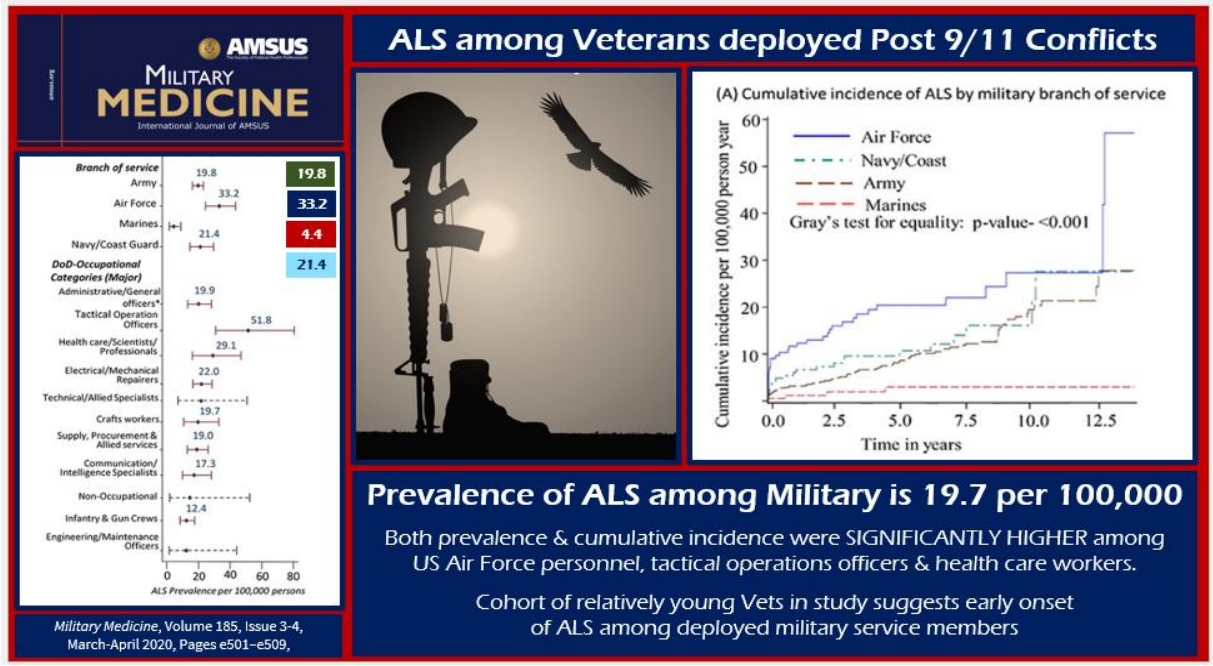
2. Veterans have a Heightened Risk of ALS

The first person to ring the alarm about this ongoing tragedy was Brigadier General Tom Mikolajcik ("General Mik"), the Commander of the 437th Airlift Wing at Charleston AFB. In 2007, he testified before the House VA Committee asking members: (a) to make ALS a service-related disease; (b) to investigate what was causing our veterans to get ALS; and (c) to get them access to every possible weapon in the medical arsenal.[99] Only one of those three objectives has been achieved.

A recent study in Military Medicine uncovered daunting statistics. Among all post 9/11 veterans, the risk of ALS is skyrocketing to 4x higher than the civilian population. Pilots and tactical operations officers have a 10x risk. Exemplifying the real-life implications of this statistic: USAF Academy graduate General Mik died of ALS in 2010. Less than a decade later, other C-141 pilots -- several who flew in his same squadron from Charleston (and Altus AFB) -- also died of ALS: USAF Academy graduate Major General Kip Self, Lt Col. Doug Hetzel, USAF Academy graduate Lt Col. Kreg Palko; Lt Col. Jim Howard; USAF Academy graduate Lt Col. Rick Nickel. The ALS community has identified many other clusters in certain units and at certain bases that are discussed in the Exposome section below.

[99] U.S. House of Representatives, Subcommittee on Health of the Committee on Veterans' Affairs. (2007). Gulf War exposures (House Hearing, 110th Congress, Serial No. 110-37). U.S. Government Printing Office. https://www.govinfo.gov/content/pkg/CHRG-110hhrg37476/html/CHRG-110hhrg37476.htm

Graphic - Military Medicine Study regarding Post 9/11 Veterans and ALS



The Military Medicine study also recognizes that these post 9/11 veterans are experiencing ALS onset at much younger ages. Exemplifying the real-life implications of this statistic:

- USN Prowler pilot Matt Bellina was diagnosed at 30 and medically retired at just 32 years old
- USN P-3 pilot Nick Warack was diagnosed at just 37 years old
- USAF F-15 fighter pilot Captain Cole Hollway was diagnosed at 27 years[100]
- USNA graduate and USMC Iraq War Veteran, Tyler Tidwell, was diagnosed at 38 and died at just 41 years old[101]

In 2007, General Mik warned that this would happen:

> *"We are currently exposing hundreds of thousands more service members to the elevated risk of this disease. There will be young men, women and families celebrating a return from Iraq and Afghanistan alive, who have no idea that they may soon be facing a certain death from ALS. We will have to answer to those families when they ask what their government has been doing to prepare for this onslaught."*

[100] Dunham, W. (2019, October 17). Resilience in the face of the reaper. U.S. Department of Defense. https://www.defense.gov/News/Feature-Stories/story/Article/1958302/resilience-in-the-face-of-the-reaper/

[101] Slater, C. (2020, December 11). Navy football's Tyler Tidwell fights ALS with toughness he learned on the field. The New York Times. https://www.nytimes.com/athletic/2247385/2020/12/11/tyler-tidwell-navy-football-als/

Unwilling to let veterans' suffering continue to be ignored, General Mik demanded a medical arsenal for people with ALS.

> *"We must prepare to offer our soldiers, sailors, airmen, and marines an opportunity to fight this disease. We cannot simply fight this battle defensively hoping to limit exposure to environmental risk.* ***We must fight it offensively as well with a medical arsenal****. Let's do what it takes to finish off this enemy once and for all. Congress can make the commitment, take the initiative, legislate a new way forward and* ***hold agencies accountable****."*

Often researchers and regulators try to offer hope about all the progress that has been made in ALS drug development. In response to them, General Mik quoted President Lyndon Johnson:

'Research is good, results are better.' He went on to add: *"It's been nearly 70 years since Lou Gehrig made his farewell speech, and we have basically nothing. One questionable drug in 70 years?"*

What Gehrig's neurologists knew then may differ a lot from what ALS neurologists know today. But the drugs are not. The outcomes are not. General Mik acknowledged that researchers need an increased understanding of this disease but reminded everyone that veterans dying of ALS today won't benefit from future discoveries and treatments. People dying today need treatments today.

Thus, General Mik challenged Congress and the FDA to step up its commitment to veterans:

> ***"We owe our veterans treatment now.*** *If these soldiers were dying in the field rather than quietly at home… we would leave no stone unturned. We would use the* ***best existing resources*** *to make sure they had* ***whatever they needed to survive****… to ensure that no man or woman is left behind."*

Over 5,000 veterans are battling ALS. When the FDA failed to approve NurOwn – a therapy that has helped Navy veteran Matt Bellina survive – it was akin to abandoning 5,000 soldiers behind enemy lines -- with nothing but a musket -- knowing that they would be tortured under the most inhumane of conditions. As General Mik asked Congress:

"How many thousands of private farewell speeches must take place before we realize we are not doing everything we can?"

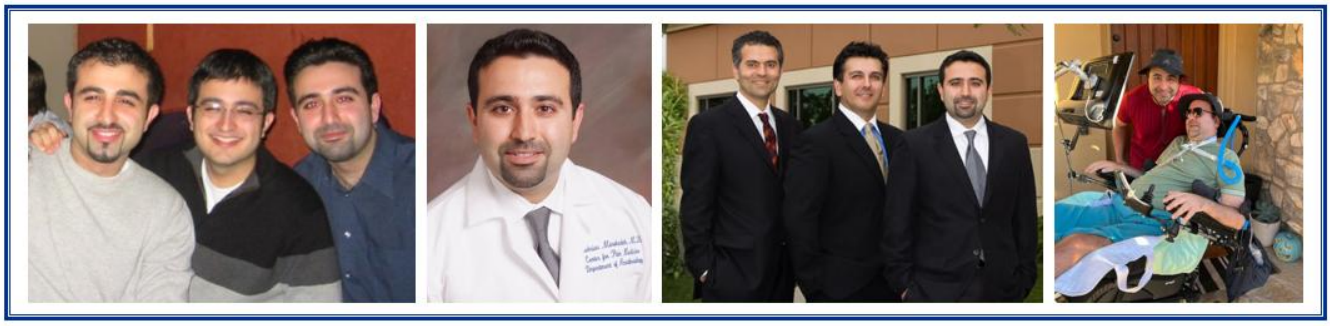
L. Other Petitioners who couldn't get Access to NurOwn

1. Petitioner Shahriar Minokadeh, MD

Petitioner Shahriar ("Shah") Minokadeh is a physician who has been battling ALS since 2011. Medicine is in his family's blood. He is the son of an anesthesiologist and one of three sons who all pursued a career in medicine. Shah was accepted into an accelerated medical studies program where he finished a bachelor's degree and medical school at the age of 24. He trained in anesthesiology at Johns Hopkins and went on to sub-specialize in pain management at UC San Diego. He was in the prime of his life when he received the devastating diagnosis of ALS at just 35 years old.

Like fellow Petitioners Mayuri Saxena and Kade Simons, Dr. Minokadeh is a carrier of a Variant of Uncertain Significance of the SETX gene: c.907 T>A (p.Ala969Ala). Shah's SETX variant is not on ClinVar.

Dr. Minokadeh's first symptoms were mostly upper motor neuron dominant and he experienced weakness when running. But his ALS was slow progressing so he continued to practice medicine until December 2015. Four years after symptom onset, he was forced to retire when he could no longer walk and his hands had become weak. However, he had no bulbar symptoms; he was still speaking and eating normally and had movement in his arms.



For many reasons, Dr. Minokadeh brings a unique perspective to Petitioners' case. First, as a patient, he participated in the NP001 trial that showed efficacy with some people stabilizing or regaining bulbar and respiratory function. But then couldn't get more of that or any other investigational drugs. Second, as an anesthesiologist, he has done thousands of lumbar punctures in his practice, the method of delivering NurOwn. Third, as a patient advocate, he has a historical perspective of fourteen years of communications with the FDA; and finally, as he went from a thriving clinical practice to a man who is now trached, he has witnessed the myriad of legislative wins and regulatory failures. Despite this historical knowledge and his quite relevant medical practice, Dr. Shahriar Minokadeh was not chosen to speak at the AdComm's Open Public Hearing. He and both his physician brothers did submit Public Comments: Shahriar, Anush and Ardalan Minokadeh.

Dr. Minokadeh was fortunate to participate in a Phase 2A clinical trial of a small molecule drug called NP001 by drug sponsor Neuraltus.[102] Even though he was on the lower dose, he believes that small molecule drug helped slow his progression. Five years later, in June 2016, he emailed Dr. Woodcock and shared his perspective.

> *"I'm writing to you as both a physician and as a patient who is suffering from the dreadful disease of ALS. I am urging you to please show your compassion and understanding for people with terminal illnesses by helping expand access to experimental drugs…. By the time a current experimental medication gets through research and FDA approval, nearly all of us alive with ALS today will be gone.*
>
> *I participated in a trial in 2011 using a drug called NP001. It's slowed my progression and multiple others have said the same. Due to a lack of funding, they have not proceeded with the next trial. Due to the strict regulations, they have begun to offer this medication to patients in Europe. I feel it's a travesty that US patients -- facing a terrible quality of life, followed shortly after by certain death -- are not given the opportunity to access these drugs. Please expand Right To Try laws and any measures that speed up access to investigational medications for people with terminal illnesses."*

Eventually the company that made NP001 went out of business and the assets were purchased by Neuvivo who now has a pending NDA[103] for a drug that worked on Shah and many others 14 years ago.

Although grateful to be a trial participant, Dr. Minokadeh has criticized the FDA's inhumane regulatory requirement for double-blind protocols in ALS trials that leave as many as 50% of dying patients on placebo without actual treatment during the trial; and then without an open label extension, they have no hope after the trial. This is unimaginable in a 100% fatal disease with rapid progression to paralysis.

But Dr. Minokadeh's lack of access to investigational drugs didn't stop with that NP001 trial:

> *"I've been locked out of any clinical trials or access to investigational treatments since 2013 because of trial restrictions. My family, friends and I have corresponded with the FDA, pharmaceutical companies and neurologists countless times**. Despite my own medical background, knowledge, and connections in medicine, I've not been able to access a single investigational therapy for seven [now eleven years].** The existing pathways of right to try, compassionate use or expanded access, to this day, have only been empty words … I and many other ALS patients heard these words repeatedly, and unfortunately most died while they fought."*

Dr. Minokadeh again wrote to the FDA:

---

[102] The book *"Personal Trials"* tells the story of the NP001 trial. Ben Harris and Rob Tison were in the same trial as Dr. Minokadeh and it helped them too. But then when the trial was over, they couldn't get more.

[103] Neuvivo, Inc. (2025, April 2). Neuvivo seeks FDA approval for its breakthrough ALS treatment NP001. https://www.neuvivo.com/news/neuvivo-seeks-fda-approval-for-its-breakthrough-als-treatment-np001

"I have been in contact with numerous other patients and neurologists throughout the years and have extensively researched and tried off-label treatments. I have never seen the results we are seeing and hearing with the Phase 3 trial of Brainstorm (Nurown). For the first time ***we have reputable people with unprecedented levels of improvement (most recently Matt Bellina from Right To Try).***

I live every day suffering and facing the possibility of dying. ***I know all diseases have heterogeneity and everyone may not have the same response, but this is the case even with chemotherapeutic agents in cancer treatments.*** *I strongly believe you all have the authority and moral obligation to allow expedited access of NurOwn…."*

In 2015 when Shah was forced to leave his medical practice, it occurred concurrently when people in the Phase 2 NurOwn trial were reporting improvements in function. Shah became good friends with Bobby Forster, one of the NurOwn participants who had a profound response and regained function in Phase 2. Shah has been aggressively fighting for the FDA's regulatory flexibility since that time. All to no avail.

Shah tried repeatedly to get access to NurOwn both via Right to Try here in the US and via the Hospital Exemption program in Israel. But even with the law and several medical professionals in his corner, Shah succeeded. Brainstorm responded to the request of Dr. Minokadeh and his physician brothers:[104]

"Investigational therapeutics, such as NurOwn® are highly regulated by the US FDA, and all patients must meet the investigational protocols… If the patient you have referenced does not meet the clinical trial eligibility, he cannot participate in the trial as all participants must meet all inclusion and exclusion criteria. Due to privacy and regulatory issues the Company cannot comment on a patient's eligibility. That is a conversation for the patient and his clinical team to discuss.

Additionally, we would direct you to the Company's publicly stated policy on Right To Try. In a perfect world, small biopharma companies like BrainStorm would have the limitless capacity and resources to give every patient access to experimental treatments, as well as the assurance of knowing that these treatments are safe and effective for every patient seeking them. But regrettably, the practical reality is resources are limited, experimental treatments must be tested for safety and efficacy, and the path to approval of a new treatment is lengthy. With the greatest sympathy for the many thousands of ALS patients seeking access to experimental treatments, BrainStorm cannot offer pre-approval access to NurOwn.

Thank you for recognizing that we are bound by many federal healthcare laws and regulations including patient confidentiality. Brainstorm stays fully committed to advancing the Company's pivotal phase 3 ALS trial towards a BLA submission.

[104] Flaccus, G. (2019, May 28). Doctor seeks experimental ALS treatment for himself. Spectrum News 1. https://spectrumnews1.com/ca/southern-california/news/2019/05/28/doctor-seeks-experimental-treatment-for-himself

If the outcome of the trial is successful, we hope to be able to bring a much-needed solution to ALS patients as quickly as possible."

That was six years ago. In 2019, Dr. Minokadeh was using NIV to breathe and had lost most motor function in his legs. But he was still able to speak some words. In 2022, he underwent a tracheostomy. Today his only way to communicate is with his eye gaze. Six years ago, Dr. Minokadeh told Spectrum News:

"People like me feel like time is running out with no options, with no treatments that we can try to save our lives."

Indeed, when he couldn't get access to NurOwn, Shah tried some of the most aggressive options. In 2016, he had an Ommaya reservoir placed in his skull. Shah used the catheter to try delivering adipose-derived mesenchymal stem cells directly to his CSF to see if he could mimic what NurOwn was doing for people who were in the trials. He did this for approximately 6 months and had absolutely no response. In his "n of 1" study, Shah proved to himself that the mesenchymal stem cells aren't what causes the disease-modifying response with NurOwn; rather, he concluded that it's the neurotrophic factors that the stem cells deliver all throughout the CNS.

2. Petitioner Mayuri Saxena

Petitioner Mayuri Saxena's first ALS symptom was in the summer of 2016 when she began stumbling and tripping. That date would soon cement her fate. Ultimately, she was diagnosed with ALS in 2017 at just 32 years old. Today she is trached, locked-in, and can barely move her eyes. But it didn't have to be that way.

Before ALS, Mayuri dreamed of becoming an Ambassador or the first Secretary of State of East Indian ethnicity. She spent her young life preparing for that dream. She traveled the world learning about different cultures and governments. She earned a double Masters degree in International Affairs and the Inspectors General Program, and was the recipient of the prestigious Presidential Management Fellowship. She tells more or her story in the documentary entitled *"My Final Act."*

Mayuri has no history of ALS in her large extended family, either in the US or in India. Thus, her neurologists at an ALS Center of Excellence rebuffed her request for genetic testing. Two years later, on May 16, 2018, her local neurologist ordered the testing, and Mayuri was surprised to learn that she carries two genetic variants associated with ALS: SOD1 and SETX.[105]

Mayuri's SOD1 variant is a rare pathogenic variant: c.131A>G (p.His44Arg). Researchers estimate the prevalence of symptomatic, familial SOD1-ALS cases at less than 1,500 globally and less than 500 in the US.[106] Notably however, SOD1 mutations are more prevalent in Asian familial populations (30%) compared to European familial populations (15%).[107]

After Mayuri learned of her SOD1 mutation, she visited Dr. Brown, the neurologist who discovered the first SOD1 variant in 1993. As a SOD1 carrier, Mayuri had hoped to enroll in Biogen's Phase 3 Tofersen trial, which ran from March 2019 to July 2021, with 108 participants enrolled across 32 sites in 10 countries.[108] The first time Mayuri applied to get Tofersen trial, she only had lower limb symptoms. In total, Mayuri applied and was refused Expanded Access to Tofesen on four separate occasions.

When another SOD1-ALS patient, Lisa Mauriello, started a national campaign to get expanded access to Tofersen, the ALS community ramped up the pressure and Mayuri applied once again, only to be refused once again. By this time, she was a quadriplegic and using a ventilator to breathe. On April 19, 2021, Mayuri received the last form rejection letter from Biogen. The drug sponsor reasoned it wouldn't be fair to people in the placebo arm. But – people cannot qualify for an EAP if they are able to get into a trial. Thus, there would have been no inequity.

---

[105] Mayuri is also a carrier of a Variant of Uncertain Significance ("VUS") in the SETX gene: c.4663C>G (p.Leu1555Val). Mayuri's SETX variant was added to ClinVar in October 2018 and is currently characterized as "likely benign." But other SETX variants are associated with juvenile onset of ALS called ALS4.

[106] Brown, C. A., Lally, C., Kupelian, V., & Flanders, W. D. (2021). Estimated prevalence and incidence of amyotrophic lateral sclerosis and SOD1 and C9orf72 genetic variants. Neuroepidemiology, 55(5), 342–353.

[107] Huang, M., Liu, Y., Yao, X., Qin, D., & Su, H. (2024). Variability in SOD1-associated ALS: Geographic patterns, clinical heterogeneity, molecular alterations, and therapeutic implications. Translational Neurodegeneration, 13(1), 28.

[108] Miller, T. M., Cudkowicz, M. E., Genge, A., Shaw, P. J., Glass, J. D., Andrews, J. A., Babu, S., Benatar, M., ... Fradette, S. (2022). Trial of antisense oligonucleotide tofersen for SOD1 ALS. New England Journal of Medicine, 387(12), 1099–1110.

On June 13, 2021, Mayuri commented on this inhumanity on her X account:
"After being denied SOD1 ALS treatment multiple times, now I'm on life support at age 36."

Mayuri's case illustrates the regulatory fallacy that 32,000 people with ALS could use EAP as an option to access investigational drugs pending Phase 3 trials. Even though Biogen is a large pharmaceutical company with a $40B market cap, significant financial resources, an extensive patient assistance program – and the treatment population was less than 500 symptomatic SOD1 carriers – Mayuri was never able to try Tofersen via Expanded Access. And by the time Tofersen was FDA-approved in 2023, Mayuri was told her ALS was too far progressed for Tofersen to help.

This is a cruel irony. As you can see in this interview with Dana Perino, this story on FOXNews, and this story in the NY Daily News, Mayuri and her brother Mayank were critical in the passage of the Act for ALS, which helped fund Expanded Access for people with ALS. But she could never get access to the one drug that, today, is helping people with SOD1-ALS halt their progression. Mayuri can only watch from the sidelines and wonder *"what if ?"* Today Mayuri's ALSFRS-R score is 0 on the 48-point scale.

3. Petitioner Patricia Manhardt

Patricia Manhardt lost her fight against ALS on February 25, 2025. Her daughter Laura shared that her Mom wanted this Dylan Thomas quote on her headstone:

"Do not go gentle into that good night....
Rage, rage against the dying of the light."

And rage Patty did. Patty was fierce ... an advocate extraordinaire. From the time she was diagnosed with ALS in July 2020, she started to fight to get quicker access to investigational drugs. Patty was critical to the passage of the Act for ALS. She did hundreds of zoom calls and sent thousands of emails. And when ALS took her voice, her Tobii continued to carry her powerful message. She advocated for sponsors for Congressman Wenstrup's Benefit Act that requires the FDA to "consider relevant patient experience data in the risk-benefit assessment framework used in the process for approving new drugs." She fought for the Promising Pathway Act – a conditional approval pathway for drugs being developed for terminal rare diseases like ALS – and was critical in getting then-Senator Vance to sponsor it. In May of 2025, I AM ALS honored Patty for her advocacy.

Patty was also one of the most outspoken advocates for NurOwn's approval. Diagnosed in July 2020, she was too late to qualify for the trial, which was fully enrolled just a few months earlier. But that didn't stop her from fighting. She submitted an impassioned Public Comment to the FDA.

You can witness Patty's fight – and her lethal decline from ALS – in the series of interviews she did over the years with Sheree Paolello of WLWT.

- 5.27.21 -- " ALS patients fight for more trials as there's few drugs available to treat deadly disease." At the end of the story is a 48-minute raw interview including one person in the NurOwn trial who benefited but died waiting when he couldn't get more.
- 11.4.21 - Dying for time: ALS patients push lawmakers to expand drug access

- 12.17.21 - ACT for ALS: A Mason mother's fights to treat ALS
- 5.11.23 -- Local patients raising national awareness for ALS, fighting for faster treatment
- 5.30.24 -- Greater Cincinnati residents make trip to Washington, D.C. for fight against ALS

Patty was relentless. But so too was her ALS. In 2022, Patty could no longer transfer on her own, but she made the inaugural trip to DC for the first annual I AM ALS flag event. Sitting in her wheelchair in front of a sea of 6,000 blue flags planted on the Washington Mall, Patty's speech moved people:

> *" We need to believe in the FDA, that they will begin approving drugs that have shown promise. Some drugs have shown more than promise as some trial participants witness themselves begin to reverse their symptoms. You would think as soon as these drugs began to reverse their symptoms that these drugs would be sped through the approval process… We need those drugs to be approved even though they're not the Silver Bullet. We need something that will help us immediately. We need urgency in the approval process. We need accelerated approval. We cannot wait. We are dying today. Because of the heterogeneity of ALS, there will never be one drug that helps every single person with ALS. That would be like saying there should be one chemotherapy that will help everyone with any kind of cancer. It just won't happen."*

In 2023, Patty again drove from Ohio to DC for the Flags on the Mall event with I AM ALS. This time when she was interviewed, she was having more trouble breathing and she had lost the use of her left arm and hand. This illustrates why the FDA must act with urgency. Every year, every month, and every day of delay, more motor neurons die. People don't get to push "pause" on the destruction while they wait on the FDA. It was on this trip that she met Murkowski, the Chair of the ALS Caucus and now-VP Vance who was her Senator from Ohio at the time. VP Vance sponsored the conditional approval, Promising Pathway Act because of Patty's outreach.

Patty closed her Public Comment by imploring the FDA:

> *"If I was in a burning building, firemen would try to save me no matter what. If I was in a sinking ship, people would try to throw me a life preserver. If I was buried in an earthquake, people would try to dig me out. We need somebody to try to rescue us, and that's where you come in. I am begging for you to give me — to give us -- a chance.* ***Approve NurOwn. We are dying waiting****."*

After the NurOwn AdComm vote, Patty, like thousands of others in the ALS community, was devastated. For years, she had been fighting for access to investigational drugs. She knew another trial would take years. Years that most ALS patients don't have. Patty knew she was already on the ALS clock. She told her local NBC anchor:

> ***"If Congress can't help us and the FDA doesn't change their mind, I will see my friends die and they will see me die"***

On October 22, 2023 after Brainstorm withdrew its BLA the ALS community was devastated. Patty lamented: *"As my grandchildren will not know me & my children will mourn me, I would like you to explain to them why I had to die."* There was nothing that she wanted more than to grow into old age watching all her kids have their own kids. The FDA's decision to delay NurOwn's approval deprived her of that chance.

Just last month in May of 2025, Patty's daughter Laura made the trip to DC without her:

> *"In her battle with ALS, my mom went anything but gently. She tried every treatment and supplement and therapy she could, spoke with anyone and everyone who would listen, and pushed her failing body as far as it would go in the pursuit of surviving this disease.* ***She raged and we raged and still ALS stole everything from her, then stole her from us."***

4. Petitioner Jamie Rose Berry

Jame Rose Berry lived life with a *joie de vivre*. When ALS tried to derail her dreams, she poured that same passion into ALS advocacy where her brilliance and unrelenting spirit were surpassed only by her brutal candor that moved everyone who crossed her path.

It all started with a limp at the end of 2019, a few months before Jamie finalized the adoption of her daughter Chloee. Two years later, in December 2021, Jamie Berry was in neuro ICU at Stanford, fighting for her life. Her Congresswoman, Anna Eshoo, rose on the floor as the House was about to vote on the Act for ALS, the bill Jamie had fought so hard to pass. Chair Eshoo quoted Jamie's "poignant" plea, imploring her to help people with ALS access investigational drugs:

> *"With ALS, a piece of you dies every day. We are simply asking for a fighting chance to live the lives we were meant to live…."*

Jamie fought hard and eventually came home, but ALS took her life on November 9, 2022 – less than 3 years after that first limp.

Before Jamie died, Congresswoman Eshoo sent Jamie a Letter that read:

> *"You are a source of inspiration to me and your highly effective advocacy has given hope to hundreds of thousands of Americans living with or impacted by ALS. It's been a great honor to amplify your powerful message and work with you to advance the Act for ALS. I will continue to work with ALS advocates to ensure all aspects of the law are implemented swiftly and effectively to deliver promising therapies for those living with ALS as soon as safely possible. I want you to know how much I admire your strength and optimism throughout your fight with this terrible disease. I keep you in my daily prayers. You are a precious partner."*

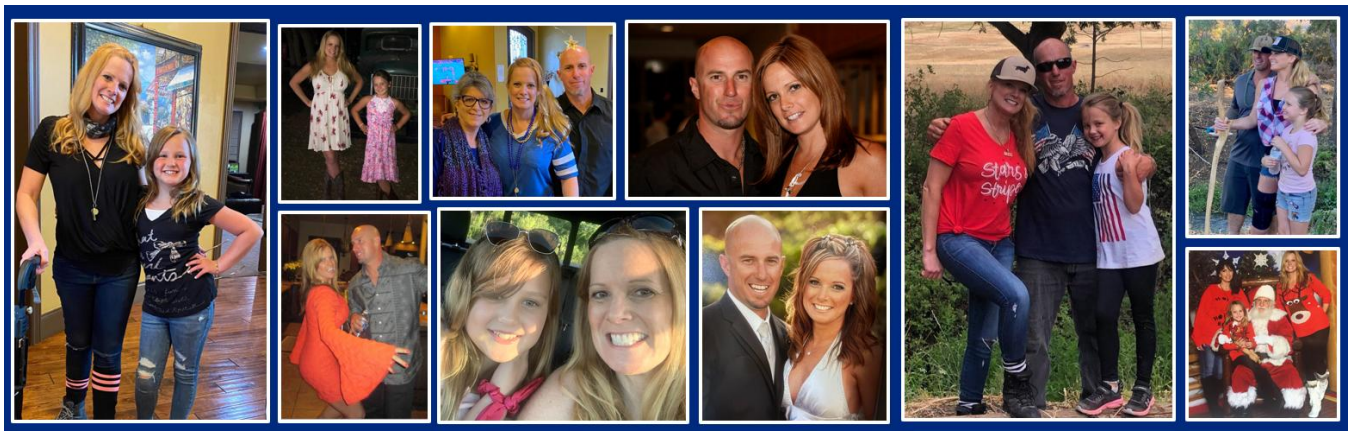
Then she visited Jamie at her ranch. She presented Jamie's family with a flag that had flown over the Capitol and the speech in the Congressional Record that mentioned Jamie.

Jamie documented her advocacy, her life with ALS, and her decline in both prose and a video diary. Reminiscent of the AIDS activists, Jamie poked and provoked you to care. In this tear-jerker of Halloween video, she pleaded for access to NurOwn:

"I am NOT giving up, but with every passing day of Hell, it is becoming increasingly difficult. What does it take to be heard? Do we need to wear matching Zebrafish outfits?"

Jamie sent all these videos to members of Congress -- as well as Dr. Janet Woodcock and Dr. Peter Marks. Petitioners implore you to watch them.

- Sept 2020 - ALS is holding us hostage
- Feb 2021 - “Lost Cause” video sent to FDA pleading for NurOwn
- Feb 25, 2021 - “Hurricane ALS” poem about ALS diagnosis
- Feb 26, 2021 - Plea to FDA: “We are asking for a chance to live. I want to live.”
- May 8, 2021 - Mother’s Day video sent to FDA
- May 19, 2021 - Poem - Dying with Red Tape
- June 22, 2021 - A Year in the Life with ALS
- June 2021 - Dancing with her walker at a Birthday Party
- July 2, 2021 - Poem - What do we have to Lose?
- Aug 28, 2021 - A Year in the Life with ALS
- Sept 21, 2021 - How ALS Destroyed my Legs in Six Months
- Sept 25, 2021 - Approve NurOwn with Phase 4 Post-Marketing Program
- Oct 3, 2021 – 2015 to Now. The Regulatory Timeline vs My Life
- Oct 23, 2021 - “Goodbye My Lover “- Jame and her husband Jason
- Oct 29, 2021 - A Halloween Plea for NurOwn - “Don’t Give up on Me”
- Nov 11, 2021 - ALS Progression is Shocking
- Dec 9, 2021 - Rep. Eshoo mentions Jamie on House floor as bill passes the House
- January 2022 - NYE 2020 to 2022: 24 months of ALS Progression
- Jan 24, 2022 - 1,000,000 Minutes with ALS
- Feb 2022 – How ALS changed my body in 18 weeks
- Feb 25, 2022 - File the BLA: 13 Women Asking the FDA to approve NurOwn
- Feb 25, 2022 - 18-week Timeline of ALS
- May 10 2022 - Poem & Video: My Beautiful Life
- May 30, 2022 - CBS-KPIX story: END ALS plowed into field south of San Jose
- June 6, 2022 - Why Every Point Matters with Chloee



Amidst all of her advocacy, Jamie was also asking why did I get ALS?

Jamie has no family history of ALS, and as such, she was surprised when her Invitae test showed she was the carrier of two VUS that might have been implicated in her ALS: ERBB4 and HFE. Her neurologists told her those VUS may not be related to her ALS and even if they were, there were no therapies targeting those mutations and there was nothing she could do. Like most ALS patients, all they offered was the advice: go home and do your bucket list while you still can. But Jamie was diagnosed at the start of the pandemic.

Never one to take no for an answer, Jamie and a friend turned into "citizen scientists" and began to do their own research. After a little more digging, they discovered a generic Parkison's drug, zonisamide, they postulated might be helpful to people with her ERBB4 variant. But researchers needed to do a lot more studying before they could tell her if it was safe to try. To this day there's been no progress investigating if either of Jamie's mutations are pathogenic, if they increased the risk or modified the expression of her ALS, or if Zonisamide could have helped her.

Unfortunately, Jamie is also the poster child for the possible Gene-Time-Environment theory of ALS. A tomgirl, Jamie, was raised on a ranch in New Almaden, California, about 12 miles south of San Jose. She sustained concussions from ATV crashes, played in fields during crop-dusting with the herbicide 2,4-D, and rolled in freshly sprayed hay. Her family ran a fertilizer and pesticide business and like many in rural communities, they burned trash in empty 50-gallon drums. Stommel et al. (2021) has reported a strong association between 2,4-D exposure and ALS risk.[109] Only Jamie's functional medicine doctor ever seemed interested in her exposures to toxins known to be associated with ALS.

In the midst of Jamie's advocacy, her 9-year old daughter, had been watching from the sidelines. She wanted to help so she recorded her own video to surprise her Mom. Chloee told the FDA:

> *"My mom has ALS. You're just trying to make a decision. Make the decision. And it should be 'yes.' My mom needs this. There's lives out there. It doesn't get better. It just gets worse. It's just not cool that you have something out there. Maybe it works on my mom, or maybe it works on those other people who have ALS. And if it does, that's a big difference because they can't walk."*

An outspoken advocate with common sense and no filters. Like mother, like daughter.

[109] Andrew A, Zhou J, Gui J,... Li M, Guetti B, Nathan R, Tischbein M, Pioro EP, Stommel E, Bradley W. Pesticides applied to crops and amyotrophic lateral sclerosis risk in the U.S. Neurotoxicology. 2021 Dec;87:128-135.

5. Petitioner Tara Collazo

Petitioner Tara Collazo was diagnosed with ALS in April 2019 at 60 years old. Her first weakness was in her non-dominant left arm, followed by fasciculations and cramping in her abdomen. Then it moved on to her left hand and next to her right hand.

a. NurOwn Trial - Did Not Qualify

Shortly thereafter, in July 2019, she traveled from Argyle, Texas to San Francisco to screen for the NurOwn trial at the Forbes Norris ALS Clinic at California Pacific Medical Center ("CPMC"). In her Public Comment, Tara talks about the cruelty of qualifying for ALS trials:

> *"In April 2019 I was faced with a crossroad: 'You have ALS.' Heartbreaking. I visualized myself at the end of my life, paralyzed and gasping for air. This picture was eye-opening. Three months later, in July 2019, I began the screening process for the NurOwn trial…. My ALS score was 44/48. After four months of screening, I faced a second heartbreaking crossroad. I declined two points on my ALS score, now 42/48. To meet the trial criteria, I was told the slope of decline needed to be at least 1 point per month…My slope was not steep enough to continue to the next phase and I was excluded from the trial. My world, my hope, was shattered."*

Without NurOwn, Tara continued to decline. Ultimately on the day of the AdComm in September 2023, she was just over 4 years post-diagnosis and her ALSFRS-R had plummeted to 19/48. She said it was no longer safe for her to live independently as she could not do most ADLs. She was unable to dress, feed or care for herself. Her hands had limited function; she could not walk and her breathing was rapidly declining. Tara's Public Comment illustrates the inhumanity of waiting for an ALS therapy to slowly meander its way through the regulatory process for the last six years:

> *"Two different, heartbreaking crossroads. When I had a chance to enter the NurOwn trial I wasn't sick enough. Now that the treatment may become available, I may be too sick to receive it."*

Despite this, and like so many with ALS, Tara sees this fight as bigger than her own mortality. It's about so many thousands of others who will come to that same heartbreaking crossroad in the future. She asked the FDA to approve NurOwn as it could *"offer the next generation of patients HOPE"* -- something our regulatory system deprived her of.

Tara eventually screened and qualified for the Healey platform trial. She started on Regimen C, Clene's CNM-Au8. The trial has not been unblinded so she doesn't know if she was on the drug or placebo, but she then had 11 months of the CNM-Au8 gold nanoparticles via Open Label Extension (OLE).

The following table summarizes her ALSFRS-R scores and loss of function from her 2019 diagnosis to today. Importantly, Tara's data demonstrates two factors that may have improperly impacted the trial results of Clene's CNM-Au8: (1) non-dominant hand ceiling effect; and (2) floor effect.

b. Non-Dominant Hand Onset May Have Impacted CNM-Au8 OLE Outcome

A ceiling effect is caused by non-dominant hand onset as described above. This may have impacted the CNM-Au8 trial and OLE results. From the time of her diagnosis until the start of Clene's trial, Tara lost function in her non-dominant left hand. The three questions in the fine motor skills domain didn't accurately assess that loss until the loss of function moved to her dominant right hand – which was predominantly during the CNM-Au8 OLE.

- **Handwriting:** not affected until loss of function moves to dominant hand
- **Cutting food and using utensils:** minimally affected as most tasks = dominant hand
- **Hygiene/Dressing:** Hygiene minimally affected as most hygiene = dominant hand; whereas dressing is somewhat impacted as things like tying shoes, pulling up pants, and fastening buttons, belts and bras do require the use of both hands.

Graphic - Tara Collazo's Real-world data - CNM-Au8 and Pridopidine Trials

TRIAL	DATE	ALSFRS-R	COVID Vax	Total Δ	Fine	Gross	Bulbar	Resp	Comments
	Apr-19	48							ALS Diagnosis - Onset in non-dominant L arm
NurOwn Screening	Jul-19	44			-1				NurOwn screening. -1 Dressing
	Aug-19	43			-1				-1 Cutting Food
	Sep-19	42		-2					NurOwn screening ended. Slow progressor. Did not qualify
	Aug-20	37		-5	-3	-2			**-1 point each in handwriting; cutting; dressing (all dominant hand); adjusting sheets; and walking**
CNM-Au8 RCT	Sep-20								CNM-Au8 trial starts.
	Nov-20	37							**LH & RH weakness; difficulty cutting food, gripping objects, weakness in arms, legs**
	Feb-21	35	x						CNM-Au8 trial ends & OLE begins. Had trouble putting on bra.
CNM-Au8 EAP	Mar-21	35	x	0					**R Hand (dominant) starts to deteriorate more.** Intense twitching.
	Apr-21	32		-3	-1			-2	**-1 point each: dressing...NIV...dyspnea**
	Jun-21	30		-2	-1	-1			**-1 each: using utensils...turning in bed**
	Aug-21	29	x	-1	-1				**-1 utensils**
	Sep-21	26		-3		-3			-3 total gross motor: walking...using stairs
	Oct-21	25		-1		-1			-1 stairs
	Nov-21	24		-1	-1				**-1 handwriting (dominant hand)**
	Jan-22	24		0					CNM-Au8 EAP ends
	Feb-22	23		-1	-1				**-1 handwriting (dominant hand)**
Pridopidine EAP	May-22	22		-1	-1				**Pridopidine EAP dosing starts. -1 Handwriting (dominant hand)**
	Aug-22	21		-1	-1				-1 assist dressing, total dependence, complete loss
	Jan-23	21							Started using toilet lift chair.
	Mar-23	20		-1		-1			-1 walking, Fell in Home Goods parking lot
	Jul-23	19		-1		-1			-1 turning in bed, adjusting sheets. Also trouble getting up from recliner and motor chair
	Dec-23	18				-1			No purposeful leg movement
	Dec-24	18							No Limb Function
	Jun-25	18							Still able to talk, eat, drink, swallow; bipap only when sleeping at night

In the 22 months from April 2019 through February 2021, she averaged a loss of .6 points per month on the ALSFRS-R scale. From February 2021 through January 2022, she lost 11 points in 11 months during the CNM-Au8 OLE. This averages out to be a 1 point per month loss of function – an increase in the speed of decline once her ALS spread to her dominant hand.

c. Floor Effect Example

Tara's ALSFRS-R scores also exemplify the real-life implications of the floor effect. She describes her hands as "completely limp and weak, like dead fish." For 3 years, she has been unable to write, feed, dress or groom herself. Thus, she has scored 0/12 points in the Fine Motor domain. But she can still text using her knuckles. She can still move her arms enough to push her hand into the wheelchair joystick – just enough to move her wheelchair unassisted. These two discrete acts allow her to maintain independence. But if she loses these functions, the ALSFRS-R won't pick up these critical losses – making it appear as if she long ago stabilized in the fine motor skills domain.

Similarly, in September 2023, Tara could not walk, climb stairs or move in bed. Thus, the gross motor skills domain score was 0/12. But – she could still stand to transfer and pivot from one chair to another. Today she is completely unable to stand and needs a Hoyer lift for transfers. She points out this slight decline was not captured in the ALSFRS-R score, but it was a significant difference in the burden on caregivers.

d. Pridopidine EAP has been Life-Changing

Despite her year of rapid decline, hope sometimes comes in unexpected ways. Three years ago, Tara joined the small Expanded Access program for Prilenia's small molecule drug Pridopidine. This is only fitting as Tara was one of the advocates who fought to pass the Act for ALS that funded this EAP. In three years in the Pridopidine EAP, she has only lost 5 points. This averages only 0.14 points per month.

Pridopidine is a selective Sigma-1 receptor (S1R) agonist[110] that targets respiratory and bulbar function. S1R activation by pridopidine exerts neuroprotective effects, including by increasing BDNF and GDNF (See Figure 4 in study) – two neurotrophic factors also impacted by NurOwn. Additionally, Pridopidine enhances neuromuscular junction (NMJ) formation and function, promotes neuronal survival via ERK pathway activation, and boosts mitochondrial functioning.[111]

Like NurOwn, Pridopidine failed to meet its primary endpoint in the Phase 2/3 trial. But just like NurOwn, Pridopidine appears to work on a subgroup of people earlier in ALS progression. So, this outcome is not surprising. In this Phase 2/3 Pridopidine trial, fast progressors who were less than 18 months from symptom onset had "substantially less decline" with a 5+ point slower progression on Pridopidine than placebo.

It had an impact on two of the four targeted domains in the ALSFRS-R: the ability to speak and breathe. But those domains were "only" secondary endpoints so they suffered the plague of the multiplicity

[110] Nuedexta, a weaker S1R agonist, also causes improvements in bulbar symptoms in ALS. It was approved in 2010 for the treatment of pseudobulbar affect (PBA). In a 2017 study in Neurotherapeutics, researchers reported that Nuedexta causes improvements in bulbar symptoms in ALS. This was confirmed in a 2022 study. It is not approved in ALS but is now prescribed off-label.

[111] Ionescu, A., Gradus, T., Altman, T., … Hayden, M., & Perlson, E. (2019). Targeting the sigma-1 receptor via pridopidine ameliorates central features of ALS pathology in a SOD1G93A model. Cell Death & Disease, 10(3), 210.

penalty on statistical endpoints. They also demonstrate why it's more appropriate to use the "Totality of the Evidence" methodology that assesses the impact on multiple domains across multiple points of time throughout the trial.

And also like NurOwn, Pridopidine's impact on breathing function is transformational because most people with ALS die of respiratory failure.[112] Thus, any extension of respiratory function – whether on Pridopidine or NurOwn – is "reasonably likely to predict a clinically meaningful impact" on extended survival. Objective changes in respiratory function should be able to be used as intermediate endpoints to support accelerated approval.[113]

Today Tara has lost all use of her limbs; she is effectively a quadriplegic. But consistent with Prilenia's trial data, Pridopidine appears to have preserved her bulbar and respiratory function. Tara only uses a bipap when sleeping at night. And she can still eat, drink, and swallow normally. Pridopidine has been life-changing for Tara. She shared how much independence Pridopidine has helped her maintain:

> *"Because of Pridopidine I can still breathe well and speak clearly. And because of newer technology, I have a voice activated, smart home. I am able to turn my TV on and off, adjust the volume and change channels with my voice. I am able to use my voice to turn on lights throughout my home. I use Ring devices to answer the front door, unlock it if I need to, using my voice. I use Alexa devices throughout my house to notify family members whenever I need help. For example, when I wake in the morning, or when I am finished in the bathroom, I call out to Alexa to call someone to provide assistance."*

And because of Pridopidine, she can still speak at Congressional town halls, read a book to the grandkids, and tell her family how much she loves them. Never doubt how clinically meaningful these things are.

Today, Tara has lived 74 months both NIV-free and trach-free. That is 45 months longer than 29 month Time-to-NIV natural history for intermediate progressors. It is also 44 months longer (2.5x) than the 30-month natural history for median trach-free survival in ALS. She believes Prilenia's Pridopidine has given her that chance to spend more time making memories with her grandkids.[114]

[112] Niedermeyer, S., Murn, M., & Choi, P. J. (2019). Respiratory failure in ALS. Chest, 155(2), 401–408.
[113] Although not the focus of this Citizens Petition, Petitioners do believe that FDA-CDER should exercise its regulatory flexibility, analyze the impact of for Pridopidine on bulbar and respiratory function alone, and rush it to market for the 32,000 Americans whose respiratory and bulbar function could be preserved with Pridopidine.
[114] Although the focus of this Petition is Brainstorm's mesenchymal stem cell therapy, NurOwn, Petitioners also believe there is ample evidence to approve Pridopidine – based on the impact on the subdomains of bulbar and respiratory function.

M. Biomarker Data is Supporting Evidence of Efficacy and Reasonably Likely to Predict a Clinically Meaningful Benefit

Brainstorm conducted one of the largest biomarkers studies ever performed in an ALS trial. This study was detailed in a secondary analysis plan for the trial focused on biomarker data, and the SAP was approved in advance of the database lock. Brainstorm is the first drug sponsor that had the foresight to collect CSF at so many points in time across an ALS trial and then to use AI and machine learning to analyze those data. These findings are informative not only in this NurOwn trial, but in all ALS trials in the future, adding significant knowledge to the dataset in ALS.

Brainstorm's longitudinal CSF biomarker data confirms that NurOwn hit its target engagement and offers a "plausible mechanism of action" to treat ALS. The biomarker results were published in Muscle and Nerve on April 10, 2024 – over six months after the AdComm.

The authors were Dr. Bowser (Barrow),[115] Dr. Windebank (Mayo),[116] Dr. Cudkowicz (Mass Gen)[117] and senior author Dr. Brown (UMass)[118] – along with other trial PIs. Dr. Windebank discussed the importance of the findings:

> *"The publication of these findings is important because it demonstrates a potential biologic mechanism by which modified mesenchymal stem cells (debamestrocel) may benefit patients with ALS."*

Petitioners note a few important things about the collection of first-in-class CSF biomarkers at 7 times during the 28-week trial:

- NurOwn caused "significant changes" in 29/45 (64%) of biomarkers analyzed.
  - 89% Neuroprotection
  - 63% Neuroinflammation (both pro-inflammatory and anti-inflammatory)
  - 50% Neurodegeneration
- No one on placebo had these biological changes in CSF biomarkers
- Participants most impacted by the floor effect (baseline ALSFRS-R ≤25) had biomarker results "largely consistent with the overall population, suggesting [NurOwn] remains biologically active regardless of clinical progression."

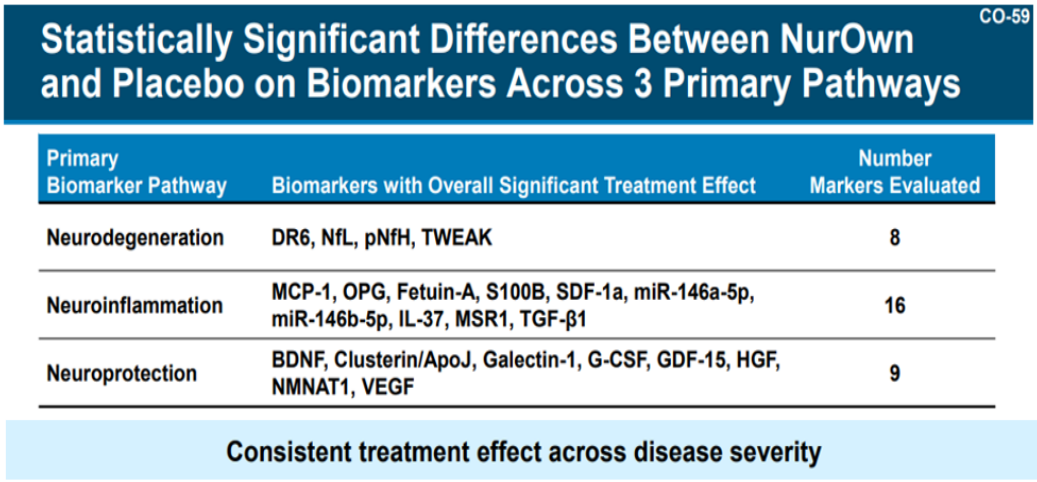
[115] Dr. Bowser is an internationally recognized KOL in ALS biomarker research. For more than 25 years, he has worked on discovering and validating ALS biomarkers. Dr. Bowser has over 120 peer-reviewed publications, has been cited over 14,000 times with an h-index of 67 and i10 index of 156. NIH just awarded he & Barrow a one-year $16.7M grant to establish a biorepository for ALS research.

[116] Dr. Windebank has published 650 scholarly articles or abstracts, including more than 300 full-length publications in peer-reviewed journals. He has been cited nearly 30,000 times with an h-index of 92 and i10 index of 284.

[117] Dr. Cudkowicz has over 500 peer-reviewed publications, has been cited nearly 33,000 times with an h-index of 101 and i10 index of 255. She was inducted into the NAM in 2019 for her work in ALS. She serves on FDA's PCNS AdComm.

[118] Dr. Brown has over 300 peer-reviewed publications, has been cited over 85,000 times with an h-index of 135 and i10 index of 440. Dr. Brown was elected to the NAM in 2010, recognized for his groundbreaking work in ALS.

Graphic - NurOwn CSF Biomarkers across 3 Primary Pathways



1. CSF Biomarkers Demonstrate Target Engagement

In its briefing document, Brainstorm presented the biomarker results from its Phase 3 study that showed "robust and favorable" changes over time among NurOwn-treated participants. The impact of NurOwn treatment across many biomarkers was rapid, as measured by the large magnitude of change from baseline recorded two weeks after the first treatment (Figure 5; Section 6.3.8), while other biomarkers had gradual change with the largest change observed from baseline at the final assessment at Week 20.

When reviewing the CSF biomarker levels over time for biomarkers that changed rapidly after the first treatment (e.g., Gal-1, TGF-β1, and MCP-1), a pharmacodynamic relationship was observed.

> *"Converging lines of evidence suggest a connection between early favorable changes in many of the neuroinflammation and neuroprotection CSF biomarkers assessed in the Phase 3 study and long-term patient outcomes, including markers of neurodegeneration, such as NfL (Beers & Appel, 2019; Beers et al., 2017). The pathophysiology of ALS is characterized by a complex interplay between inflammation and neurodegeneration. Inflammatory processes, involving microglia and glial cells, can contribute to the progressive damage of motor neurons; while protein misfolding, excitotoxicity, and mitochondrial dysfunction collectively contribute to the degenerative process (Liu & Wang, 2017; Zhang et al., 2023). Hence, NurOwn's early effect on neuroinflammation and neuroprotection, with the change detectable as early as two weeks post-dosing in some biomarkers and lasting over several weeks/months, are important to halting the self-perpetuating cycle of neurodegeneration (Zhang et al., 2023)."*

(Sponsor's Brief pages 24-25).

a. Dr. Bowser's Presentation at 2023 AdComm

Dr. Bowser presented the biomarker data at the NurOwn AdComm. In the published study, Brainstorm reported that treatment with NurOwn led to "significant changes in 64% of the 45 analyzed biomarkers," spanning critical pathways involved in ALS: neuroinflammation, neurodegeneration and neuroprotection. Table S3 in the supplement identifies 23 of those biomarkers with statistically significant p-values ranging from 0.037 to less than 0.001.

Graphic - NurOwn Biomarker Changes (Table S3 in Muscle & Nerve)

TABLE S3 Excerpt: Biomarker Baseline & Percentage Change from Baseline

			Baseline		% Change relative to Baseline			
Type	Benefit	Biomarker	NurOwn (N=93)	placebo (N=92)	NurOwn (N=93)	Placebo (N=92)	Delta	p-value
Neuroprotection	↑	BDNF	0.129	0.13	102	23.4	78.6	0.261
		Clusterin/ApoJ	10570630.27	11090114.1	29	1.7	27.3	<.001
		G-CSF	90.135	94.287	28	1.5	26.5	0.001
		GDF-15	304.427	322.694	41.8	1.2	40.6	<.001
		Galectin-1	6000.05	5424.42	51.5	2	49.5	<.001
		HGF	253.146	259.786	21.7	1.8	19.9	0.005
		LIF	0.41	0.187	262.1	51.7	210.4	0.021
		NMNAT1 (NPX)	7.276	5.854	57	1.5	55.5	0.01
		VEGF	5.731	6.355	368.7	-12	380.7	<.001
Neuroinflammation (ANTI)	↑	Fetuin-A	1684109.383	1600013.914	48.9	-4.7	53.6	<.001
		LAP (TGF-β1)	2603.447	2441.684	45.4	-11.2	56.6	0.001
		IL-37	1.997	2.226	105.8	-6.1	111.9	<.001
		MSR1 (NPX)	106.244	108.1	98.4	10.1	88.3	<.001
		hsa-miR-146a-5p	0.041	0.037	115.4	24.8	90.6	0.02
		hsa-miR-146b-5p	0.012	0.012	196.7	8.3	188.4	<.001
Neuroinflammation (PRO)	↓	Chitotriosidase-1	12844.554	15430.29	-4.6	-1.5	-3.1	0.374
		MCP-1	487.048	519.493	-31	-0.2	-30.8	<.001
		OPG	12.848	12.995	-69.7	-0.3	-69.4	<.001
		S100B	26.346	29.453	-24.9	-6.9	-18	0.004
		SDF-1a	861.792	911.282	-13.9	-0.2	-13.7	0.004
		TREM-2	451.406	444.899	-3.3	6.1	-9.4	0.137
Neurodegeneration	↓	Caspase-3	9.802	8.463	-11.3	13.8	-25.1	0.237
		DR6	1019.576	1127.639	-51.2	-6.6	-44.6	<.001
		NfL	5209.214	5687.925	-11	-1.6	-9.4	0.037
		TWEAK	1025.487	1156.138	-42.9	0.5	-43.4	<.001
		Tau	60.743	68.045	-2	4.5	-6.5	0.216
		UCH-L1	2401.012	2456.133	-5.2	1.1	-6.3	0.217
		pNfH	3240.308	3471.033	-13.1	-6.4	-6.7	0.183
Other		Follistatin	31.703	30.048	66.1	2.6	63.5	<.001
		hsa-miR-124-3p	0.065	0.064	-24.8	10.4	-35.2	0.022
		hsa-miR-132-3p	0.014	0.012	97.2	25.2	72	0.166

Source: Muscle & Nerve, Supplement (April 9, 2024)

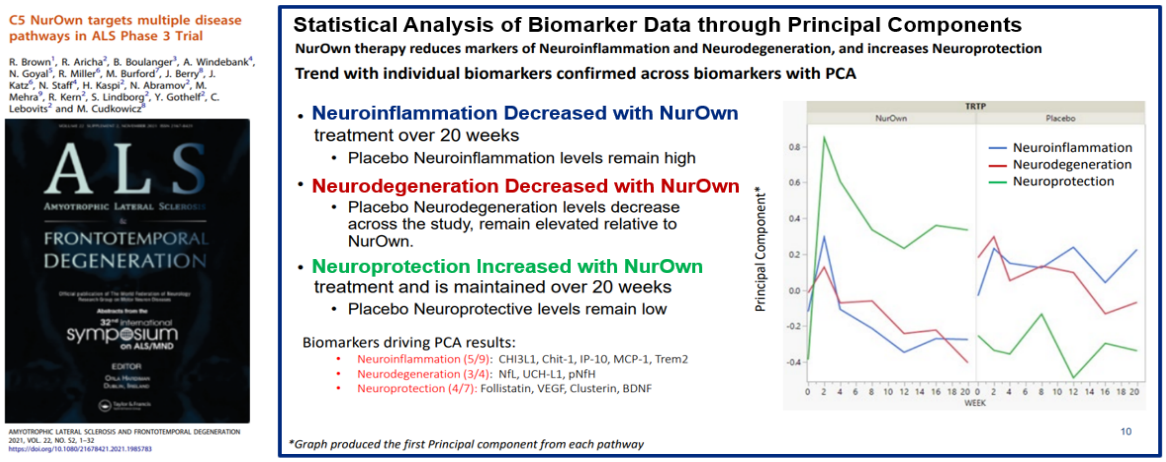
b. Dr. Brown's 2021 Presentation of the CSF Biomarkers

At the 2021 ALS-MND Scientific Conference on December 7, 2021, Dr. Robert Brown presented the early results from NurOwn's biomarker analyses. Dr. Brown overviewed the three approaches they used to assess the impact of NurOwn on ALS disease pathways of neuroprotection, neurodegeneration and neuroinflammation:

1. Analysis of individual biomarkers
2. Principal Component Analysis (PCA) of all biomarkers simultaneously within each pathway
3. Regression modeling using machine learning to predict outcome

In the presentation slides are the initial data linking the plausible mechanism of action to NurOwn's impact on ALS progression. As mentioned above, NurOwn significantly and consistently elevated markers of neuroprotection and lowered markers of neuroinflammation and neurodegeneration over time – all as compared to placebo. Those Individual biomarker findings were confirmed by the PCA analysis,[119] which revealed distinct patterns that differentiated responders from non-responders. The PCA analysis is yet another way of looking at the totality of the evidence – across the entire duration of the trial, and across various CSF biomarkers – rather than just looking at one biomarker at one static point in time at the end of the 28-week trial.

Graphic - NurOwn CSF Biomarkers PCA across 3 Primary Pathways



But notably, pre-specified statistical modeling leveraged machine learning and highlighted biomarkers that are predictive of a treatment response with NurOwn with high accuracy (>80%).

[119] PCA is a critical tool for understanding CSF biomarkers in ALS due to the disease's complex heterogeneity. PCA simplifies multidimensional data by reducing it into principal components that capture the most significant patterns of variability, enabling researchers to identify key biomarker combinations that predict progression rates (e.g., ALSFRS-R slope), and assess objective biological response rates. This approach is particularly valuable in ALS, where traditional single-biomarker analyses often fail to account for the diverse clinical presentations and genetic factors whereas PCA can highlight underlying biological processes—like inflammation or neurodegeneration—that drive disease severity and survival outcomes.

Beyond the slides what was important was what Dr. Brown said. Commenting on the PCA analysis, he noted that the neuroprotective biomarkers increased "very sharply" in the NurOwn treated group but remained "quite low" in the placebo treated groups. As to NfL, he noted that the *"direction here is frankly eye-popping."*

c. Totality of CSF Biomarkers Demonstrate a Treatment Effect and Validate the Plausible Mechanism of Action

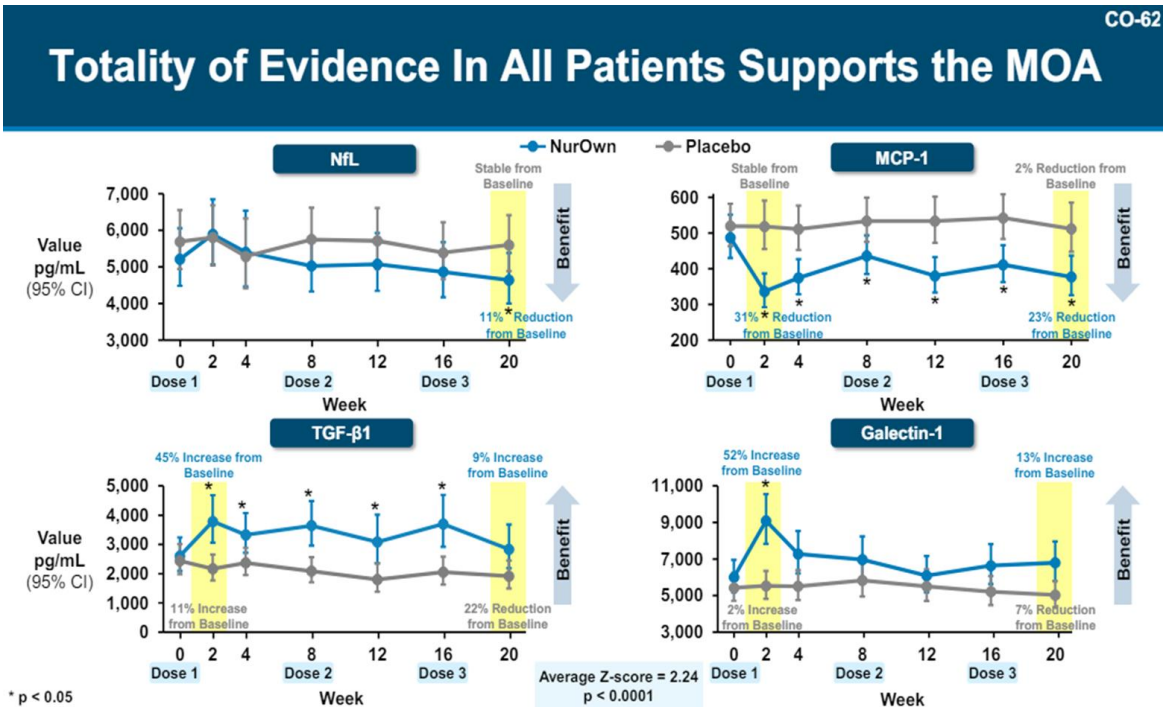
Using Dr. Lee-Jen Wei's Totality of the Evidence methodology, Dr. Bowser presented these data at the NurOwn AdComm. Commenting on the strength and consistency of this statistical analysis, Dr. Bowser remarked:

> *"The likelihood of observing this consistency in data if there's no treatment effect is very small. In fact, the **p-value is less than 0.0001**."*

The first three biomarkers were identified as predictive of the clinical outcomes in the trial. Dr. Bowser explained that the fourth one, MCP-1, was included for completeness and because it too has been identified as important in ALS.

- Neurodegeneration: Neurofilament Light
- Neuroprotection: Galectin-1
- Anti-inflammatory: TGF-β1
- Pro-inflammatory: MCP-1

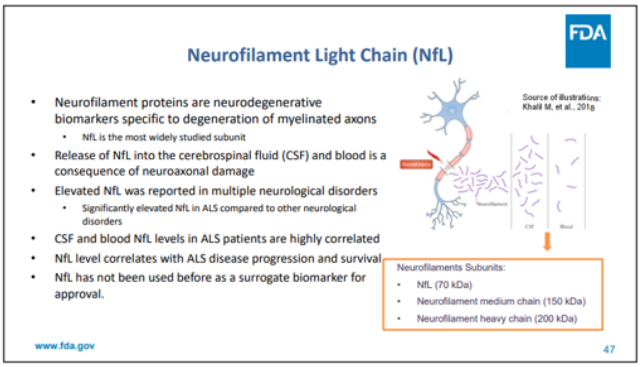
Graphic - Totality of CSF Biomarker Evidence Supports Mechanism of Action

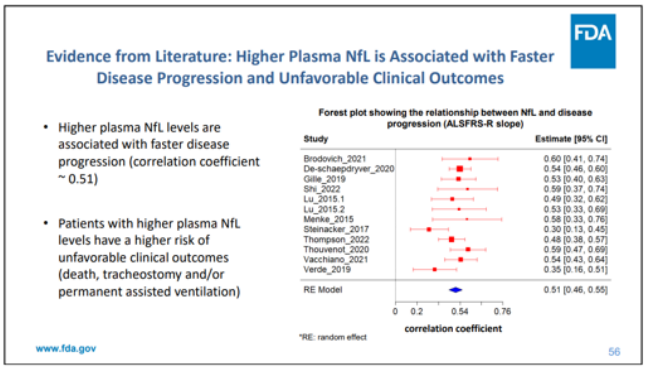


2. Neurodegeneration Biomarker, Neurofilament Light in ALS

In March 2023, for the first time, the FDA utilized neurodegeneration biomarker Neurofilament Light as a basis to grant Accelerated Approval. As part of its Presentation, the FDA included the following slide of a literature-based meta-analysis as evidence of the prognostic value of changes in NfL:

Graphic - FDA Slides about Neurofilament Light from Tofersen AdComm





Further, the FDA-CDER's presentation stated that a reduction in plasma NfL indicates reduced neuronal damage; and that NfL reduction is expected to lead to slower clinical function decline. The FDA's Briefing Document in the Tofersen AdComm said, in part:

> *"Neurofilament Light Chain (NfL) is one of the neurofilament proteins that are highly expressed in myelinated axons. Elevated levels of NfL in the CSF and blood are … a consequence of axonal damage. Neurofilament levels in the plasma and the CSF… are significantly elevated in patients with ALS compared to other neurodegenerative diseases…. Several independent studies have recently reported that NfL levels are correlated with disease severity, disease progression rate, and survival in patients with ALS. A meta-analysis of published literature findings on NfL in ALS demonstrated a correlation between the rate of disease progression and plasma NfL level. Additionally, higher levels of neurofilament were associated with a higher risk of unfavorable clinical outcomes, including death, tracheostomy, and/or permanent ventilation. NfL was reported to have a stronger association than other candidate biomarkers with ALS progression rate and survival. T**hese findings offer support for the utility of NfL as a prognostic biomarker for ALS disease progression and survival**."*

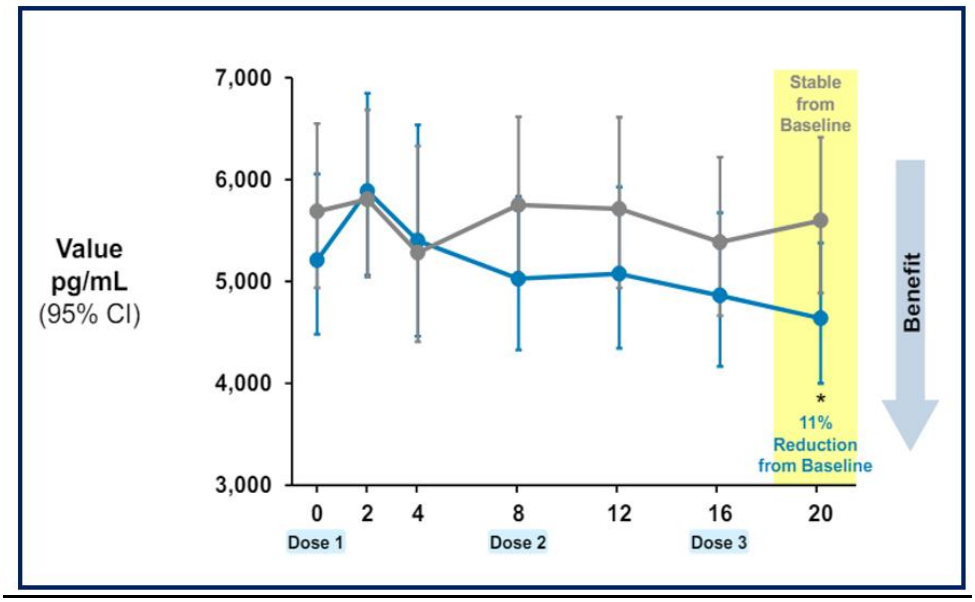
When speaking about the importance of biomarker Neurofilament Light at an AdComm for another ALS therapy, CDER's former Director of the Division of Neurology Products, neurologist Billy Dunn said:

"Neurofilament Light [NfL] is an "important aspect of a development program targeted at mitigating neurodegeneration ... It is a marker of neurodegeneration or neuronal injury. Should we [see] an effect on Neurofilament, we would [pay] attention to that …. It is a measure that -- while not suitable for use as a standalone measure -- one could certainly envision a situation where an effect, in what ostensibly is a beneficial direction here, [could] provide important contextual & supportive information of again, an ostensibly important effect on a clinical measure… We think it's appropriate to capture it here. Quite honestly, in the interest of having an effective medication available to ALS patients, all of us in the space would [prefer to see] a directional benefit there that is convincing…. That shouldn't be construed as elevating the use of neurofilament to some kind of independent measure that's suitable on its own for assessment, but we do think it's a very important part of the contextual picture."

a. Neurofilament Light, Demonstrated a Beneficial Decrease during the 28-week NurOwn Trial

Below is the graph from the NurOwn AdComm. There was a small (11%) decrease in Neurofilament Light in NurOwn arm during the 28-week trial. But as you can see the lines are beginning to diverge more with time.

Graphic - NurOwn's Neurofilament Light Results from Phase 3



And as you can see in the table below, there was a significant difference when comparing the EAP population who received additional doses of NurOwn.

b. Neurofilament Light Shows Long-term, Beneficial Impact during EAP.

The more NurOwn doses that people received, the more their harmful NfL levels decreased. The six people who received NurOwn during the trial had a 4% decrease at the end of the Phase 3 trial, then a 9-28 month gap in dosing followed by a 27% decrease at the end of the first round of EAP; then another 7-9 month gap in dosing followed by a 36% decrease at the end of the second round of EAP.

In contrast, the four who were on placebo in the trial had a 37% increase in harmful NfL at the end of the Phase 3 trial and went as much as 42 months without their first dose of NurOwn. Then when they crossed-over to receive NurOwn, their NfL levels still showed a 17% increase but not as drastically as previously. Then finally by the end of the second round of EAP, they experienced a 5% reduction in NfL.

Graphic - NurOwn's Neurofilament Light Results from Phase 3 and EAP

Percent Change from Baseline NFL in NurOwn Phase 3 & EAP								
	Phase 3				EAP Round 1		EAP Round 2	
Trial Status	TOTAL Phase 3 Population		Sx to Trial Dose #1 (months)	EAP Participants in Phase 3 (2017-2020)		Gap to EAP Dose #1 (months)	EAP 1 (2021)	Gap to EAP Dose #4 (months)	EAP 2 (2022)
NurOwn P3	95	<11%>	12 - 25	6	<4%>	9 - 28	<27%>	7 - 9	<36%>
Placebo P3	94	<1.6%>		4	37%	29 - 42	17%	6 - 9	<5%>
Difference	189	9.4%		10	41%		44%		31%

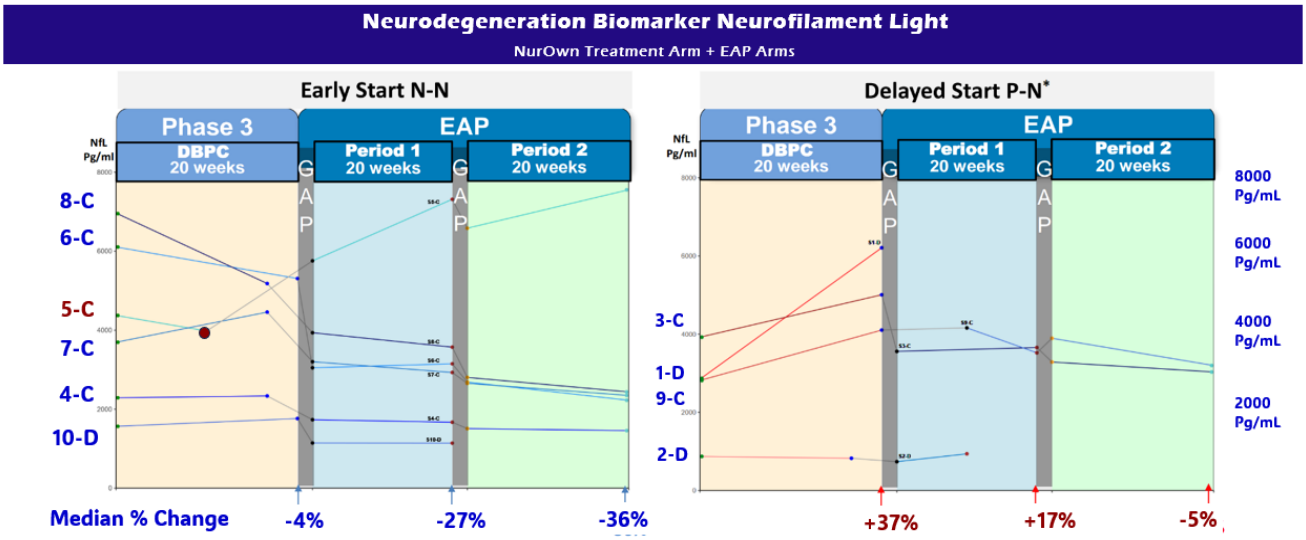
At the end of the Phase 3 trial, there was a 41% difference in NfL levels in favor of the 6 people on NurOwn versus the 4 people who crossed over from placebo. And at the end of each round of EAP – where everyone received NurOwn – that difference persisted as neurodegeneration continued to decrease. Ultimately, the NurOwn EAP arm demonstrated a 44% and 31% beneficial difference in NfL levels in favor of the 6 people who had received NurOwn since the beginning of the trial.

The conclusion: treat people early and often to see the largest reduction in harmful Neurofilament Light. But – people later in progression also experience benefits! Imagine if these people could have received NurOwn every two months on the prescribed dosing schedule. The only way we will know what these NfL data would have looked like with long-term use is if NurOwn is approved with a Phase 4 post-marketing study.

c. Repeated Dosing Creates a Long-term, Beneficial Impact on Neurodegeneration Biomarker, Neurofilament Light

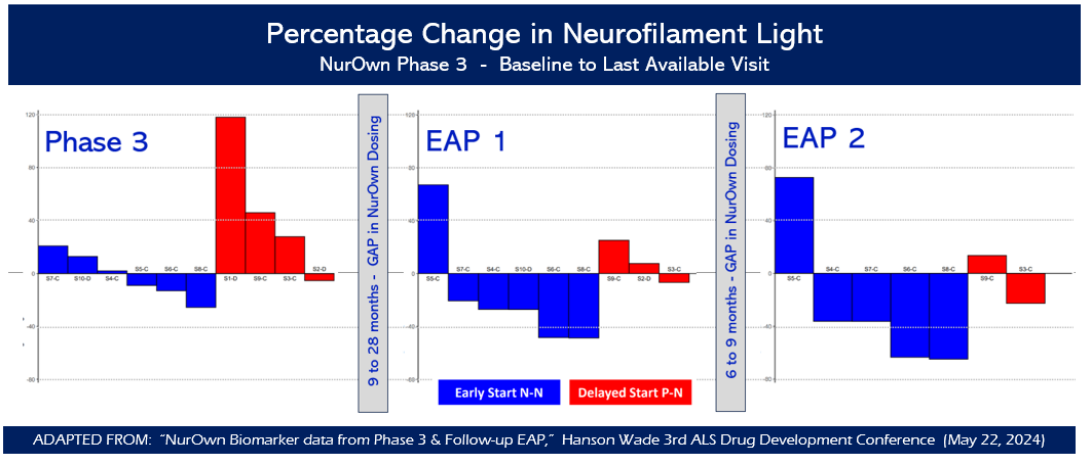
In the graphic below, which Brainstorm presented at the ALS Drug Development Summit in May 2024 and in a NEALS Poster in October 2024, you can see the compelling neurodegeneration biomarker Neurofilament Light (NfL).

Graphic- NurOwn's Neurofilament Light Results from Early Start vs Delayed Start in EAP

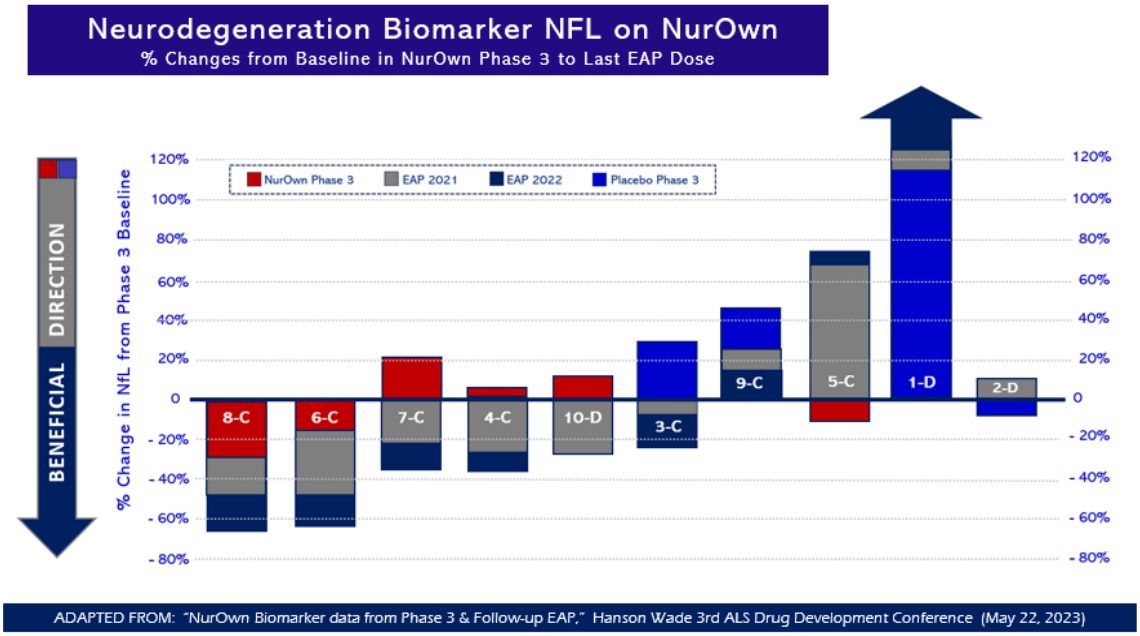


NfL levels increased when on placebo but consistently decreased or stabilized when people received NurOwn. In the early start NurOwn arm, note the consistency in how 6-C, 7-C and 8-C all have similar slopes in both rounds of EAP as do EAP participants 4-C and 10-D. By the end of EAP round #1, NfL levels are virtually stable in 5 of 6 people who began NurOwn during the Phase 3 trial. And impressively, NfL continued to decrease during gaps in dosing that were sometimes as long as 2 years – demonstrating NurOwn's biological durability. Brainstorm presented the below NfL data at the 2024 ALS Drug Development Summit attended by Mitze Klingenberg. Petitioners consolidated the images into one per each EAP participant.

Graphic - NurOwn's Neurofilament Light Results - Percentage of Change Bar Chart



Graphic - NurOwn's Neurofilament Light Results - Percentage of Change - by Participant



In the graphic above, the navy bar represents the NfL levels after EAP round 2 in 2022; the gray bar represents the NfL levels after EAP round 1 in 2021. The red bar represents the NfL levels in the NurOwn arm at the end of the Phase 3 trial; and the bright blue bar represents the NfL levels in the placebo arm at the end of the Phase 3 trial. The beneficial direction is downward.

Following are some general observations from the consolidated graphic:

- 70% (7/10) = decrease in NfL levels from baseline dose #1 to last dose in EAP
- 83% (5/6) on NurOwn = decrease in NfL from baseline to last dose in EAP
- 86% (6/7) who completed EAP #2 = decrease in NfL from baseline dose #1 to last dose in EAP
- 78% (7/9) who completed EAP #1 = decrease in NfL from baseline dose #1 to last dose in EAP
- 71% (5/7) with baseline ≥ 31 mean = decrease in NfL from baseline to last dose in EAP
- 67% (4/6) with baseline ≥ 40 = decrease in NfL from baseline to last dose in EAP
- 50% (2/4) in placebo crossover group = decrease in NfL in each round of EAP
- 25% (1/4) in placebo crossover group dropped out before completion of EAP round #1

d. NfL Changes in NurOwn's EAP vs. Tofersen Trial, OLE and EAP.

The Tofersen and NurOwn trials both measured Neurofilament Light in the plasma (pNfL) and cerebrospinal fluid (cNfL) respectively.[120] Both continued to measure NfL after the end of the 28-week trials: Tofersen in an OLE with no gaps in dosing and NurOwn in an EAP with significant gaps in dosing. In both extension studies, patients remained blinded to their original treatment assignment in the Phase 3 studies.

Notably even with the gaps in treatment between dosing, the NurOwn EAP shows a similar pattern as the NfL changes seen in the Tofersen trial – which had no gaps in dosing.[121]

According to the FDA's Tofersen Brief, pNfL was reduced by 55% compared to a 12% increase on placebo at week 28. The NfL reduction driven by Tofersen plateaued at Week 16 and was sustained at the end of treatment at Week 28 (Figure 3). Comparatively at 12 months in the Tofersen trial, pNfL levels decreased. With no gaps in dosing, the early-start Tofersen group (those who received tofersen in the trial) showed a 51% reduction in NfL levels compared to baseline. The delayed-start tofersen group showed a 41% reduction in plasma NfL levels at the 12-month time point.[122]

People in the NurOwn EAP who were treated early in progression with 9 doses experienced more than a 60% decrease in their NfL levels.

[120] (Falzone 2021) found a robust correlation between pNfL and cNfL levels, reflecting their utility as biomarkers of neuroaxonal damage. Both biomarkers were predictive of disease progression and survival, ($p < 0.0001$ for both in relation to mortality). Further, cNfL levels in ALS patients are typically 10–100x higher than pNfL levels cNfL ~1,000–10,000 pg/mL vs. pNfL ~10–100 pg/mL). The study also noted that CSF NfL levels were significantly higher (median ~2,000 pg/mL) than plasma levels (median ~50 pg/mL), but their proportional relationship held across disease stages.

[121] Studies consistently show a strong positive correlation between CSF NfL and plasma NfL levels, with correlation coefficients typically ranging from 0.7 to 0.9 in ALS and other neurological conditions.

[122] Miller, T. M., et al. (2022). "Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS." New England Journal of Medicine, 387(12), 1099–1110. DOI: 10.1056/NEJMoa2204705

3. UNC13 Genetic Biomarker Supports Accelerated Approval

TWO new papers from two different top universities -- The Gitler Lab[123] at Stanford and the Fratta Lab[124] at University College of London -- both created a buzz in the scientific community when they published their papers about the splicing errors in a gene called UNC13A.

Gitler explained that in every publication about the genetics of ALS, UNC13A is always discussed but they never understood how the SNPs could contribute to risk for ALS. In this article from Stanford Medicine, they describe the connection as follows:

> *"Think of TDP43 as a DELETE button that edits typos out of a sentence, with that sentence being a long sequence of molecular information coding for the UNC13A protein. When TDP43 is no longer in the nucleus, it's like the DELETE button no longer exists. Just like typos make sentences hard to read, these cryptic exons interfere with the cell's ability to read the genetic instructions to make the proper proteins.*
>
> *It's important to note that the mutation in UNC13A, in itself, is not a cause of ALS. If TDP43 is present in the nucleus, like it is in a healthy cell, the DELETE button can remove the harmful "junk." In that sense, UNC13A is a "risk factor," meaning that the mutation in UNC13A can help predict a person's risk for developing & for the disease's progression.*

NINDS immediately published a press release about the findings.[125] TDP-43 depletion leads to a cryptic exon in UNC13A mRNA, resulting in nonsense-mediated decay and decreased UNC13A protein. Single-nucleotide polymorphisms (SNPs) with ALS or FTD risk in UNC13A exacerbate the cryptic exon inclusions when TDP-43 function is lost. According to Chen (2022), the UNC13A gene plays an essential role in the disease onset and progression of ALS. UNC13A as a susceptibility gene for ALS and FTD and the minor "C" allele of UNC13A is strongly linked with shorter survival in ALS patients. These two new studies published in NATURE have established a causal link between TDP-43 loss and UNC13A downregulation, and reveal its underlying mechanisms. Therefore, the authors conclude that UNC13A is identified as a genetic modifier of ALS survival mediated by nuclear TDP-43 loss, and "might be a promising therapeutic target to slow disease progression, which may work in most ALS patients, about half of FTD patients, and other TDP-43 proteinopathies."

---

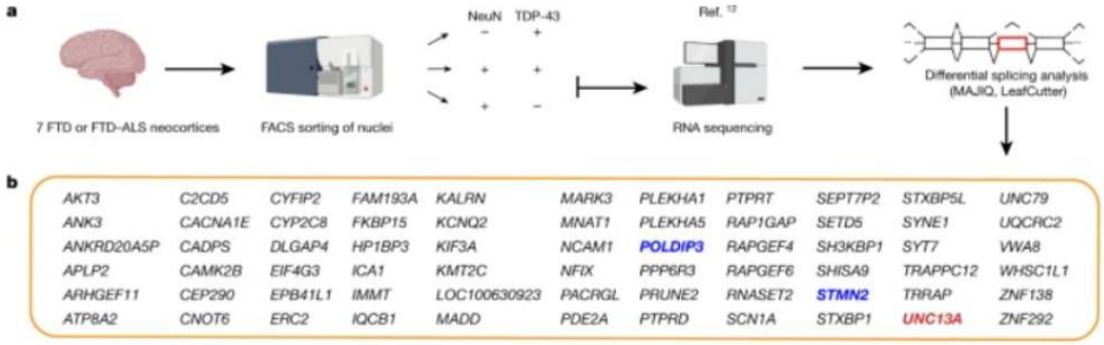
[123] Akiyama T, Koike Y, Petrucelli L, Gitler AD. Cracking the cryptic code in amyotrophic lateral sclerosis and frontotemporal dementia: Towards therapeutic targets and biomarkers. Clin Transl Med. 2022 May;12(5):e818.
[124] Brown, AL., Wilkins, O.G., Keuss, M.J. et al. TDP-43 loss and ALS-risk SNPs drive mis-splicing and depletion of UNC13A. Nature 603, 131–137 (2022).
[125] National Institute of Neurological Disorders and Stroke. (2025, February 7). Scientists discover new molecular pathway shared by two neurodegenerative disorders [Press release]. https://www.ninds.nih.gov/news-events/news/press-releases/scientists-discover-new-molecular-pathway-shared-two-neurodegenerative-disorders

In this [presentation at the ALSOne Conference](), Dr. Aaron Gitler at Stanford discusses cryptic splicing targets in ALS and one of the genes, UNC13A. He shows photos of how TDP-43 translocates from the nucleus to the cytoplasm of the cell. When that happens, there's a loss of TDP-43 function in the nucleus, as well as a toxic impact in the cytoplasm.

The genes listed in the graphic below are other genes that may have splicing errors but UNC13A was the most prominent.

Graphic - UNC13A and the 66 Mis-splicing Genes in ALS

Fig. 1: Nuclear depletion of TDP-43 causes CE inclusion in *UNC13A* RNA and reduced expression of UNC13A protein.

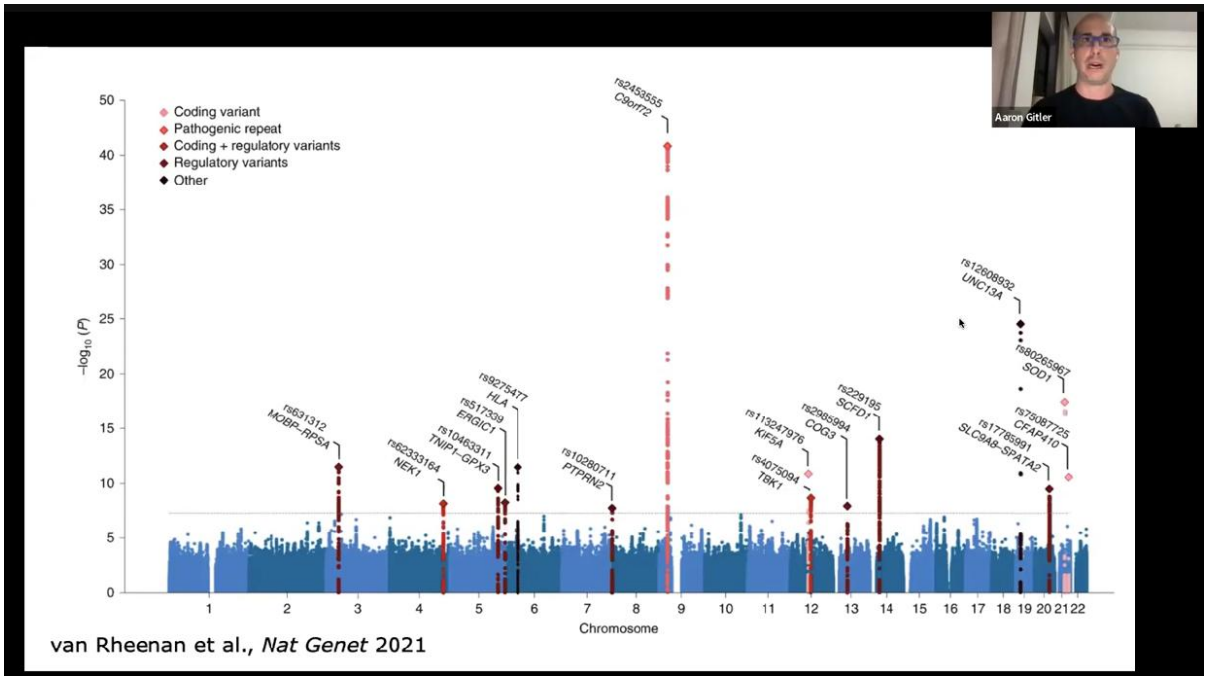


AKT3	C2CD5	CYFIP2	FAM193A	KALRN	MARK3	PLEKHA1	PTPRT	SEPT7P2	STXBP5L	UNC79
ANK3	CACNA1E	CYP2C8	FKBP15	KCNQ2	MNAT1	PLEKHA5	RAP1GAP	SETD5	SYNE1	UQCRC2
ANKRD20A5P	CADPS	DLGAP4	HP1BP3	KIF3A	NCAM1	POLDIP3	RAPGEF4	SH3KBP1	SYT7	VWA8
APLP2	CAMK2B	EIF4G3	ICA1	KMT2C	NFIX	PPP6R3	RAPGEF6	SHISA9	TRAPPC12	WHSC1L1
ARHGEF11	CEP290	EPB41L1	IMMT	LOC100630923	PACRGL	PRUNE2	RNASET2	STMN2	TRRAP	ZNF138
ATP8A2	CNOT6	ERC2	IQCB1	MADD	PDE2A	PTPRD	SCN1A	STXBP1	UNC13A	ZNF292

The researchers at the Gitler Lab identified 66 alternative splicing events that were occurring in the nucleus of neurons from human brains that lacked TDP-43. Two had already been validated as spiking TDP-43 but the Dr. Gitler's lab identified 64 others. Genes in BLUE are previously identified TDP-43 splicing targets. According to the press release from Stanford, results from the "genetic reanalysis pointed to cryptic exons in other genes."

The one that immediately caught researchers' attention was UNC13A. If you exclude the C9 locus which causes the most common type of genetic ALS, UNC13A is the top GWAS hit for ALS. And past genetic studies showed that UNC13A was obviously connected to ALS. Gitler explained that *"It was on everyone's radar, but no one[knew] how it contributed to the disease. This finding connects the two: the most common pathology with one of the most common genetic risk factors."*

<u>Graphic</u> - UNC13A in ALS GWAS



STATNews reported that "scientists take key step toward unraveling the genetic roots of ALS" in a pair of studies:[126]

> *"66 genes that were spliced differently in patients with ALS. One of them, UNC13A, immediately caught Gitler's eye. That's because the protein, which regulates how neurons send chemical signals to one another, had been linked to ALS in previous genetic studies. The authors found that UNC13A RNA in ALS patients included an extra stretch of genetic sequence. This sequence ONLY SHOWED UP IN CELLS MISSING TDP-43 FROM THEIR NUCLEUS, suggesting that the protein ordinarily helps snip out this region. Splicing errors were even more frequent among patients with genetic variants of UNC13A associated with a higher risk of ALS.... These variants, known as single nucleotide polymorphisms weren't just in any random part of UNC13A — they were in or near the site of the error. And patients with two copies of the variants died more quickly after diagnosis than those with one or none."*

In this study out of Leonard van den Berg's lab in The Netherlands,[127] the authors genotyped 2,216 people with UNC13A (rs12608932) and that resulted in the following distribution of:

[126] Kwon, D. (2022, Febr 23). Scientists take key step toward unraveling the genetic roots of ALS in a pair of studies. STAT.
[127] van Es, M. A., Veldink, J. H.,... van den Berg, L. H. (2020). The distinct traits of the UNC13A polymorphism in amyotrophic lateral sclerosis. Annals of Neurology, 88(4), 796–806. https://doi.org/10.1002/ana.25841

- 374 C/C alleles = 16.9%
- 988 A/C alleles = 44.6%
- 854 A/A alleles = 38.5%

The C allele was associated with:

- Shorter survival
  (median in months A/A 33.3, A/C 30.7, and C/C 26.6; $p < 0.001$)
- Higher age at symptom onset
  (median years A/A 63.5, A/C 65.6, and C/C 65.5)
- More frequent bulbar onset
  (A/A 29.6%, A/C 31.8%, and C/C 43.1%)
- higher incidences of ALS-FTD
  (A/A 4.3%, A/C 5.2%, and C/C 9.5%)
- lower FVC at diagnosis
  (median percentage A/A 92.0, A/C 90.0, and C/C 86.5)

Since those two seminal papers were published in 2022, the field has exploded with additional UNC13A research.

- TDP-43 loss and ALS-risk SNPs drive mis-splicing and depletion of UNC13A (Fratta Lab)[128].
- Cracking the cryptic code in ALS & FTD: Towards therapeutic targets & biomarkers (Gitler Lab)[129]
- Association of UNC13A with increased ALS risk, bulbar onset, and LMN involvement in a Norwegian ALS cohort[130]
- Quantification of serum TDP-43 & NfL in patients with ALS stratified by UNC13A genotype (Nov 2024)[131]
- Molecular mechanisms linking loss of TDP-43 function to ALS/FTD-related genes (Nov 2024)[132]
- Creation of de novo cryptic splicing for ALS and FTD precision medicine (Oct 2024)[133]

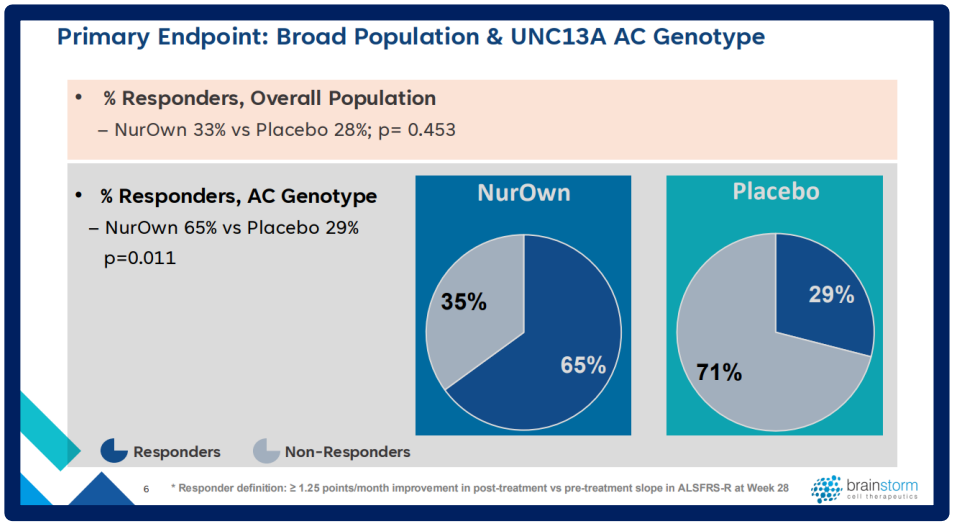
[128] Brown, AL., Wilkins, O.G., Keuss, M.J. et al. TDP-43 loss and ALS-risk SNPs drive mis-splicing and depletion of UNC13A. Nature 603, 131–137 (2022).
[129] Akiyama T, Koike Y, Petrucelli L, Gitler AD. Cracking the cryptic code in amyotrophic lateral sclerosis and frontotemporal dementia: Towards therapeutic targets and biomarkers. Clin Transl Med. 2022 May;12(5):e818.
[130] Novy C, Tysnes OB, Busk ØL, Jaioun K, Holmøy T, Holla ØL, Høyer H. Association of UNC13A with increased ALS, bulbar onset, and lower motor neuron involvement in a Norwegian ALS cohort. Amyotroph Lateral Scler Frontotemporal Degener. 2024 Dec 30:1-7.
[131] Giulia Gianferrari et al., Quantification of Serum TDP-43 and Neurofilament Light Chain in Patients with Amyotrophic Lateral Sclerosis Stratified by UNC13A Genotype, 466 J. Neurological Scis. 123258 (2024),
[132] Yuki Koike, Molecular Mechanisms Linking Loss of TDP-43 Function to Amyotrophic Lateral Sclerosis/Frontotemporal Dementia-Related Genes, 208 Neuroscience Rsch. 1 (2024),.
[133] Matthew A. White et al., Creation of De Novo Cryptic Splicing for Amyotrophic Lateral Sclerosis and Frontotemporal Dementia Precision Medicine, 147 Brain 3597 (2024),

- Abnormal Splicing Events due to Loss of Nuclear Function of TDP-43: Pathophysiology & Perspectives (July 2024)[134]
- Role of the UNC13 family in human diseases: A literature review (Dec 2023)[135]
- TDP-43 & other hnRNPs regulate cryptic exon inclusion of a key ALS/FTD risk gene, UNC13A (March 2023)[136]
- UNC13A in ALS: From genetic association to therapeutic target (Feb 2023)[137]
- Association of the risk factor UNC13A with survival & UMN involvement in ALS (Feb 2023)[138]
- Clinical & Metabolic Signature of UNC13A rs12608932 Variant in ALS (Oct 2022)[139]
- UNC13A Gene Brings New Hope for ALS Disease-Modifying Drugs (Nov 2022)[140]
- Genetic factors for survival in ALS: An integrated approach combining a systematic review, pairwise and network meta-analysis (June 2022)[141]

UNC13A is important in the NurOwn trial as 65% of people with the A/C genotype had a -1.25 change in their slope (responders to primary endpoint). This is significant because – as Aaron Gitler stated – the two seminal UNC13A studies connected "the most common pathology (TDP-43) with one of the most common genetic risk factors (UNC13A)." And now Brainstorm has the first therapy to show a profound impact on that very gene/pathology combination. (p=0.011).

[134] Anaïs-Camille Vancraenenbroeck et al., Abnormal Splicing Events due to Loss of Nuclear Function of TDP-43: Pathophysiology & Perspectives, 18 Frontiers Neuroscience 1402938 (2024).
[135] Weijing Liu et al., Role of the UNC13 Family in Human Diseases: A Literature Review, 16 Frontiers Molecular Neuroscience 1320919 (2023).
[136] Sean W. Willemse et al., TDP-43 and Other hnRNPs Regulate Cryptic Exon Inclusion of a Key ALS/FTD Risk Gene, UNC13A, 68 J. Hum. Genetics 157 (2023).
[137] Annelies M. Maessens et al., UNC13A in Amyotrophic Lateral Sclerosis: From Genetic Association to Therapeutic Target, 94 J. Neurology, Neurosurgery & Psychiatry 649 (2023).
[138] Andrea Manini et al., Association of the Risk Factor UNC13A with Survival and Upper Motor Neuron Involvement in Amyotrophic Lateral Sclerosis, 14 Frontiers Aging Neuroscience 1055236 (2023)
[139] Andrea Calvo et al., Clinical and Metabolic Signature of UNC13A rs12608932 Variant in Amyotrophic Lateral Sclerosis, 8 Neurology Genetics e200011 (2022).
[140] Weijing Liu et al., UNC13A Gene Brings New Hope for Amyotrophic Lateral Sclerosis Disease-Modifying Drugs, 38 Neuroscience Bull. 1411 (2022).
[141] Huifang Shang et al., Genetic Factors for Survival in Amyotrophic Lateral Sclerosis: An Integrated Approach Combining a Systematic Review, Pairwise and Network Meta-Analysis (Rsch. Square, Working Paper, 2022).

<u>Graphic</u> - UNC13A (A/C) Responder Analysis in NurOwn Phase 3 Trial



Thus, the NurOwn-UNC13A connection creates more evidence contributing to the totality of the evidence that NurOwn has a plausible mechanism of action. And as such, Petitioners suggest that the FDA could use its regulatory flexibility to approve NurOwn using the Accelerated Approval pathway – based on both the CSF biomarkers as well as the UNC13A genetic biomarker.

4. <u>FDA Failed to Grant RMAT Designation for Stem Cell Therapy despite Potential to Treat ALS, a Rare Disease with a Critical Unmet Need</u>

In 2016, Congress passed the 21st Century Cures Act, which among other things, created the Regenerative Medicine Advanced Therapy Designation ("RMAT") -- less than one year before the start of the NurOwn trial in late 2017. RMAT is an expedited designation to help rare disease drugs get approved more quickly. It requires the FDA to meet frequently with the drug sponsor to discuss the development of potential biomarker data, which can be used as surrogate endpoints for Accelerated Approval.

Sometime in 2017, CBER refused to extend RMAT designation to NurOwn even though it easily met all the required elements:

> *"As described in Section 3033 of the 21st Century Cures Act, a drug is eligible for RMAT designation if:*
>
> 1. *The drug is a regenerative medicine therapy, which is defined as a cell therapy;*
> 2. *The drug is intended to treat, modify, reverse… a life-threatening disease; and*
> 3. *Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition"*

Without RMAT designation, Brainstorm was deprived of a chance to have in-depth meetings with CBER's OTAT officials to discuss its innovative and first-in-class CSF biomarkers – the first company ever to collect CSF biomarkers longitudinally in an ALS trial.

Had OTAT granted RMAT status, Brainstorm could have coordinated what would be needed for biomarker collection to support Accelerated Approval. Instead, Brainstorm didn't even seek Accelerated Approval when it filed its BLA over Protest. Petitioners are not aware of the reasons it chose not to do so. Presumably that was based on feedback from the OTAT/OTP officials at the Type A meeting post-RTF.

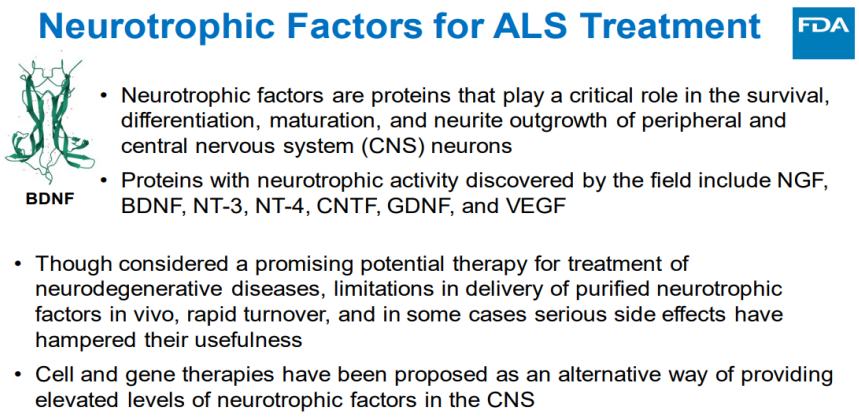
N. "Plausible Mechanism of Action" of Stem Cells Enhanced with Neurotrophic Factors

BrainStorm Cell has taken a personalized medicine approach to treating ALS. Its investigational therapy, NurOwn, uses autologous mesenchymal stem cells from a patient's own body. This avoids the problems necessitating immunosuppressant drugs as is common with allogeneic stem cells from a donor source.

The mesenchymal stem cells ("MSCs") are harvested via a bone marrow aspiration in the iliac crest, very similar to the harvesting of bone marrow for oncology patients. Unique from traditional stem cell therapies, BrainStorm then treats those MSCs with neurotrophic factors (MSC-NTF). These differentiated MSCs are then injected into the patient's cerebral spinal fluid ("CSF") via a lumbar puncture. Contrary to many small molecule therapies that can't pass the blood brain barrier when people take them orally or via IV, these MSC-NTF work directly on motor neurons and glial cells.

According to the FDA's AdComm Presentation, *"neurotrophic factors are proteins that play a critical role in the survival, differentiation, maturation, and neurite outgrowth of peripheral and central nervous system (CNS) neurons."*

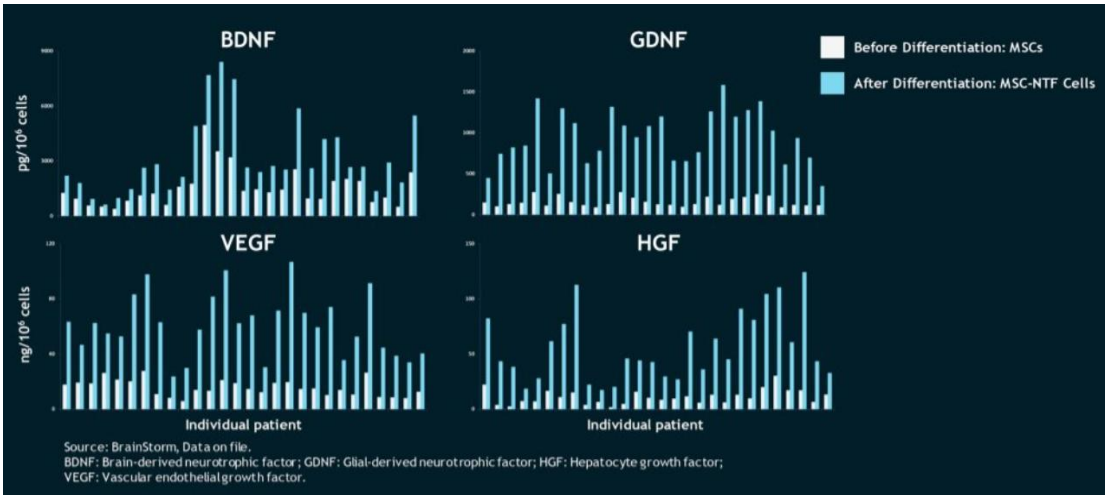
Graphic - FDA's Presentation Slide of Neurotrophic Factors for ALS Treatments



Petitioners defer to Brainstorm and its experts to further discuss NurOwn's mechanism of action in sufficient detail to support a conditional approval. But a brief summary[142] follows.

The modified MSCs secrete neurotrophic factors such as brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), vascular endothelial growth factor (VEGF), and hepatocyte growth factor (HGF), among others. An example of the impact of the differentiated cells can be seen on Brainstorm's website:

Graphic - Neurotrophic Factors for ALS: BDNF, GDNF, EGF and HGF



These neurotrophic factors are critical for neuronal survival and repair and support the conclusion that NurOwn provides a plausible mechanism of action.[143]

- **BDNF** is a neurotrophic factor critical for neuronal survival, synaptic plasticity, and neurogenesis, potentially counteracting motor neuron dysfunction.[144] BDNF also reduces microglial activation and neuroinflammation, a secondary contributor to ALS progression. Preclinical studies show BDNF protects motor neurons in ALS models. It binds to TrkB receptors, activating PI3K/Akt, MAPK/ERK, and PLCγ pathways to promote motor neuron survival and inhibit apoptosis.

[142] Berry, J. D., Cudkowicz, M. E., Windebank, A. J., Staff, N. P., … & Maragakis, N. J. (2019). NurOwn, phase 2, randomized, clinical trial in patients with ALS: Safety, clinical, and biomarker results. Neurology, 93(24), e2294–e2305.
[143] Henriques, A., Pitzer, C., & Schneider, A. (2010). Neurotrophic growth factors for the treatment of amyotrophic lateral sclerosis: Where do we stand? Frontiers in Neuroscience, 4, 32; Tovar-y-Romo, L. B., Santa-Cruz, L. D., & Tapia, R. (2014). Experimental models for the study of neurodegeneration in ALS . Molecular Neurodegeneration, 9, 31.
[144] Henriksen, M. G., & Mackenzie, I. R. (2010). Brain-derived neurotrophic factor (BDNF) in neurodegenerative diseases: Therapeutic implications. Neuroscience & Biobehavioral Reviews, 34(6), 803–811.

- **VEGF** is primarily an angiogenic factor that uniquely supports vascular health but it also has neurotrophic and neuroprotective properties.[145] It enhances blood-brain barrier integrity and increases CNS blood flow, improving nutrient delivery to motor neurons. VEGF upregulates glutamate transporter (EAAT2) expression, reducing glutamate toxicity, and activates PI3K/Akt and MAPK pathways to promote neuronal survival and reduce oxidative stress.

- **HGF** is a neurotrophic factor that protects motor neurons from excitotoxicity and oxidative stress. It enhances the expression of anti-apoptotic proteins (e.g., Bcl-2) and reduces caspase activation. It promotes axonal sprouting and regeneration. HGF modulates glial cell activity, reducing microglial activation and neuroinflammation, which exacerbate ALS pathology. It also supports astrocyte function, improving the neuronal microenvironment. Similar to VEGF, HGF enhances vascular stability and blood-brain barrier function, facilitating nutrient and oxygen delivery to motor neurons. Preclinical studies in SOD1 transgenic mice demonstrate that HGF overexpression delays motor neuron degeneration and extends survival.[146] It also activates downstream signaling pathways, including PI3K/Akt, MAPK/ERK, and STAT3.[147]

- **GDNF** is a neurotrophic factor that supports motor neuron and dopaminergic neuron survival.[148]
  It specifically promotes axonal sprouting and repair, potentially compensating for motor neuron loss. It also enhances astrocyte function to support neuronal health and reduces toxic environments. GDNF binds to GFRα1 and RET receptors, activating PI3K/Akt and MAPK pathways to prevent motor neuron apoptosis.

The goal of NurOwn's MSC-NTF is to slow or stabilize ALS disease progression. If delivered earlier enough in disease progression or damage, it is postulated that some of these neurotrophic factors may be able to restore some function through the neuroprotective growth factors and reduction of neuroinflammation.

Recently, at the ALS Drug Development Summit in May 2024, Brainstorm presented data from three additional pre-clinical experiments to corroborate NurOwn's plausible mechanism of action.

[145] Tovar-y-Romo, L. B., Ramírez-Jarquín, J. O., Lazo-Gómez, R., & Tapia, R. (2014). Trophic factors as modulators of motor neuron physiology and survival: Implications for ALS therapy. Frontiers in Cellular Neuroscience, 8, 61.
[146] Sun, W., Funakoshi, H., & Nakamura, T. (2002). Overexpression of HGF retards disease progression and prolongs life span in a transgenic mouse model of ALS. Journal of Neuroscience, 22(15), 6537–6548.
[147] Kadoyama, K., Funakoshi, H., Ohya, W., & Nakamura, T. (2009). Hepatocyte growth factor (HGF) attenuates gliosis and neuronal death in a mouse model of amyotrophic lateral sclerosis. Journal of Neuroscience Research, 87(8), 1895–1903.
[148] Allen, S. J., Watson, J. J., Shoemark, D. K., Barua, N. U., & Patel, N. K. (2013). GDNF, NGF, and BDNF as therapeutic options for neurodegenerative diseases. Neurochemistry International, 62(5), 697–708.

1) PBMCs - in vitro experimental model of immune activated peripheral blood mononuclear cells, (PBMCs), that were co-cultured with NurOwn cells. NurOwn inhibited the secretion of pro-inflammatory cytokines and decreased the proliferation of certain types of T cells, CD4 cells and CD8 cells that are involved in the inflammatory process.

2) Neurite Outgrowth - neurite outgrowth model in which human neuroblastoma cells were co-cultured with NurOwn cells. It showed that NurOwn enhanced growth of neurites, supporting a neuro-regenerative role for NurOwn.

3) Hypoxia model - in vitro hypoxia model examined the effect of NurOwn on a motor neuron cell line that had been subjected to hypoxic stress in a low oxygen environment and resulted in about one in three cells dying. When these cells were co-cultured with conditioned media collected from their own cell cultures, viability was restored to 96.5% of normoxic conditions, providing evidence of a neuroprotective effect.[149]

Petitioners submit that all the data above demonstrates that **NurOwn provides a "plausible mechanism of action" to treat people dying of 100% fatal ALS.**

O. NurOwn Drug Development and Israel's Role in Stem Cell Innovation

In 2004, that "plausible mechanism of action" for NurOwn was innovated in Israel by renowned neurologist and Parkinson's researcher Eldad Melamed MD[150] and prominent neuroscientist Daniel Offen, PhD[151] – both professors at Tel Aviv University.

[149] This Hypoxia model is particularly interesting to military pilots like Matt Bellina, Petitioner Nick Warack as well as all the pilots who flew in General Mik's squadron. Post-9/11 pilots have a 10x risk of getting ALS. One of the hypothesized reasons for their increased risk is because of their hypoxia training and exposure.

[150] Dr. Melamed was a professor at Tel Aviv University. He served 7 years as the president of the Israel Neurological Association and was a ten-year member of the Michael J. Fox Scientific Advisory Board. His research contributions focused on Parkinson's Disease but also included ALS. Dr. Melamed published an eye-popping 450+ papers including topics such as the "dying-back" phenomenon of motor neurons in ALS. He also published multiple papers about the use of stem cells in neurodegenerative diseases. He has been cited over 36,000 times; he has an h-index of 101 and an i-10 index of 363.

[151] Professor Offen is a co-founder of several biotechnology companies developing gene and cell therapies for neurological disorders. Professor Offen studied molecular biology, specializing in RNA processing, at the prestigious Weizmann Institute of Science in Israel. One study explored the long term beneficial effect of neurotrophic factors-secreting mesenchymal stem cells transplantation in a mouse model of autism. He holds over a dozen patents, and co-founded biotechnology companies focused on gene and cell therapies for neurological disorders.

Dr. Offen, a graduate of the Weizmann Institute,[152] is a neuroscientist who heads the Neurology Laboratory in the Department of Human Genetics and Biochemistry at Tel Aviv University. His work focuses on developing innovative treatments for neurological disorders using stem cells, gene therapy, and peptides, with a strong emphasis on neuroprotection and nerve regeneration in conditions like ALS, and Parkinson's. Dr. Offen's research has led to the publication of 200+ articles, review papers and book chapters. He has been cited over 18,000 times; he has an h-index of 74 and an i-10 index of 189.

Dr. Offen and Dr. Melamed co-authored several papers including "The "dying-back" phenomenon of motor neurons in ALS."[153] This phenomenon describes a pattern where motor neuron degeneration begins at the nerve terminals and progresses retrogradely toward the cell body. The authors discuss how this process contributes to the loss of motor function in ALS, highlighting underlying mechanisms such as oxidative stress, mitochondrial dysfunction, and impaired axonal transport. They emphasize that the distal axonopathy in ALS may precede motor neuron death, suggesting that early intervention targeting these peripheral processes could offer therapeutic potential.
Doctors Melamed and Offen conducted preclinical proof-of-concept studies on the efficacy of MSC-NTF cells in treating Parkinson's disease, Huntington's disease, multiple sclerosis and ALS. While the mechanisms underlying these neurological diseases are different, the treatment with MSC-NTFs showed early benefits in all. In ALS specifically, results in a mouse model showed slowed progression, regained function and improved survival.

In a lengthy interview at the Movement Disorders Conference in 2013,[154] Dr. Melamed was asked about what he felt his most important research contributions were. Obviously he spoke about his work in Levodopa and Parkinson's Disease; but the other two accomplishments he mentioned were his work to understand why neurodegenerative diseases progress; and how stem cells can help with their neuro-restorative capabilities.

Dr. Melamed explained that his lab had switched its research focus to the restorative properties of stem cells. When Dr. Matthew Stern asked about the hype around stem cell research, Dr. Melamed clarified why stem cells must be enhanced to optimize efficacy in neurons:

[152] The Weizmann Institute is a world-renowned research institution specializing in science and technology. The Weizmann Institute's Leiden ranking is 6th globally in the field of Biomedical and Health Sciences, and has produced numerous Nobel laureates and scientific breakthroughs. Its biomedical research – including work on disease mechanisms and drug development– is globally influential. Weizmann's 6th place ranking places it among elite US institutions. For example, Weizmann's strength in biomedical research and its impact closely makes it exceptionally competitive with US institutions, achieving a 20% P(top 10%) rate that matches or approaches Stanford, MIT, and UCSF, and is only slightly below Harvard and Johns Hopkins (25–30%). Its small size (2,500 researchers) amplifies its per capita impact, making it a global standout among institutions specializing in biomedical research.

[153] Dadon-Nachum, M., Melamed, E., & Offen, D. (2011). The "dying-back" phenomenon of motor neurons in ALS. Journal of Molecular Neuroscience, 43(3), 470–477.
[154] Melamed, E. (2013, June). Oral history 2013: Matthew Stern interviews Eldad Melamed [Video]. YouTube.

"We research stem cells, adult stem cells because we think we could bring them faster to the shelf… I'm cautiously optimistic …. There's been a lot of hype about stem cells, there's no question about it…. What we have done is we have taken bone marrow derived adult mesenchymal stem cells and we can convert them easily to dopaminergic neurons. But ***I don't believe in simple replacement therapy*****.**

So we have ***converted those cells into astrocyte-like cells that produce large amounts of BDNF, GDNF, VEGF*** *so that they will be hopefully* ***used as nano-pumps*** ***that will release this type of trophic factors*** *and we will* ***overcome the problem of delivery*** *of these molecules."*

Dr. Melamed identified his work to understand the complexities of misfolded protein diseases as the second most important contribution and emphasized why he believes researchers should focus on stopping or slowing progression as the first goal:

"The story of the misfolded alpha-synuclein [protein] as a possible killer of the dopaminergic and other neuronal populations: Why does it kill the cells? Is it responsible for the propagation of the disease from one cell to the other? … To me, it is less important to decide: when does the disease start? Where does it start? Even why does it start? The major thing is why does it progress? … Keep in mind, it is the progression that goes on from the beginning to the end…."

Given this perspective, it is easy to see why Dr. Melamed was excited about the potential of NurOwn to slow or halt ALS progression. If NurOwn could slow progression, it would be reasonably likely to have a clinically meaningful impact on survival and overall mortality.

P. NurOwn's Phase 1/2a Trials in Israel

From June 2011 to October 2014, BrainStorm conducted Phase 1/2 clinical trials in people with ALS at the Hadassah Medical Center in Israel. Both were open-label trials with no placebo arm. The Phase 1 study dosed NurOwn intrathecally and intramuscularly, in 6 people each. Only the intrathecal injections showed promise, so the Phase 2a trial studied NurOwn in 14 people receiving intrathecal injections only. Both trials showed the MSC-NTF cells to be safe and well-tolerated and revealed preliminary signs of efficacy.

The results of the Phase 1/2a studies were published in JAMA Neurology. The results of the study were: 87% of patients showed at least 25% improvement in ALSFRS or FVC slopes at 6 months.[155]

[155] Petrou, P., Gothelf, Y., Argov, Z., Gotkine, M., Levy, Y. S., Kassis, I., ... & Karussis, D. (2016). Safety and clinical effects of mesenchymal stem cells secreting neurotrophic factor transplantation in patients with amyotrophic lateral sclerosis: Results of Phase 1/2 and 2a clinical trials. JAMA Neurology, 73(3), 337–344. https://doi.org/10.1001/jamaneurol.2015.4321

The principal investigators in the Phase 1/2a trials were leading Israeli neurologists and neuroscientists: Daniel Offen, PhD; Eldad Melamed, MD; and Dimitrios Karussis, MD, PhD,[156] et al.

Q. NurOwn's Compassionate Use Program – in Israel

Concurrent with the Phase 1/2a studies, Brainstorm also began a "Compassionate Use" program in Israel. Four ALS patients received NurOwn transplants at Hadassah starting in 2012. All four had improvements in respiratory function or muscle power lasting 3 to 6 months, according to Hadassah's Dr. Karussis. Indeed, one patient, Omri Chotam, a former paratrooper in his 20s, experienced functional improvements and **halted his ALS progression for about 18 months**.[157]

Another well-known patient that astounded Dr. Karussis was Rabbi Rafoel Shmuelevitz, who had been diagnosed with both ALS and myasthenia gravis. In 2010, the Rabbi's diagnoses were confirmed at the Mayo Clinic in Minnesota. As of the summer of 2012, both diseases had progressed to an advanced stage, constraining the rabbi to a wheelchair and limiting his ability to speak and breathe. Dr. Karussis told the non-profit Israel21c:[158]

> *"The most impressive response was in the rabbi, who had a very severe and unique combination of ALS and myasthenia gravis.* ***He improved for about six months substantially****, started walking and speaking, and then the effects faded and then* ***we did a second injection and he had even more impressive improvement.*** *This makes it* ***highly unlikely to be a placebo effect.****"*

While the NurOwn treatment was not a cure, it did provide a reprieve and slowed the Rabbi's progression. He eventually succumbed to ALS on January 18, 2016 – six years after his diagnosis at Mayo. His remarkable response was documented in a case study published in Muscle and Nerve:

> *One month after transplantation, the patient and his family reported significant improvement in cognition, speech, and muscle power. He was able to walk at least 20 meters without any support. The dysarthria improved to the extent he was able to clearly deliver a speech to an audience.* ***ALSFRS-R*** *(performed at all time points by the same evaluator and confirmed by a second senior examiner)* ***score rose from 36 to 44, and respiratory forced vital capacity (FVC) and cognitive function also improved significantly….***

---

[156] Dr. Karussis is the Head of the Multiple Sclerosis Center and Unit of Neuroimmunology and Cell Therapies, in the Department of Neurology at Hadassah Medical Center in Jerusalem. He specializes in developing stem cell therapies for neurodegenerative diseases. He has 150+ peer-reviewed publications; he has been cited over 11,350 times; he has an h-index of 51 and an i-10 index of 101.

[157] https://www.israel21c.org/revolutionary-stem-cell-als-treatment-begins-advanced-trials/
By Abigail Klein Leichman August 26, 2014, Updated June 18, 2015

[158] ISRAEL21c is a non-profit organization of journalists who are "committed to telling stories that humanize Israelis and show their positive impact on our world."

In 2012, principal investigator, Dr. Dimitrios Karussis, told a local Israeli news station:

> *"Within a few weeks following injection with NurOwn cells, the patient showed dramatic improvement in a variety of functions including breathing, speech, walking, muscular strength, and overall well-being….*

Dr. Karussis cautioned the media that they should not draw scientific conclusions based on the outcome of an individual patient. But he added, *"these results are extremely encouraging…. I believe we are in the first stages of something new and revolutionary."*

R. Update on the Israeli NurOwn Recipients

Several of the people who received NurOwn in those early Israeli trials continued to see durable, long-term benefits from NurOwn.

1. Long-term Survivors from NurOwn's Early Trials

In 2023, Dr. Karussis spoke at the NurOwn AdComm. He shared seminal facts about both safety and efficacy of NurOwn in those early Phase 1/2 trial participants. Although he was a PI in the trials, he confirmed that he has no ongoing financial relationship with BrainStorm.

> *"My motivation to talk in this meeting is since we have so much experience, I think one of the best experience, with the use of different types of mesenchymal stem cells in ALS starting from 2006… And also, I was involved in this study with BrainStorm which was a Phase 1/2 trial…. I would like very much to share with you the long term safety observations that we had with these patients … Up to 15 years after the trial, we do not see any -- have not seen ANY -- unusual side effects, so this is a good signal for long-term safety."*

He then went on to share the unprecedented, long-term, overall survival observations:

> ***What is highly unlikely is that the number of patients still alive after 15 to 16 years from the onset of the disease is close to 50%*** *.... alive and partially functioning and this is very unlikely as compared to any other cohort of ALS patients. I believe these safety and mortality data are very important because 'real life' information observation is better in the long term and can provide sometimes the clues in order to see whether, especially in the rare diseases, orphan diseases like ALS, we can use a different type of treatment ….* ***So, my view is that NurOwn cells can provide -- in terms of safety and mortality rates and efficacy -- much more than the existing therapies for ALS and should be approved as an alternative option for this orphan disease."***

2. One of Dr. Bedlack's Documented ALS "Reversals" was a NurOwn Recipient

NurOwn's unprecedented benefits are potentially supported by the "ALS reversal" documented by Dr. Richard Bedlack of Duke's ALS Clinic. On July 6, 2016, Dr. Bedlack published a blog on the ALS Association's website entitled: *"ALS Reversals: What Are They and How Can We Make Them Happen More Often?"* This blog identified a NurOwn recipient as one of those reversals:

> ***"Some of the other treatments associated with ALS reversals include … bone marrow-derived stem cells through Brainstorm Cell."***

The identity of this NurOwn reversal is unknown, but based on the date of the blog, it is anticipated that this person received NurOwn in the Israeli Phase 1/2 trials or the compassionate use program.

Dr. Bedlack defines a "reversal" as someone who had *"dramatic and persistent recovery of lost motor function and ability."* For example: (a) Ventilator dependent → now breathing independently; (b) Gastrostomy dependent → now swallowing normally; (c) Loss of speech → now speaking normally; or (d) Wheelchair dependent → now walking.

At the time of a subsequent February 2024 MND blog, Dr. Bedlack had confirmed 60 ALS reversals of the millions of people living with ALS/MND worldwide since the first reversal was documented in 1988. After ruling out ALS-mimics, Dr. Bedlack hypothesized that there were three other possible explanations for ALS reversals:

A. Positive effects from a new treatment
B. Removal of some toxic environmental trigger
C. A genetic factor that made them "resistant" to the disease (like the HIV elite controllers)

Indeed, Dr. Bedlack has discovered a gene that may be related: IGFBP7 (with an alteration in an area called rs424007). He reported that people with at least one copy of this alteration are 14x more likely to have a reversal than someone without it, and 14% of reversals who were genotyped have two copies of this alteration (homozygous).

IGFBP7 is involved in the regulation of **insulin-like growth factor 1**, (IGF-1). In animal models of ALS, increasing levels of this growth factor in the CNS slows ALS progression; in ALS registries, people with the highest levels of IGF-1 progress the slowest; and older studies suggested therapeutic IGF-1 conveyed benefit to people with ALS. Importantly, IGF-1 is a neurotrophic growth factor that stimulates protein synthesis in neurons, oligodendrocytes, glia, inhibiting apoptosis and favoring neuronal survival. A 2009 review[159] by neurologist Eva Feldman at the University of Michigan found that IGF-1 has the potential to be a safe and efficacious therapy for ALS.

[159] Sakowski SA, Schuyler AD, Feldman EL. Insulin-like growth factor-I for the treatment of amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2009 Apr;10(2):63-73.

Neurotrophic factor IGF-1 shares commonalities with the neurotrophic factors in NurOwn. All four neurotrophic factors (BDNF, GDNF, VEGF[160] and IGF-1) activate PI3K/Akt and MAPK/ERK pathways. Each factor supports motor neuron survival by reducing apoptosis, oxidative stress, and excitotoxicity -- all key ALS pathologies. All aim to slow ALS progression by preserving motor neuron function and counteracting degenerative processes. In SOD1 mouse models, all four factors have shown benefits, such as delayed motor neuron loss and extended survival.[161]

It is not known if the NurOwn reversal had his genome sequenced and if he is carrier of the favorable IGFBP7 mutation. Likewise, it is also not known if this person is still alive today or if NurOwn slowed his progression long enough to extend his survival for the last 9 years. It is not known if NurOwn upregulates IGF-1.

What is known is that NurOwn worked. And it worked so well that Dr. Bedlack (and the team of neurologists who scrutinize medical records of possible reversals) concluded that this NurOwn recipient had a large enough magnitude improvement in function and that he sustained that improvement over a long enough period of time to meet the strict criteria to qualify as a confirmed reversal.

S. Congressional Hearings and Documentaries on Expediting ALS Drug Development, Regulatory Flexibility, Conditional Approval & Urgency

Nearly everyone that speaks before Congress tells the story of NY Yankee, Lou Gehrig, who was diagnosed with ALS in 1939 and died on June 2, 1941 – just a few days before his 38th birthday. But what is often missed is how little progress we've made since Gehrig died 84 years ago. The FDA can rewrite that story by approving NurOwn.

Researchers and regulators try to offer hope, speaking about how much more we know about ALS today. In his 2007 testimony before the House VA Committee, Brigadier General Tom Mikolajcik called for accountability and quoted President Lyndon B. Johnson: *'Research is good, results are better.'* He went on to add:

> *"It's been nearly 70 years since Lou Gehrig made his farewell speech and we have, basically, nothing. One questionable drug in nearly 70 years?"*

Today, we have two questionable drugs in 86 years. The others are all stuck in the clinical trial morass. What Gehrig's neurologists knew then may differ a lot from what Petitioners' neurologists know today. But the results do not. The suffering does not. The lifespan does not.

[160] Sakowski, S. A., Schuyler, A. D., Kwan, K. Y., & Feldman, E. L. (2009). Vascular endothelial growth factor enhances motor neuron survival in a mouse model of amyotrophic lateral sclerosis. Molecular Therapy, 17(6), 1058–1065.
[161] Tovar-y-Romo, L. B., Ramírez-Jarquín, U. N., Lazo-Gómez, R., & Tapia, R. (2014). Neurotrophic factors as therapeutic targets in amyotrophic lateral sclerosis: Preclinical and clinical evidence. Neurotherapeutics, 11(3), 532–546.

General Mikolajcik acknowledged that researchers need an increased understanding of this disease, but he reminded everyone that people dying of ALS today won't benefit from future discoveries and treatments. **People dying today need treatments today**.

1. 2000 – Senate Hearing on Stem Cells & Neurotrophic Factors

Twenty-five years ago, the Senate Appropriations Committee held a hearing specifically focusing on ALS. Throughout the hearing, Pennsylvania's Senator Arlen Specter repeatedly asked questions about the use of stem cell therapies in ALS. NINDS Director Dr. Gerald Fischbach testified about the *"terrible and inexorable march"* of ALS. But he also thought there was *"reason for hope"* and mentioned the very early promising discussions about stem cell therapies. Senator Harry Reid emphasized that we need to increase research efforts and act with urgency in this tragic illness as *"ALS patients don't have the luxury of time."*

2. 2000 - Jenifer Estess testified about Promising Stem Cell Research in ALS

A few months later on May 23, 2000, Project ALS co-founder Jenifer Estess testified[162] before the Senate HELP Committee, alongside actor and quadriplegic Christopher Reeves, about the importance of stem cell therapies:

> *"My life and millions of others are in the hands of Congress. We are already seeing the incredible potential of stem cells to replace what is destroyed in ALS, but we need the federal government to mentor research along in the most responsible, humane way…. Project ALS, which I built with my sisters, has assembled and funded a dream team of scientists. In the last nine months these scientists have produced stunning evidence that neural stem cell replacement can replace damaged motor neurons. These new cells may one day allow me to do the things I miss so much like brushing my hair and laughing out loud. Each day I speak from inside my body, which has now become a prison… Make no mistake, ALS is a national disaster…. I hope that Congress, the NIH and the FDA will* ***join Project ALS in pursuing the safest, shortest distance between stem cells and the patients who desperately need them****."*

In September 2000, Jenifer spoke to the Senators again. This time, she joined Michael J. Fox on a panel testifying about the importance of stem cell research in neurodegenerative diseases. Jenifer -- visibly weakened by ALS and pausing to take breaths from her respirator -- highlighted stem cells' potential to generate healthy motor neurons. But equally importantly, she emphasized the time-sensitive nature of research for ALS patients.

[162] U.S. Senate, Subcommittee on Labor, Health and Human Services, and Education, and Related Agencies, Committee on Appropriations. (2000, May 23). Stem cell research, part 2 (S. Hrg. 106-413). U.S. Government Printing Office. https://www.congress.gov/bound-congressional-record/2000/05/23/senate-section/article/s4325-4352

"Five months ago, I came here to tell you about my story, my work and to ask for your help. Since that time, while we wait, I have come to rely on this ventilator. That is because ALS is destroying the muscles I use to breathe. Three years into the illness, I was very into putting the organization together and I thought we're going to do it; we're going to find it in time; the research is going to catch up with me. But as I get sicker – and it's been 6 years now – it's a different world for me. I live in a different world now."

Tragically Jenifer died waiting for the stem cell therapies that she fought so hard to get. But she left a legacy to help all the hundreds of thousands who came after her.

(See "Three Sisters" documentary for excerpts of Jenifer's testimony).

3. 2016 Documentary - Die Trying: the Battle for ALS Treatments

In 2016 Angelina Fanous was working at HBO Vice when she was diagnosed with ALS at just 29 years old. Battling ALS herself, VICE editor Angelina Fanous meets with patients and researchers across the US to find out what's being done to tackle this devastating disease and the regulatory hurdles faced by ALS patients and drugmakers alike.

The film follows the stories of ALS patients, their families, and advocates as they navigate the desperate search for effective treatments amidst a slow and rigid research and regulatory morass. It highlights the emotional and physical toll of the disease, showcasing patients' determination to access experimental therapies through clinical trials or "right to try" laws. The documentary critiques the bureaucratic delays in the FDA's drug approval process, which often outpaces the rapid progression of ALS, leaving patients to die waiting.

In this documentary, Angelina shares her story, as well as the fight of others diagnosed with ALS: Beth Hebron, who was diagnosed at 26; Wissam Majid who traveled to Lebanon to try stem cell therapies; and Eric Valor, a gifted young scientist with ALS who self-experimented with compounded ALS drugs purchased abroad; Kevin Haas who participated in the NurOwn Phase 2 trial; and Matt Bellina who spoke about his inability to qualify for any clinical trials from the moment he was diagnosed.

Angelina then interviewed Dr. Woodcock and asked about the FDA's position on access to ALS therapies.

"For a disease" like ALS – where a drug can work for one person and not necessarily the other because no two ALS patients are alike – what's the harm in just releasing a drug? … If a patient is willing to take the risk, I spoke to a Navy jet pilot who has the disease and he's willing to sign off on it; I'm willing to sign off on it; Again, what is the harm of releasing a drug?

Dr. Woodcock responded that people could use the FDA's Expanded Access program. While EAP may work for small populations, unfortunately, it is not a large-scale option for all 32,000 people with ALS. We know from the people who have tried for YEARS – like Mayuri Saxena and Shahriar Minokadeh – that it's a fallacy that Expanded Access is a reasonable alternative to a Phase 4 approval and post-marketing study. Likewise, Matt Bellina was the only person with ALS who was able to use the Right to Try law that was named after him.

Illustrating that point, Angelina interviewed Neuraltus CEO Rich Casey about its promising drug NP001 that had worked on a sub-population of people in the trial. When asked how it felt when he had to turn down ALS patients who wanted the small molecule drug:

> *"It's a horrible horrible feeling. I mean you feel like less than human because these people were doing well and of course I wanted to give it to him but there was no way; we had no money at that time. There was a question about whether we would survive as a company. It's really heart-wrenching, you know. It's a really heart-wrenching discussion with these patients and then of course, most of them end up dying, so it's very tragic."*

Sadly, Neuraltus did indeed go out of business,[163] and tens of thousands of people with ALS died, without ever getting Expanded Access to NP001. (See section III.C.2 below).

[163] Neuvivo, a company formed by former Neuraltus founders Ari Azhir (CEO) and Michael McGrath (Chief Scientific Officer), acquired the rights to NP001 after Neuraltus folded. Neuvivo was established to continue developing NP001, a sodium chlorite-based immunotherapy aimed at regulating macrophage activation to slow ALS progression by addressing neuroinflammation. Neuvivo reanalyzed Neuraltus's clinical trial data, focusing on a subset of patients aged 40–65, and reported a 36% slower decline in functionality compared to placebo in this group. In October 2024, Neuvivo submitted a New Drug Application (NDA) to the FDA for NP001, supported by data from Neuraltus's Phase IIa (NCT01281631) and Phase IIb (NCT02794857) studies, as well as biomarker and survival analyses. Today the ALS community is still waiting for the FDA to approve NP001.

T. ALS Guidance Document – PROs and Regulatory Flexibility

One of the repeated discussions during the 2021 E&C hearing was "regulatory flexibility." The agency said its final guidance on ALS, provides industry "with the FDA's current scientific thinking so that effective treatments with a favorable benefit to risk profile can be most efficiently developed, and made available to patients." Among other things, the Guidance Document outlines design factors to consider for clinical trials; urges drug sponsors to limit exposure of patients to placebo groups by adopting master protocols for clinical trials that enable simultaneous of testing of multiple treatments with a common placebo group; and recommends use of adaptive clinical trials, with Bayesian statistics that allow for continuous recalculation of outcome probabilities as new data are added.

But among the most important changes are contained in the section on efficacy endpoints:

- Effectiveness = treatment effect ("less decline, stabilization or improvement") in ADLs, as measured by ALSFRS-R
- In addition to the primary endpoint, sponsors should include various effectiveness outcomes including patient-reported outcomes (PROs). These data would be supportive.
- PROs should assess ADLs across spectrum of disease & severity
- PROs useful to assess "clinical meaningfulness of an objective finding (e.g., muscle strength) – even of a relatively small magnitude
- Existing COA may be appropriate but FDA supports use of new COAs measuring clinically meaningful effects

Unfortunately, it took six years to draft this eight-page document. And when it was implemented in September 2019, it was too late to incorporate the Guidance into the NurOwn Phase 3 trial, which was already enrolling.

U. Procedural History

Brainstorm was granted 'Fast Track' status for NurOwn in 2014 and it began to enroll the Phase 2 study. In 2016, Congress passed the 21st Century Cures Act, which among other things, created the Regenerative Medicine Advanced Therapy Designation ("RMAT"). Sometime in 2017, CBER refused to extend RMAT designation to NurOwn even though it easily met all the required elements:

> *"As described in Section 3033 of the 21st Century Cures Act, a drug is eligible for RMAT designation if:*
>
> 1. *The drug is a regenerative medicine therapy, which is defined as a cell therapy;*
> 2. *The drug is intended to treat, modify, reverse… a life-threatening disease; and*
> 3. *Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition"*

Without RMAT designation Brainstorm was deprived of a chance to have meetings with CBER officials to discuss its innovative and first-in-class CSF biomarkers – the first company ever to collect CSF biomarkers longitudinally in an ALS trial.

On November 17, 2020, Brainstorm announced its topline data from the Phase 3 trial. Less than one month later, on December 14, 2020, Brainstorm announced that the FDA had authorized an expanded access protocol for patients less severely affected by ALS, in accordance with the recently announced topline data from its Phase 3 trial. During the ensuing two years, in 2021 and 2022, 10 people of the 194 in the Phase 3 trial received additional doses of NurOwn via expanded access.

BrainStorm submitted its Biologics License Application (BLA) to CBER on September 9, 2022, and received a Refusal to File (RTF) letter from the FDA on November 8, 2022. The RTF letter asserted that NurOwn failed to meet the "substantial evidence" standard. This unfortunately meant those in the trial and EAP would not be given an opportunity to share their real-world evidence at an Advisory Committee meeting. In response:

- Team Stevens issued a Press Release requesting an AdComm (Nov 21, 2022)
- Veterans with ALS issued a Press Release & Open Letter to Dr Marks (Nov 23, 2022)
- I Am ALS Board Member & person with ALS, Dan Tate, delivered a Petition to Dr. Marks with over 30,000 signatures requesting an AdComm (Dec 14, 2022).
- People with ALS and the family members communicated repeatedly with Congress demanding a chance to be heard
- Members of Congress communicated with Dr. Califf and Dr. Marks
- Nicole Cimbura sent an email to Dr. Marks requesting an in-person AdComm, as well as giving trial and EAP participants more time to be heard

On January 11, 2023, the FDA held the Type A Meeting with Brainstorm regarding the RTF Letter & its Request for Advisory Committee meeting. At this time, the trial was still blinded to both the patients and PIs. While Petitioners don't know the specific attendees or content of that Type A meeting, we do know that some of the NurOwn trial PIs were present as they asked their EAP patients (who had additional NurOwn dosing) for HIPAA authorization to share the clinical data and expert observations that NurOwn worked.

On February 6, 2023, with the commitment by FDA to accept amendments that were filed to address items raised in the RTF letter, BrainStorm requested that CBER utilize the FDA's File Over Protest procedure and filed an amendment to the BLA to respond to outstanding questions the FDA posed. On March 27, 2023, BrainStorm announced that the FDA would hold an AdComm but didn't specify a date. On June 6, 2023, BrainStorm announced that the AdComm date would be on September 27, 2023. That CTGT AdComm voted 17-1-1 not to recommend approval of NurOwn and on October 18th, Brainstorm announced they were withdrawing the BLA, without prejudice.

After a Type C meeting, the FDA and Brainstorm have agreed on a Special Protocol Assessment ("SPA") for the anticipated Phase 3b trial. The Amended IND has been accepted.

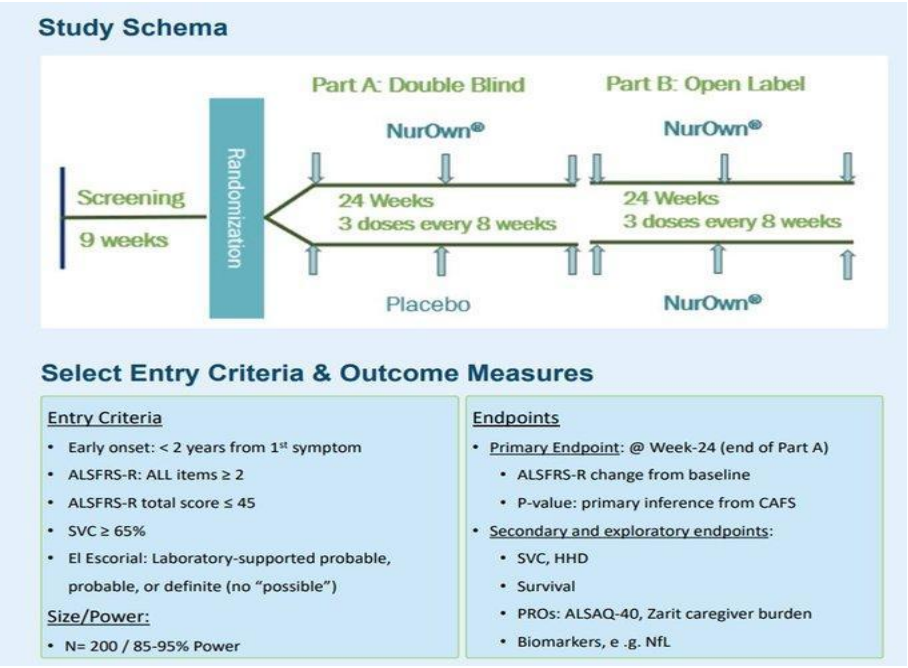
V. NurOwn's Phase 3B Trial Design

On May 15, 2025 Brainstorm published its Phase 3B trial (NCT06973629) on clinicaltrials.gov. It has an anticipated start date of June 30, 2025 and estimated primary completion date of November 1, 2028, with a study completion date of May 1, 2029.

The trial qualifications have some critical distinctions from the prior Phase 3A trial. Most importantly to minimize the impact of the floor effect, people must have a minimum score of 2+ on all 12 ALSFRS-R questions. Similarly, to minimize the impact of the ceiling effect, people must already have demonstrated decline with an ALSFRS-R score no higher than 45 on the 48-point scale.

The other critical distinctions relate to the trial design and endpoints. Instead of a 28-week trial, the time to collect data is almost one year: a 24-week trial followed by a 24-week Open Label Extension. Critically, this means 100 people will receive 6 consecutive doses of NurOwn. In the US, only Matt Bellina has ever received that many consecutive doses; and Matt, not surprisingly had a larger magnitude and longer duration improvements than those in the Phase 3A trial. The people in EAP received up to 9 doses but they were broken up into 3 rounds of 3 doses each, separated by as much as 2 years between rounds.

Graphic - NurOwn's Phase 3B Trial Design



This Phase 3B trial is estimated to end in 2029:

- **10 years after Matt Bellina stood up out of his wheelchair unassisted and no longer needed a bi-pap to breathe**
- **9 years after the Phase 3 trial showed efficacy in some**
- **14 years after the Phase 2 trial showed some efficacy in some**
- **17 years after some regained function in the Phase 1/2a trials in Israel**
- **25 years after NurOwn's pre-clinical development began in Israel**

In a 100% fatal, heterogeneous disease, "some" should be enough. Nothing about this delay makes common sense. Our regulatory law must act with the same urgency as ALS is killing people.

W. Drug Development Timeline doesn't Match the Urgency of ALS

Commissioner Makary has repeatedly asked why the drug development timeline takes 10 years. It's much longer in ALS and tragically, the drug development timeline far exceeds ALS lifespan.

A recent study by the NIH and FDA looked at FDA-approved therapies from 2010-2020. The authors concluded that the clinical development time of a typical innovative drug is 9.1 years.[164] The FDA's expedited pathways shorten that time, but not significantly.[165] However, the study did not analyze the drugs for neurodegenerative diseases like ALS, diseases with "critical unmet needs," nor did it compare CBER's gene and cell therapies to CDER's small molecule drugs. Another study[166] found that the average time for drug development -- including preclinical and clinical phases -- is approximately 12-15 years, noting longer timelines for complex conditions like neurodegenerative diseases.[167]

Another recent study reported a mean lag of 13 years from genetic target identification to the first clinical trial, with total development often extending to 15-19 years including regulatory approval.[168] A second study of non-cancer therapies found a median time of 25 years from genetic target discovery to drug approval.[169] But due to the complexity of ALS, even this genetic target timeline is understated.

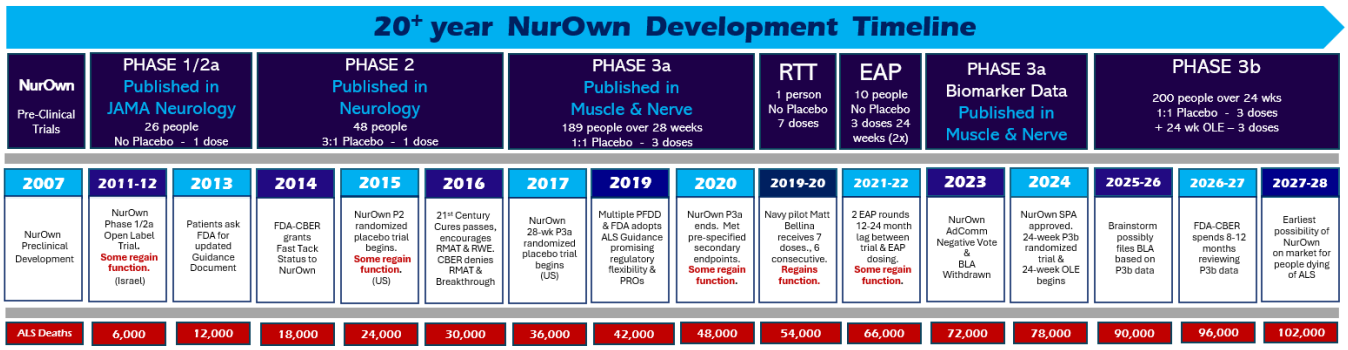
[164] Brown DG, Wobst HJ, Kapoor A, Kenna LA, Southall N. Clinical development times for innovative drugs. Nat Rev Drug Discov. 2022 Nov;21(11):793-794.
[165] Drugs using FDA expedited pathways had a reduced clinical development time for Accelerated Approval by 1,100 days. Priority review status decreased review times by 103 days. The study did not analyze RMAT status. In contrast, orphan designation is associated with an increase in clinical development times of 552 days. Failures to win approval within the first review cycle increased review times by 829 days and likewise increased clinical development time by 643 days.
[166] DiMasi, J. A., Grabowski, H. G., & Hansen, R. W. (2016). Innovation in the pharmaceutical industry: New estimates of R&D costs. Journal of Health Economics, 47, 20–33.
[167] Vijverberg, E. G. B., Scheltens, P., & Pijnenburg, Y. A. L. (2022). Timing of investigational drug development in relation to novel genetic targets in neurodegenerative diseases. Nature Reviews Neurology, 18(10), 561–570.
[168] Traas, R., Havrdova, K. E., Murphy, R. L., Rind, D. M., Wang, H., Vo, P. J., ... & Kimmelman, J. (2022). Disease stages and therapeutic hypotheses in two decades of neurodegenerative disease clinical trials. Scientific Reports, 12, 17708.
[169] Minikel, E. V., Painter, J. L., Dong, C. C., & Schreiber, S. L. (2023). Impact of genetic polymorphisms on human health: 25 years to translate insights into novel therapies. Nature, 620(7975), 725–734.

The first ALS-causing gene, SOD1, was identified in 1993 by Dr. Robert Brown of UMass[170] (who was also a NurOwn PI in the Phase 2 & 3 trials). Today we know that SOD1 has over 200 variants[171] and it affects 2% of the ALS population.[172] Yet Tofersen, the only disease-modifying therapy in ALS, was not approved until March 2023[173] – 30 years later.

NurOwn has languished in the drug development regulatory morass and financial quandary for 21 years since innovation and … and counting. Now the FDA has asked the company to do a second Phase 3 trial, which will add another 4-5 years to the timeline.

NurOwn first worked on some in Israel in 2011-2012 in the open label trials in Phase 1/2a. It worked on some in Israel's Compassionate Use and Hospital Exemption programs. With just one dose, it worked again on some in 2015 during the Phase RCT in the US. It worked on some during the Phase 3 trial in 2017-2020; It worked on all during EAP in 2021 and 2022; and it worked on the only one to receive it during Right to Try in 2019-2020. In the graphic below, the data in red reflects the cumulative number of Americans with ALS who have died waiting for NurOwn's approval.

<u>Graphic</u> - NurOwn's 20+ Year Drug Development Timeline



[170] Rosen, D. R., Siddique, Brown, R. H. et al (1993). Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature, 362(6415), 59–62

[171] Miller, T. M., Cudkowicz, M. E., Genge, A., Shaw, P. J., Sobue, G., Bucelli, R. C., Chiò, A., Van Damme, P., Ludolph, A. C., Glass, J. D., Andrews, J. A., Babu, S., Benatar, M., McDermott, C. J., Cochrane, T., Chary, S., Fisher, S., Fournier, C., Zhou, Y., … Ferguson, T. A. (2022). Trial of antisense oligonucleotide tofersen for SOD1 ALS. New England Journal of Medicine, 387(12), 1099–1110.

[172] Brown, C. A., Lally, C., Kupelian, V., & Flanders, W. D. (2021). Estimated prevalence and incidence of amyotrophic lateral sclerosis and SOD1 and C9orf72 genetic variants. Neuroepidemiology, 55(5), 342–353. https://doi.org/10.1159/000516752

[173] U.S. Food and Drug Administration. (2023, April 25). FDA approves treatment of amyotrophic lateral sclerosis associated with a mutation in the SOD1 gene.

PETITIONERS' MEMORANDUM

"Post-approval monitoring in Big Data will allow the FDA and researchers to see safety signals in real time and evaluate effectiveness in the real world. This is particularly important for products addressing rare diseases. "
JAMA Viewpoints

Dr. Prasad has expressed that the FDA's goal should be to approve drugs that help people "live longer and live better." NurOwn does both.

The "totality of the evidence," the RWE/RWD, the biomarker data, the respiratory evidence, the long-term slowing of ALS progression – and most importantly the survival data – support Petitioners' request for approval of NurOwn with a Phase 4 post-marketing study. The unprecedented survival data has never-before-been-seen in any ALS trial.

The survival data, alone, justifies approval under both the "Substantial Evidence" test as well as the "Reasonable Likelihood" test for Accelerated Approval. As such, to reach a decision to approve NurOwn, initially the inquiry was on whether the biomarkers predict a clinically meaningful impact on survival; or if the post hoc data of the subgroup early in progression was able to be trusted; whether the floor effect caused the placebo group to overperform; if the change in ALSFRS-R is clinically meaningful "enough;" or if all the patient experiences could be believed. The answer to all these questions is "YES." But these data should all be "supporting evidence" of efficacy. The survival data are dispositive evidence of efficacy that no other ALS trial has ever had!

Petitioners submit that the two most important questions are:

1. Does NurOwn cause people to live longer?
2. If the FDA delays approval and waits for data from yet another phase 3 trial, what are the risks to people dying of ALS?

Below is a summary of the dispositive and supporting evidence of efficacy.

Congress specifically amended the statutory provision so "substantial evidence of effectiveness" could come from one adequate and well-controlled clinical investigation plus confirmatory evidence (obtained prior to or after such investigation).[174] The FDA's 2019 Draft Guidance Document, "*Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products,*" outlines both the quality and the quantity of evidence necessary for approval under the traditional approval pathway.

In certain circumstances, FDA accepts one adequate and well-controlled clinical investigation that has generated compelling results as the basis to demonstrate substantial evidence of effectiveness, when

[174] See section 115(a) of FDAMA, amending 136, 21 U.S.C. § 355(d).

the single trial is supported by additional data from the natural history of the disease that reinforce the very persuasive finding.

> *For example, a **single trial showing marked improvement in survival** compared to a control group, either external to the trial or concurrent, could be supported by **data from separate sources** (e.g., a natural history study, case report forms, or registries) that **demonstrate a very limited median survival time** or other clinically highly important outcome without treatment. In this case, the natural history data would represent confirmatory evidence.*

I. NurOwn Survival Data Meets or Exceeds Outcomes of Other FDA-Approved Therapies

"Survival is the ultimate clinically meaningful outcome measure for a fatal disease like ALS."
-FDA's Briefing Document

Brainstorm pre-specified Overall Survival (OS) and Trach-free Survival (TFS) as Secondary Endpoints. But in a 28-week trial in ALS, it was unlikely to collect enough data to draw any conclusions about survival. The FDA's Brief discusses the challenges for having survival as an efficacy endpoint because survival trials typically require a much larger number of study subjects and longer follow-up time. In recent years, most ALS trials enrolled fewer patients and had shorter post-treatment follow-up time (e.g., 6 months), which makes detecting a survival benefit more challenging. In fact, many ALS trials do not show a difference in survival between treatment and control groups during the short (e.g., 6-month) study follow-up period.

Indeed, on page 36 of the FDA's Brief, it admits that *"survival data were available for less than 10% of study subjects after the final study visit."* And even among that small population of 12/189 people, the FDA's Kaplan-Meier Curve of OS showed little difference.

Five years after the end of the phase 3 trial – and 30,000 deaths later – we now have survival data. While the population of that EAP survival data is admittedly small, the magnitude of the response is huge.

Dr. Peter Marks once said:

> "*The treatment has to create a large enough effect that it is apparent to a non-statistician that something has happened significantly to those individuals…."*[175]

NurOwn's treatment effect? Living. People with ALS are living longer and living better.

[175] BioSpace. (2024, January 18). FDA's Marks advocates for flexibility in rare disease gene therapy trials.

A. New Long-Term Evidence of Overall Survival and Trach-free Survival

NurOwn outperformed the two therapies currently approved for ALS. More importantly, it dwarfs the survival data for dozens of cancer therapies. The FDA's Guidance document for "Substantial Evidence" provides that:

> *"A single trial showing **marked improvement in survival compared to a control group**, either external to the trial or concurrent, could be supported by data from separate sources (e.g., a natural history study, case report forms, or registries) that demonstrate a very limited median survival time or other clinically highly important outcome without treatment. In this case, the natural history data would represent confirmatory evidence."*

Although the press release is no longer available on the FDA's website, on September 23, 2019 Commissioner Sharpless issued a PR announcing the release of the ALS Guidance Document. In it, the FDA said it is **"open to considering alternative approaches to meeting our requirements for approval."** Petitioners submit that the unprecedented EAP respiratory and survival data justify that open-minded approach and use of regulatory flexibility.

1. NurOwn's Survival Data Beats Riluzole and Radicava

For sporadic ALS, there are only two drugs specifically approved to slow ALS progression and extend survival: Riluzole and Radicava (Edaravone). Yet they offer only modest survival benefits. And their use is limited by side effects that can sometimes discourage patient adherence. Riluzole commonly causes nausea, fatigue, elevated liver enzymes, and dizziness, leading some patients to discontinue treatment.[176] Edaravone, originally administered through IV infusion cycles, was associated with gait disturbances.[177] Based on clinical trials and real-world data, the following lists the survival benefits of these therapies at the time of their FDA approvals and in current data.

a. Riluzole

Riluzole, a glutamate antagonist, was approved by the FDA in 1995 as the first drug for ALS. Early trials demonstrated a modest survival benefit of 2-3 months.[178] After 18 months of follow-up, 57% on

[176] Bensimon, G., Lacomblez, L., & Meininger, V. (1994). A controlled trial of Riluzole in amyotrophic lateral sclerosis. New England Journal of Medicine, 330(9), 585–591.
[177] Abe, K., Itoyama, Y., Sobue, G., Tsuji, S., Aoki, M., Doyu, M., ... & Yoshino, H. (2014). Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of Edaravone (MCI-186) in amyotrophic lateral sclerosis patients. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 15(7-8), 610–617.
[178] Lacomblez, L., Bensimon, G., Leigh, P. N., Guillet, P., & Meininger, V. (1996). Dose-ranging study of Riluzole in amyotrophic lateral sclerosis. The Lancet, 347(9013), 1425–1431.

Riluzole survived "trach-free" compared to 50% on placebo.[179] Indeed commenting on the number of people who stabilized in Phase 2, Dr. Merit Cudkowicz told BioNap:[180]

> *"I've been treating patients with ALS for over 25 years and we very rarely see instances of 100% improvement…. Improvement is very rare in ALS. The trajectory is almost always downhill.* ***We do not see this type of response on riluzole."***

Real-world studies now have suggested a greater survival benefit than observed in initial Riluzole trials. A 2020 analysis of 15 population-based studies found that Riluzole extended median survival by 6–19 months compared to Riluzole-free patients, significantly surpassing the 2–3 months reported in RCTs.[181] While Riluzole's benefits may be more substantial in clinical practice, its effect remains modest, and **it does not halt disease progression**.

b. Radicava

Edaravone is a free-radical scavenger targeting oxidative stress; the IV method of delivery was approved by the FDA in May 2017 based on a phase 3 RCT conducted exclusively in Japan. Edaravone slowed functional decline by approximately 33% over 24 weeks, as measured by a 2.49-point lesser decline in ALSFRS-R scores compared to placebo (p=0.0013).[182] No definitive survival benefit[183] was established at the time of approval.

Recent real-world evidence has provided mixed results into Edaravone's survival benefits. A 2024 study from the ALS/MND Natural History Study Consortium reported a median survival of 31.1 months for patients on Edaravone plus Riluzole versus 28.8 months for Riluzole alone, a difference of 2.3 months.[184] A 2022 retrospective analysis of U.S. administrative claims data (2017–2020) used propensity score matching and found that Edaravone -- often combined with Riluzole -- was associated with a 27% lower risk of death (p=0.005), with a 6-month difference in median survival (29.5 vs. 23.5 months) for non-Edaravone-treated patient – but obviously that survival benefit could have been boosted by Riluzole or the synergistic impact of Riluzole and Edaravone.[185] However, a 2022 German cohort study found no significant survival or trach-free survival benefit for Edaravone plus Riluzole over

[179] Bensimon, G., Lacomblez, L., & Meininger, V. (1994). A controlled trial of Riluzole in amyotrophic lateral sclerosis. New England Journal of Medicine, 330(9), 585–591.
[180] BioNap. (2016, November 28). Interview with neurologist: ALS KOL sheds light on NurOwn therapy [Interview]. Yahoo Finance.
[181] Hinchcliffe, M., & Smith, A. (2017). Riluzole: Real-world evidence supports significant extension of median survival times in patients with amyotrophic lateral sclerosis. Degenerative Neurological and Neuromuscular Disease, 7, 61–70.
[182] Abe, K., Itoyama, Y., Sobue, G., Tsuji, S., Aoki, M., Doyu, M., ... & Yoshino, H. (2014). Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of Edaravone (MCI-186) in amyotrophic lateral sclerosis patients. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 15(7-8), 610–617.
[183] Sawada, H. (2017). Clinical efficacy of Edaravone for the treatment of amyotrophic lateral sclerosis. Expert Opinion on Pharmacotherapy, 18(7), 735–738.
[184] ALS News Today. (2024, June 18). Radicava found to prolong survival in real-world analysis.
[185] Brooks, B. R., Pioro, E. P., Katzin, L., & Moore, D. H. (2022). Intravenous Edaravone treatment in ALS and survival: An exploratory, retrospective, administrative claims analysis. eClinicalMedicine, 50, 101510.

Riluzole alone after one year, highlighting conflicting results.[186] These discrepancies suggest that Edaravone's benefits may depend on patient selection, disease stage, or treatment duration; and further RCTs are needed to confirm if there are any survival benefits at all.

NurOwn's Survival data beats the survival data of Riluzole and Radicava, both at the time they were approved as well as now. NurOwn gives people with ALS the best chance to live. Please, give people in the ALS Community a chance to live longer.

B. NurOwn Evidence Exceeds Evidence supporting Accelerated Approval for Therapies Targeting Cancer

Petitioners believe that Dr. Pazdur's team at the Oncology COE has properly exercised regulatory flexibility for terminal oncologic diseases. As one would expect of a compassionate regulatory structure, that regulatory flexibility extended to some cancer therapies – even if they were second or third line treatments. We are asking CBER to extend that same humanity to ALS therapies – especially as the new evidence we have presented in this Petition meets or exceeds the improvements demonstrated by many approved cancer therapies.

During the AdComm, Dr. Windebank shared:

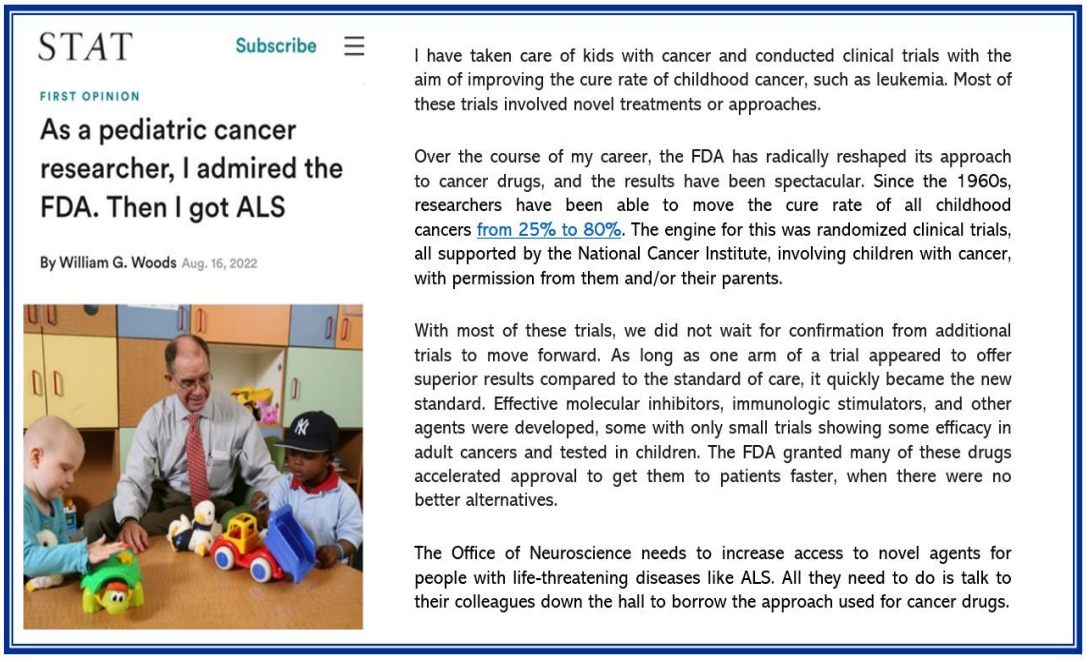
> *"As someone who is involved in ALS and cancer research for decades, we have seen incredible advances in cancer treatments built on many I think incremental steps. We need to take the approach to build on research. The FDA has exercised regulatory flexibility in drug approvals and promises to continue to do so…. Importantly, we can't afford to lose a potentially valuable treatment simply because of complex data…."*

Several oncologists submitted Public Comments asking the FDA to use the cancer model when addressing the risks and benefits of this ALS therapy:

> *"There is an unmet clinical need in ALS that by many measures exceeds that of many malignancies...the clinical data looks very promising and exceeds the benchmarks which have led to the approval of many drugs in oncology."*

See Public Comment of Dr. Koshkin, UCSF oncologist. In an OpEd for STATNews, Dr. Willam Woods offered his assessment of how the FDA has transformed pediatric cancer with a flexible approach to the use of Accelerated Approval and he encouraged the FDA to do the same for ALS. Sadly, after saving the lives of thousands of children with cancer, Dr. Woods died waiting.

[186] Witzel, S., Maier, A., Steinbach, R., Grosskreutz, J., Koch, J. C., Sarikidi, A., ... & Meyer, T. (2022). Safety and effectiveness of long-term intravenous administration of Edaravone for treatment of patients with amyotrophic lateral sclerosis. JAMA Neurology, 79(2), 121–130.



STAT Subscribe

FIRST OPINION

As a pediatric cancer researcher, I admired the FDA. Then I got ALS

By William G. Woods Aug. 16, 2022

I have taken care of kids with cancer and conducted clinical trials with the aim of improving the cure rate of childhood cancer, such as leukemia. Most of these trials involved novel treatments or approaches.

Over the course of my career, the FDA has radically reshaped its approach to cancer drugs, and the results have been spectacular. Since the 1960s, researchers have been able to move the cure rate of all childhood cancers from 25% to 80%. The engine for this was randomized clinical trials, all supported by the National Cancer Institute, involving children with cancer, with permission from them and/or their parents.

With most of these trials, we did not wait for confirmation from additional trials to move forward. As long as one arm of a trial appeared to offer superior results compared to the standard of care, it quickly became the new standard. Effective molecular inhibitors, immunologic stimulators, and other agents were developed, some with only small trials showing some efficacy in adult cancers and tested in children. The FDA granted many of these drugs accelerated approval to get them to patients faster, when there were no better alternatives.

The Office of Neuroscience needs to increase access to novel agents for people with life-threatening diseases like ALS. All they need to do is talk to their colleagues down the hall to borrow the approach used for cancer drugs.

Michael Drazer, MD, PhD shared his support for Accelerated Approval in his Public Comment and he also mentioned that mathematical issue that Dr. Woodcock discussed at the BIO Conference. The underpowered small trial has a higher risk of a Type II error.

> *"As an oncologist and physician scientist with friends and loved ones diagnosed with ALS, I frequently review ongoing clinical trials in this space with the goal of familiarizing myself with this disease and to identify potentially promising therapeutic options that may help my loved ones…. I have reviewed the recent debamestrocel cellular therapy with intrigue, as cellular therapies are frequently used in the hematology/oncology and cancer space…. I was struck by the inclusion of a hard endpoint (CSF biomarker changes) as well as the successful improvement in biomarkers in this study…. this drug strikes me as a classic candidate for the Accelerated Approval pathway, with a plan to perform a larger clinical trial to determine the potential for benefit in particular subgroups. As an oncologist, this is a very common pathway that has been used in our field for the benefit of patients and subgroups of patients on numerous occasions. This enables us to [sic] while we await definitive clinical studies for novel agents while also benefiting patients who are willing to try novel therapies….*
>
> *Of note, this analysis was a pre-specified **subgroup analysis that was underpowered in the phase III trial** - meaning that it is **at risk for false negative results** and which would warrant a dedicated study. This agent should be subsequently investigated in a larger cohort of patients only with ALSFRS-R >= 35. This study could take years to complete; in the meantime, I would encourage the FDA to employ the Accelerated Approval mechanism for debamestrocel for the benefit of patients in the ALS community."*

Indeed, during the 2021 hearing before the Energy & Commerce Committee, Dr. Cavazzoni admitted that the FDA has *"fully deployed"* the expedited regulatory pathways in oncology where it has made *"tremendous gains"* over the past 20 years. She then added that the FDA has the *"same tools at our disposal when it comes to regulatory flexibility that have led to tremendous advances in oncology."*[187]

Following are some of the many comparisons between the evidence supporting NurOwn's approval versus cancer therapies that received Accelerated Approval. Petitioners are asking this FDA to use those same tools – the regulatory flexibility, Accelerated Approval and the Conditional Approval pathway – to make the same advances in ALS in the next 20 years that it has made in oncology in the last 20 years.

a. Tukysa Comparison - "Some is Enough"

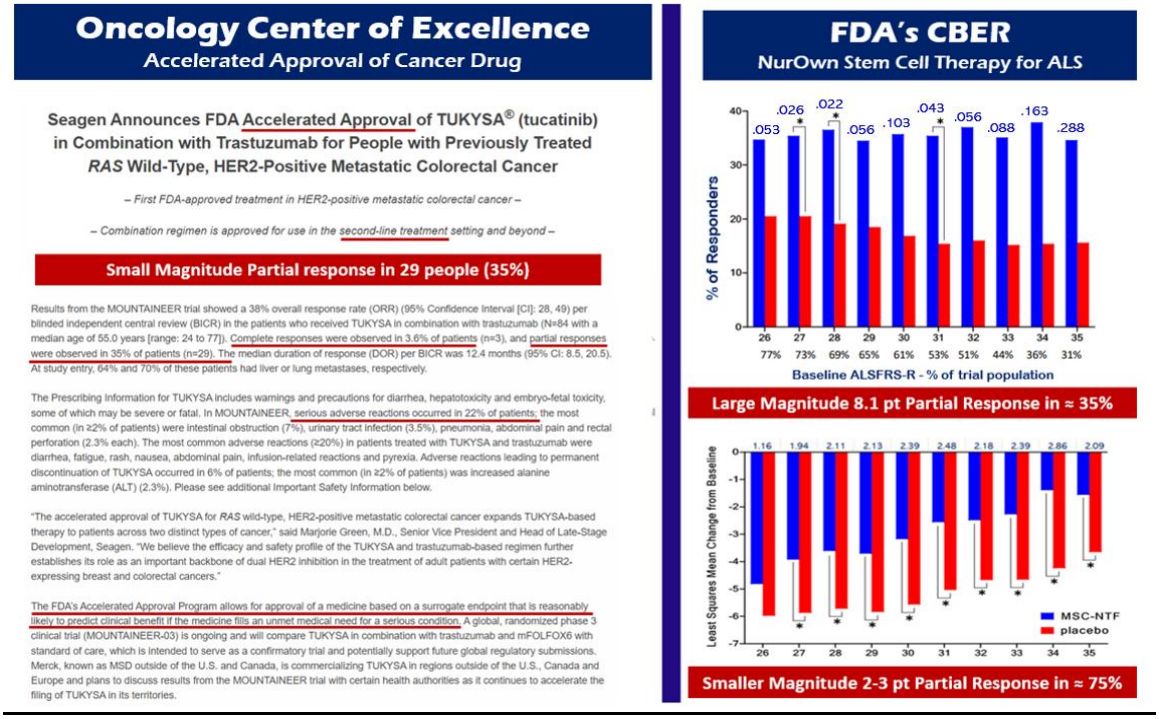
When the FDA approved Tukysa, it demonstrated that "some is enough" to approve a therapy for a terminal disease with a critical unmet need. Merck/Seagen's Tukysa (tucatinib), in combination with trastuzumab, received FDA Accelerated Approval for treating a type of colorectal cancer that progressed after chemotherapy. The approval was based on results from the small Phase 2 MOUNTAINEER trial (NCT03043313) with 84 trial participants. **It did not work on 50 of the 84 cancer patients.**

- 3.6% achieved complete responses
- 35% achieved partial response
- 61.4% demonstrated no response
- Median duration of response was 12.4 months demonstrating durable anti-tumor activity
- Median OS: 24.1 months (20.3–36.7 months)
- Median PFS: 8.2 months (4.2–10.3 months)

This marked the first FDA-approved therapy for RAS wild-type, HER2-positive unresectable or HER2-positive metastatic colorectal cancer, addressing an unmet need for this aggressive cancer subtype. A phase 4 confirmatory trial is ongoing to validate these findings. Meanwhile "some" people with this fatal colorectal cancer have hope and a chance.

[187] *"The Path Forward: Advancing treatments and cures for neurodegenerative diseases."* Hearing before the Health Subcommittee of the Committee on Energy and Commerce, House of Representatives, 117th Cong. (2021, July 29).

Graphic - "Partial response:" - NurOwn Efficacy Data vs. Tukysa Efficacy Data



Petitioners assert that "some" should be enough in ALS as well. Like Tukysa, the people in the NurOwn Trial achieved a partial response in 35% of participants. Looking at the primary endpoint, approximately 35% of people achieved the large magnitude -1.25 point per month change in slope. This happened consistently in the subgroup with an ALSFRS-R score ≥27. In this subgroup, the data met statistical significance.

Comparatively, of the 189 people in the NurOwn Phase 3 trial, the subgroup of 138 people with baseline scores ≥27 on the 48-point ALSFRS-R demonstrated an (unadjusted) statistically significant "partial response."

- Larger magnitude Primary Endpoint of approximately an 8-point slowing in progression
  - 35% of trial population met endpoint (p=0.046)
  - 41% with No Floor Effect met endpoint (p= 0.035)

- Smaller magnitude Secondary Endpoint of a 2-3 point difference between NurOwn and placebo
  - 73% met endpoint = 1.94 point difference between NurOwn & placebo (p=0.026)
  - 56% with No Floor Effect = 2.31 point difference between NurOwn & placebo (p=0.040)

Notably, in the Tukysa trial, 61% of people demonstrated no response at all. In contrast, many people demonstrated partial responses in the NurOwn trial. For example, on the secondary endpoint, approximately 75% of people showed a 1 to 2 point difference from placebo. Comparatively, the only

subgroup that didn't show a statistically significant difference was the subgroup with scores of ≤26 (aka the floor effect subgroup).

To that end, Dr. Suchit Patel offered insights about the disparate way the FDA has treated ALS versus cancer therapies. As a radiation oncologist and a PhD neuroscientist who is friends with Petitioner Mayuri Saxena, Dr. Patel has unique insights:

> *"Why this has been so difficult in ALS is because of the rarity of the disease and how trials have to be structured for a disease that is universally fatal and rapidly progressing. There was a recent [NurOwn] trial that failed to meet its endpoint and was declared a "failed trial." Yet 35% percent of patients had an objective response. As a practicing oncologist,* ***if there was an oncology trial that had a 35% objective response rate (ORR), we would be rejoicing for a rare oncologic condition****. That would be an amazing trial. Yet for ALS, we declare that as a failed trial and that's only because of the structural limitations of a clinical trial in a rare neurodegenerative disease that's universally fatal."*

Just as Dr. Patel asserted, Petitioners assert that if "some is enough" in colorectal cancer, it should likewise be enough in ALS.

b. Opdivo's 7% Increase in OS

NurOwn's results in ALS exceed Opdivo's results in non-small cell lung cancer (NSCLC). In the Phase 3, randomized, open-label study, researchers studied Opdivo plus platinum-based chemotherapy versus chemotherapy alone in patients with resectable NSCLC (stage IB-IIIA). In the NEJM, the trial was characterized as having demonstrated a "significant improvement" in survival:[188]

- 7% increase in OS at one year (48% chemo alone to 55% with Opdivo plus chemotherapy)
- 10.8 months of longer median event-free survival (31.6 months vs. 20.8 months).

These results led to the FDA approval of Opdivo plus chemotherapy as a neoadjuvant treatment for adults with resectable NSCLC, establishing it as a standard of care in NCCN guidelines.

Several things stand out about the Opdivo approval. Comparatively Opdivo resulted in a 7% increase in OS at one year and nearly 11 months of event-free survival. The survival data in the NurOwn trial and EAP far exceeds that. In the NurOwn EAP (also open-label), 100% lived at least five years. This is 30 months longer than the median trach-free ALS natural history of 30 months, and 5 times longer than the expected 20% five-year survival rate. Moreover, several people are approaching 90 months trach-free survival – a 300% increase over ALS natural history.

[188] Forde, P. M., Spicer, J., Lu, S., Provencio, M., Mitsudomi, T., Awad, M. M., Felip, E., Broderick, S. R., Brahmer, J. R., Swanson, S. J., Kerr, K., Wang, C., Ciuleanu, T.-E., Saylors, G. B., Tanaka, F., Ito, H., Chen, K.-N., Liberman, M., … Chaft, J. E. (2022). Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. New England Journal of Medicine, 386(21), 1973–1985

Additionally, Petitioners note that the Opdivo results are for stage IB-IIIA resectable NSCLC. Understandably, the therapy doesn't work as well on people with late stage NSCLC – just like NurOwn doesn't work as well on late stage ALS. A post hoc analysis found that NurOwn had a clinically meaningful impact on those earlier in progression – those people with ALSFRS-R scores ≥27/48 as well as those with no floor effect.

The OCE would never deny Opdivo access to the population that it benefits simply because it doesn't work as well on people with stage IIIB/IV NSCLC. Yet that is precisely what has happened with NurOwn.

c. Farydak's 3.8 Month OS Data in 25 People

Farydak (panobinostat) was approved in February 2015 for multiple myeloma under the FDA's accelerated approval pathway. It was developed by Novartis and indicated for patients with relapsed or refractory multiple myeloma who had received at least two prior therapies, including bortezomib and an immunomodulatory agent.

The pivotal trial included a **subgroup analysis of 25 patients** with relapsed/refractory multiple myeloma.[189] While the full trial enrolled 768 patients, a smaller cohort within a prior Phase 2 study (conducted by the University of Pittsburgh) only had 25 people. This smaller study reported OS data, showing a median OS of approximately 17.5 months with panobinostat plus bortezomib and dexamethasone compared to 13.7 months with placebo – though the difference was not statistically significant due to the small sample size. The FDA's approval leaned on progression-free survival (PFS) as the primary endpoint, but the OS data from this small cohort was considered supportive, highlighting a potential survival benefit in this rare disease subset – **even though it was only 3.8 months of additional survival.**

Similarly, in the NurOwn trial there is ample evidence that NurOwn worked on the much larger trial population of people early in ALS progression; but the 5-year survival data is found in the population of 10 people in the EAP.

Like Farydak, the trial population is small but NurOwn's effect size is significantly larger.

- 5.5 month improvement = OS data when compared to matched controls as of 2022
- 3 - 5 years longer than median trach-free survival

[189] Laubach, J. P., San-Miguel, J. F., Hungria, V. T. M., Hou, J., Moreau, P., Mateos, M.-V., ... & Richardson, P. G. (2015). Panobinostat for the treatment of multiple myeloma. *Clinical Cancer Research*, 21(21), 4767–4773.

d. Heterogeneous NTRK gene fusion Cancer Therapies

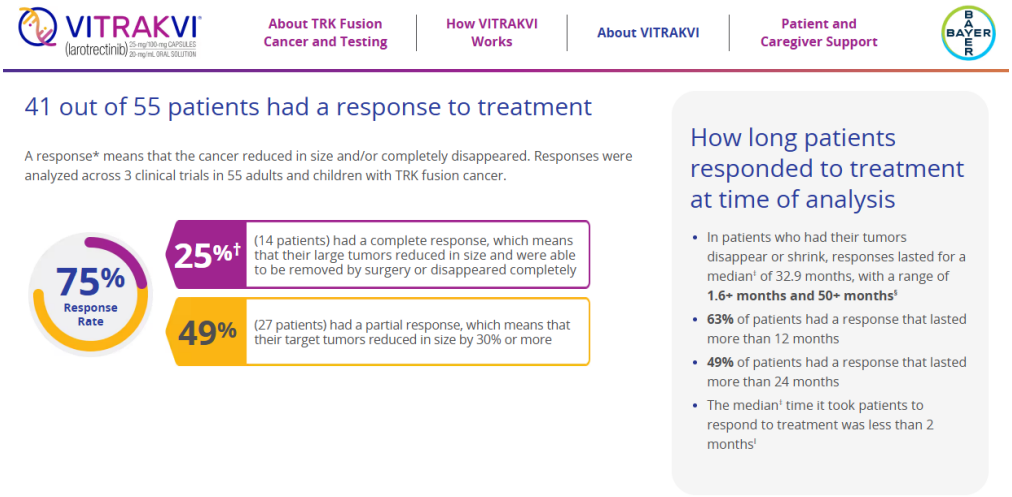
Similarly, two cancer therapies for solid tumors with NTRK gene fusions notably relied upon post hoc data for accelerated approval: Vitrakvi (post hoc OS data of 33.5 months in 55 people)[190] and Rozlytrek (post hoc OS of 23.9 months in 66 people). The Vitrakvitrial involved 17 heterogeneous TRK fusion–positive tumor types. The primary endpoint was an 80% ORR overall response rate (ORR).

- 13% (7 patients) had a complete response
- 62% (34) had a partial response
- 13% (7) had stable disease
- 9% (5) had progressive disease
- 4% (2) early withdrawal for clinical deterioration.

Bayer's website reported that 41/55 had a response to treatment. This equals 74.5%. The median OS of 33.5 months was derived from a post hoc analysis. Due to the small sample size and heterogeneous tumor types, the FDA accepted this post hoc OS data as supportive evidence, despite the lack of a control arm, citing the rarity of NTRK fusion-positive cancers and unmet need.

Comparatively, in the Phase 3 trial, people earlier in ALS progression 138/189 (subgroup of ≥27), NurOwn met unadjusted statistical significance on the secondary endpoint (p=0.026). This equals 73% of the trial population. Similarly, the trial data also show disease stabilization at the cut point population ≥34.

Graphic - Vitrakvi



[190] Drilon, A., Laetsch, T. W., Kummar, S., DuBois, S. G., Lassen, U. N., Demetri, G. D., ... & Doebele, R. C. (2018). Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. New England Journal of Medicine, 378(8), 731–739.

Petitioners suggest that the FDA should exercise its regulatory flexibility and consider the post hoc data just like it did for this rare cancer. Just like Vitrakvi and Rozlytrek, NurOwn was developed for a terminal rare disease with extreme heterogeneity and a critical unmet need. In contrast, NurOwn had a placebo-controlled arm, and the data met unadjusted statistical significance for those earliest in their ALS progression. Most importantly, in the 10 people in EAP, NurOwn met or exceeded Vitrakvi OS (33.5) months and Rozlytrek OS (23.9 months). In fact, NurOwn extended trach--free survival by a minimum of 30 months beyond the 30 month median from symptom onset. And for the 6 people still alive today, trach-free survival is as much as 92 months and counting!

e. Pemazyre (pemigatinib) for cholangiocarcinoma[191]

Approved on April 17, 2020, under accelerated approval, Pemazyre targets a rare subset of cholangiocarcinoma. The pivotal trial was a single-arm, open-label study with 107 patients, using overall response rate (ORR) as the primary endpoint (36% ORR). The FDA's approval incorporated the totality of evidence, including ORR, duration of response (median 9.1 months), and supportive data from natural history studies and a Phase 2 basket trial with **18 patients**. **OS data was not a pre-specified endpoint but was included post hoc, showing a median of 21.1 months**, which bolstered the case despite the lack of a control arm.

The parallels between NurOwn and Pemazyre are illustrative. The sample sizes are similar (107 vs. 106 in the group ≥27). As mentioned above, NurOwn demonstrated a 35% response rate on the primary endpoint in the subgroup of early progressors without a floor effect. In both the Pemazyre and NurOwn EAP, the OS data was not pre-specified but was so compelling that it boosted its persuasiveness. Additionally, NurOwn's OS exceeded Pemazyre's OS data (which was less than 2 years). Currently NurOwn has extended survival in EAP participants by as much as 3-5 years beyond median survival!

f. Temozolomide

During a 2021 webinar, Mayo's Dr. Nathan Staff was asked how the ALS community can help advance ALS research and drug development. In response, he spoke about the obvious need for increased research funding, but also highlighted the disparate ways the FDA concludes what is a "clinically meaningful" change in survival in brain cancer versus ALS:

> *"We need the FDA to start thinking about ALS clinical trials in a new way. They've been working on it. But I saw a slide recently talking about one of the best medications that's used for brain cancer. Nobody bats an eye about it. It's their favorite medication; it's called temozolomide. It prolongs life in brain cancer by three months.*

[191] U.S. Food and Drug Administration. (2020, April 17). FDA grants accelerated approval to pemigatinib for cholangiocarcinoma with an FGFR2 rearrangement or fusion. FDA News Release.

They don't think about ALS in that way. We all want to have a cure and that will be an obvious thing when it happens, but the FDA and the government need to recognize that if we get enough small wins that we don't recognize yet whether some of those small therapeutic wins may actually synergize with the other therapeutic approaches that we're having and can actually start to bring out real meaningful life prolongations in ALS."

Indeed Dr. Staff was correct. In 2016, the National Cancer Institute (NCI) celebrated the news that the standard treatment for some types of brain cancer was likely to change, based on findings from two large clinical trials of temozolomide (TMZ) that were presented at the American Society of Clinical Oncology (ASCO) annual meeting. It reported about the beneficial changes on progression-free survival (PFS), one-, two- and five-year survival rates, as well as overall survival (OS) rates in patients with glioblastoma[192] and a rare brain cancer, anaplastic glioma.

In glioblastoma, median overall survival improved in patients treated with both temozolomide and radiation versus radiation alone. The combination improved OS by **1.6 months** (9.3 vs. 7.6) and "modestly" improved PFS. **T**he largest magnitude change occurred in patients whose tumors had a mutation in the MGMT gene, improving OS by **5.8 months** (13.5 vs. 7.7).

In glioblastoma, results published in the NEJM demonstrated that the addition of temozolomide to radiation therapy improved survival in patients with glioblastoma. **PFS increased by 2 months** (7.0 vs. 5.0). In 2 years, **OS improved by 16.1%** (26.5% vs. 10.4%). But **only half of the patients derived a great benefit from temozolomide.**

In 2024, researchers funded by the NCI presented the "striking results" as a late-breaking abstract at the Society of Neuro-Oncology's 2024 SNO Annual Meeting." The Phase 3 trial followed 172 patients with grade 2 gliomas. The ten-year survival rate improved by 23% (70% vs. 47%) with the combined treatment of temozolomide and radiation, compared to radiation alone.

NurOwn significantly outperformed TMZ in survival statistics. In glioblastoma, the largest magnitude change occurred in patients whose tumors had a mutation in the MGMT gene, improving OS by 5.8 months. The NurOwn EAP data presented by Brainstorm showed a 5.5 month improvement in OS over matched controls. In contrast, in the EAP population as well as the fast-progressing bulbar population,

[192] Per Cancer Connect, approximately 20,000 people are diagnosed with primary brain cancer in the US each year. Primary brain cancer is cancer that originates in the brain and has not spread from cancer already located elsewhere in the body. Glioblastoma is one of the most common, and fatal, types of primary brain cancer. When glioblastoma is present, glial cells become malignant and grow out of control. Glial cells are the most abundant cells present in the nervous system, providing many supportive functions that facilitate the majority of processes conducted by neurons (cells that transmit impulses between the brain, spinal column and nerves). Standard treatment options for glioblastoma consist of surgical removal of the cancer if possible, radiation therapy and/or chemotherapy. **However, even with the most aggressive treatment available, most patients will survive less than one year after diagnosis.** Because of the poor prognosis for patients with this disease, researchers are attempting to develop more effective treatment strategies to improve survival and/or improve quality of life of glioblastoma patients…. to live better and live longer.

NurOwn has improved trach-free survival not just by months – but YEARS!

2. Other Oncology Approvals

Both Overall Survival and Tracheostomy-free Survival were pre-specified secondary endpoints in the NurOwn Phase 3 trial. But in a 28-week trial, not enough time passed for these endpoints to be assessed. Seven years after the Phase 3 trial began enrolling and nearly three years after the end of the EAP, we now have the objective, gold-standard survival data to corroborate what people in the Phase 2 and Phase 3 trials have saying for the last decade: NurOwn helps people live longer and live better.

Even though the EAP sample size is small, the magnitude of the impact on survival is large. And the comparative magnitude is quite compelling as NurOwn's survival data meets or exceeds the survival data for the cancer therapies on the market today and many were approved using the Accelerated Approval pathway. (See Exhibits A and B).

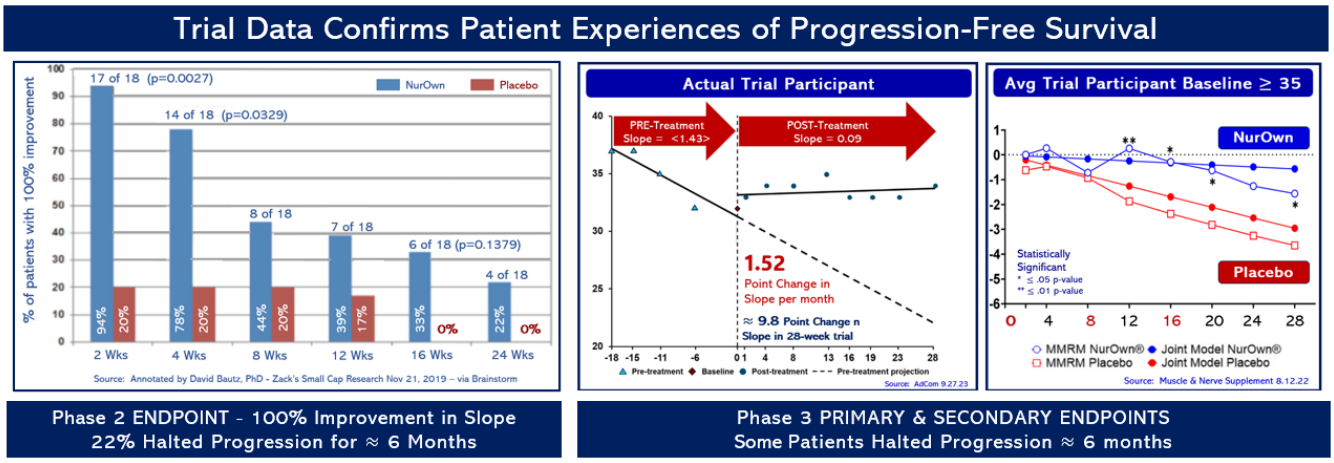
- **NurOwn EAP Survival Data**
  - 5.5 month improvement in OS over matched controls -- as of 2022
  - 100% Five-year Survival Rate vs 20% ALS natural history – as of 2025
  - ≈ 2x-3x Improvement in Trach-free Survival over median ALS natural history – as of 2025
  - Progression-free Survival as much as 17 months – as of 2025

- **Cancer Overall Survival Data – Examples**
  - 23 improved OS by less than 6 months
  - 9 improved OS by 6-12 months
  - 4 improved OS by than 12-24 months
  - 4 improved OS longer than 24 months (range 25-40)
- **Cancer Progression-free Survival Data – Examples**
  - 28 caused PFS of less than 6 months
  - 7 caused PFS of 6-12 months
  - 8 caused PFS longer than 12 months

Throughout the last decade, people in the NurOwn trial and EAP have repeatedly shared their real-world evidence, with Congress and with the FDA, proving that NurOwn improved how they felt and functioned. Their experiences were reinforced by the trial data, not inapposite to it.

The trial data in both Phase 2 and Phase 3 showed approximately 6 months of progression-free survival in some and a dose-dependent response by the times those trials ended at 24 and 28 weeks, respectively.

<u>Graphic</u> - Phase 2 and 3 Data Confirms Some Patients Halted Progression



In Phase 2, Mike Cimbura and Bobby Forster said the impact of one dose of NurOwn began to wash out after a few months and their improvements began to wane. But about 1 in 5 people maintained their "progression-free survival" for at least 6 months. That's what the trial data showed.

In Phase 3, people received three doses and some people earlier in disease progression, like Lesley Krummel and Kade Simons, said they halted their progression and/or regained some function. And that too is what the evidence showed. Indeed, Roberto Muggli proclaimed: ***"This is what ALS remission looks like."***

For those who received more than three doses, the large magnitude and long-term impact could not be more compelling. These biological changes matched the functional changes people in EAP have reported for years.

Ultimately, all the people in the Expanded Access Program and many people in Phase 3 trial lived longer and lived better. And today, many of them still are. And even when the progression resumed, it was much slower than before receiving NurOwn. For example, NurOwn Petitioners:

- **Josh Smith** – living 7 years (84 months) after symptom onset
  During the trial and EAP, Josh had 8 months of progression-free survival with 3 doses in the trial but as much as 13 months (from May 2022 to June 2023) during and after 9 cumulative doses in the second round of EAP. Today, Josh refuses to use a wheelchair, is still taking shuffling steps with a walker, still eating and drinking, has no feeding tube, and is not using a bipap to breathe.

- **Matt Klingenberg** – living 7.6 years (91 months) after symptom onset
  During the trial and EAP, Matt halted his progression for up to 17 months during the trial and 4-6 months in EAP. Today, Matt can still stand to transfer. He has limited use of his hands for ADLs but he operates his own wheelchair. His swallow study was normal and his speech is soft but still intelligible. He only uses a bipap, occasionally, at night, as needed.

- **Lesley Krummel** – living 7.8 years (94 months) after symptom onset
  During the trial, Lesley experienced 18 months of progression-free survival. Today her speech is soft and slurred, but still intelligible. She can still stand to transfer. She can use her hands to operate her power chair but she can no longer text and uses a Tobii for written communications. She is still eating without a feeding tube and she is still not using a bipap to breathe.

- **Eric Stevens** – living 6.25 years (75 months) after symptom onset
  During the trial and EAP, Eric halted his progression for 4-5 months during the trial and EAP. Today Eric can still stand and walk short distances around the house with his wife by his side. He uses a wheelchair when out. He has limited use of his hands but he can still operate his own wheelchair, text and scroll. Even though he had bulbar onset, he only uses a bipap at night. Most importantly, he can still speak clearly to his two young children.

Most importantly, they are still making memories with the people they love. We hope that this new FDA will listen to our experiences and evidence. We hope the FDA will value our unprecedented progression-free survival with the same regulatory flexibility as the OCE does the progression free survival for so many cancer therapies.

If some is enough for terminal cancer therapies then some must be enough for ALS. Moreover, in many of these cancer therapies, the approved therapy is the second or third-line treatment option. In sporadic ALS, there are no disease-modifying treatment options. There is a critical unmet need in ALS, a brutal 100% fatal, heterogenous rare disease.

In sum, Petitioners and thousands of people with ALS are asking the FDA to show us the same due process… show us the same humanity…. give us the same chance… give us the same hope. Please use your regulatory flexibility and approve NurOwn with a Phase 4 post-marketing study -- just as the Oncology Center of Excellence commonly does for cancer.

C. Despite Limitations with Bounded Scales and MCID, NurOwn Data are as Clinically Meaningful for ALS just as Brineura was for Batten Disease

Batten disease (CLN2) is a rare, autosomal recessive neurodegenerative disorder caused by a TPP1 deficiency, leading to language and motor decline, seizures, blindness, and early death.[193] The treatment, Cerliponase alfa (Brineura), is an enzyme replacement therapy administered via intracerebroventricular infusion. The pivotal trial was a non-randomized, single-arm study (n=22) comparing treated patients to a historical control group (n=42). Ultimately, Brineura was approved to slow ambulation loss in symptomatic children aged 3+ (expanded to all ages in 2024).[194]

In Batten disease, the bounded scale used for clinical trial endpoints is called the CLN2 Clinical Rating Scale. In the Brineura trials, the CLN2 motor-language domain was used. The study's key findings:

- All 7 matched Brineura-treated children under 3 years maintained a motor score of 3 (grossly normal gait) from baseline to final assessment, indicating delayed disease onset.
- 11 of 18 (61%) children in the natural history cohort experienced an unreversed 2-point decline or a score of 0 by the final assessment.
- Treatment slowed motor function decline and delayed disease onset, even in children under 3 years.

The Primary Endpoint was a decline in motor function, as assessed based on the time to a 2-point decline in the CLN2 Clinical Rating Scale (motor-language domain, range 0-6). Treated patients showed a slower decline (0.27 vs. 2.12 points per 48 weeks, $p<0.001$).[195] The trial did not achieve its two-point target but did meet a 1. 85 delta.

The study suggested that a 1-point change (e.g., from 3 to 2) was clinically meaningful, based on expert consensus and natural history data showing a 2.1-point decline per 48 weeks in untreated patients. However, this MCID was not empirically derived. Experts bridged this gap by contextualizing the slower disease progression (e.g., 0.27 vs. 2.12 points decline per 48 weeks in treated vs. untreated patients) as a meaningful benefit for patients with a rapidly progressive disease.[196]

The study pointed out the problems assessing MCID in small rare disease trials. But it also relied upon expert opinions, including clinicians from Batten Disease Centers of Excellence. Those experts emphasized that a slower decline in motor-language scores translated to meaningful patient benefits, such as prolonged ability to walk or communicate – and was supported by caregiver reports.

---

[193] Mole, S. E., Schulz, A., … de Los Reyes, E. C., Dulz, S., … Williams, R. E. (2021). Guidelines on the diagnosis, clinical assessments, treatment and management for CLN2 disease patients. Orphanet Journal of Rare Diseases, 16(1), 185.
[194] FDA. (2020, March 24). FDA approves first treatment for a form of Batten disease. U.S. Food and Drug Administration.
[195] Schulz, A., Ajayi, T., Specchio, N., de Los Reyes, E., Gissen, P., Ballon, D., … Kohlschütter, A. (2018). Study of intraventricular cerliponase alfa for CLN2 disease. New England Journal of Medicine, 378(20), 1898–1907.
[196] Schulz, A., Ajayi, T., Specchio, N., de Los Reyes, E., Gissen, P., Ballon, D., … Kohlschütter, A. (2018). Study of intraventricular cerliponase alfa for CLN2 disease. New England Journal of Medicine, 378(20), 1898–1907.

Although the lack of a validated MCID for the bounded scale could have jeopardized the approval, regulators relied heavily on expert interpretation to deem outcomes clinically meaningful.[197]

Here is how expert testimony can help overcome the limitations in the use of a bounded scale in a rare disease.

- Interpreting Small Sample Sizes: Experts can assess whether changes in COAs are meaningful based on their understanding of disease progression and patient needs.[198]

- Validating Surrogate Endpoints: Experts help regulators determine if these endpoints reflect meaningful patient benefit, especially when MCID thresholds are uncertain.[199]

- Contextualizing Historical Controls: Expert input was crucial to validate the comparability of historical data and interpret differences in disease progression (e.g., a slower decline in motor-language scores) as clinically meaningful.[200]

The FDA's approval leveraged the orphan drug and breakthrough therapy designations, allowing flexibility for rare diseases with unmet needs. The use of a historical control and single-arm design was justified by the rarity of CLN2 and **ethical concerns about placebo-controlled trials in a fatal disease**.

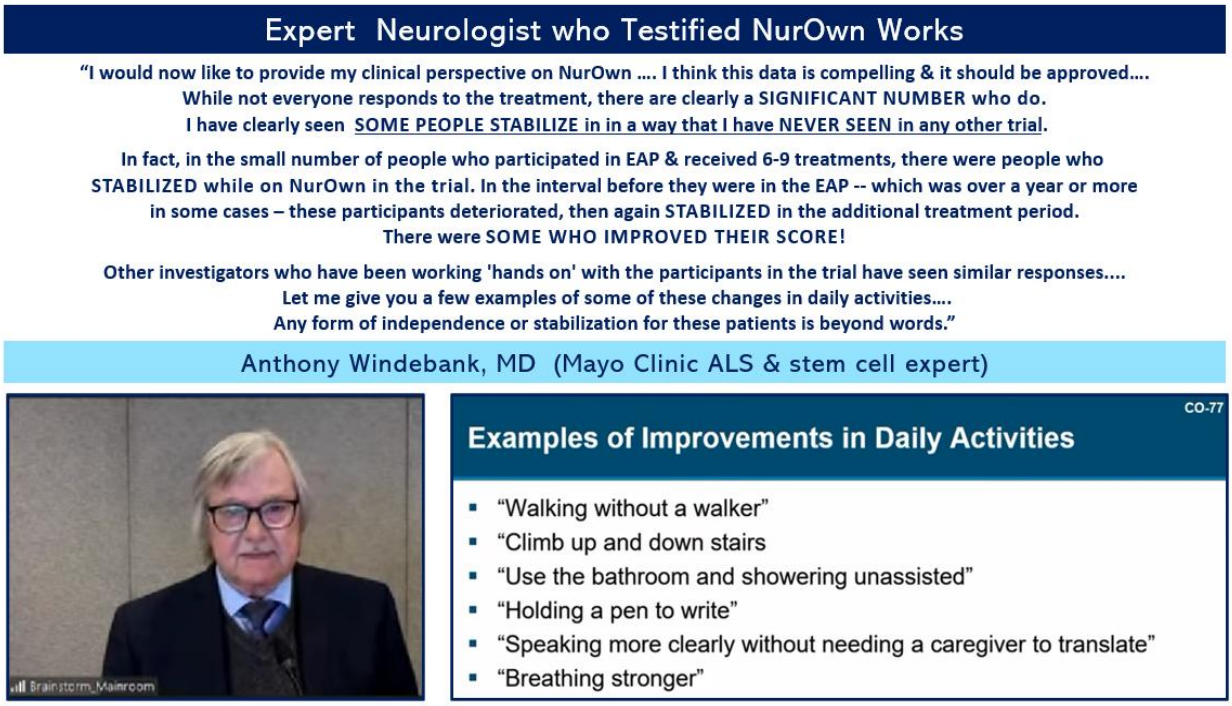
The parallels between NurOwn and Batten's disease are obvious. Expert neurologists testified about the critical unmet need and that the changes they obsessed were more than clinically meaningful. Like Brineura, NurOwn:

- Slowed ambulation loss
- Improved OS by 5.5 months when compared to the PRO-ACT natural history database
- Caregivers and Patients themselves report reduced frequency and intensity of clonus, spasticity and fasciculations (just like Battens' caregivers reported reduced seizure frequency)
- Slower decline in respiratory function translated to meaningful patient benefits, such as prolonged ability to breathe without NIV or trach, and in turn, longer survival.

[197] Canadian Agency for Drugs and Technologies in Health. (2019). Clinical review report: Cerliponase alfa (Brineura): Indication: For the treatment of neuronal ceroid lipofuscinosis type 2 (CLN2) disease, also known as tripeptidyl peptidase 1 (TPP1) deficiency. Ottawa, ON: CADTH.
[198] Schulz, A., Ajayi, T., Specchio, N., de Los Reyes, E., Gissen, P., Ballon, D., … Kohlschütter, A. (2018). Study of intraventricular cerliponase alfa for CLN2 disease. New England Journal of Medicine, 378(20), 1898–1907.
[199] Lewis, G., Morrill, A. M., Conway-Allen, S. L., & Kim, B. (2020). Review of cerliponase alfa: Recombinant human enzyme replacement therapy for late-infantile neuronal ceroid lipofuscinosis type 2. Journal of Child Neurology, 35(5), 348–353.
[200] Schulz, A., Specchio, N., de Los Reyes, E., Gissen, P., Nickel, M., Trivisano, M., … Cohen Pfeffer, J. (2021). Safety and efficacy of cerliponase alfa in children with neuronal ceroid lipofuscinosis type 2 (CLN2 disease): An open-label extension study. Lancet Neurology, 20(1), 48–58.

With both Batten Disease and ALS, the limitations in the subjective bounded scales may not accurately reflect all the clinically meaningful changes. But just like the FDA relied on expert opinions to help understand what kind of changes are clinically meaningful to children with this neurological disease, Petitioners submit that CBER should defer to the opinions of neurologists like Dr. Tony Windebank and Dr. Nathan Staff of Mayo, and Dr. Bob Brown of UMass. At the AdComm, Dr. Windebank offered testimony accompanying this slide explaining why these changes were very clinically meaningful to his patients. (See Sponsor's Presentation CO-77).

Graphic - ALS KOL, Mayo's Dr. Windebank AdComm Testimony that NurOwn Works



And like Batten's disease, people dying of ALS also have repeatedly raised ethical concerns about requiring another Phase 3 placebo-controlled trial in a 100% fatal disease.

Petitioners are asking the FDA to use the same regulatory flexibility in ALS therapies as the OCE does in cancer therapies. In various ways, NurOwn's efficacy data significantly outperformed several therapies that are already on the market.

II. NurOwn Meets Regulatory Thresholds for Approval With A Phase 4 Post-Marketing Study and Patients' Mandatory Participation in a Biorepository and Natural History Database

"The President has told us to do everything possible
to accelerate more cures for Americans."
~ Commissioner Marty Makary
(May 9, 2025)

The totality of the efficacy data supports NurOwn's approval under multiple regulatory pathways. First, Brainstorm pre-specified OS and trach-free survival as trial endpoints and survival is the gold-standard for drug approvals. Moreover, a "substantial evidence" finding relates both to the quantity but more importantly, the quality of the evidence. As such, the new unprecedented survival data demonstrates a much larger magnitude improvement in survival than many other FDA-approved therapies on the market today.

Those survival data are buttressed by a variety of supporting evidence including the totality of the evidence that NurOwn caused "clinically meaningful" and "statistically significant" changes in a subgroup of people earlier in ALS progression (akin to a drug working on stage I/II cancer).

That substantial evidence includes the opinions of the world-renowned clinician-researchers who were principal investigators during the NurOwn trial and EAP. Those neurologists opined that NurOwn had a clinically meaningful impact on many of the trial and EAP participants, causing progression-free survival and improvements in some – something they had never seen in their 40-plus years of conducting ALS clinical trials. They also shared their observations about the cyclical impact of NurOwn during EAP: people improved when they received it and declined when they didn't. The FDA must prioritize their opinions.

The above substantial evidence is further supported by the types of evidence outlined in the 21st Century Cures Act such as real world evidence and real world data documented outside the phase 3 trial by treating neurologists and other health care professionals who witnessed NurOwn improve how people felt and functioned. And importantly, that supporting evidence also includes the now-unblinded, patient experiences of people who lived better and lived longer because of NurOwn.

Moreover, that supporting evidence also includes multiple "n of 1" cases of people – like Navy pilot Matt Bellina as well as the people in EAP – who experienced profound, unprecedented, and durable changes as a result of receiving NurOwn's neurotrophic-treated stem cells.

Thus, the NurOwn data meets the "substantial evidence" threshold for approval with a single phase 3 trial and Expanded Access program.

Second, NurOwn caused changes in both surrogate and intermediate endpoints commonly used in accelerated approvals, all of which are "reasonably likely to predict a clinically meaningful benefit." Those surrogate endpoints include first-in-class changes in CSF biomarkers across biological disease pathways of neuroinflammation, neurodegeneration and neuroprotection. In addition, UNC13A is the most common genetic biomarker affecting people with sporadic ALS, and 65% of the people who are carriers of the A/C allele were " responders" who met NurOwn's large magnitude primary endpoint. Collectively these biomarker data demonstrate target engagement that is reasonably likely to predict a clinically meaningful benefit.

As outlined above, NurOwn also demonstrated a probative impact on surrogate and intermediate endpoints commonly used in accelerated approvals for other disease therapies such as progression-free survival.

Admittedly the use of these surrogate and intermediate endpoints is unprecedented in ALS. Even though these intermediate endpoints were not pre-specified, the unprecedented nature of these changes coupled with the magnitude of response justifies their use to support accelerated approval with phase 4 confirmatory studies. The intermediate endpoints include such things as improvement in respiratory function. In ALS, respiratory function is unequivocally associated with and is the single most important factor in predicting survival. NurOwn caused large magnitude and unprecedented improvements in both FVC as well as long-term durability of improvement in breathing function as evidenced by the large magnitude improvements in time-to-trach and time-to-NIV.

Third, NurOwn also meets the new "plausible mechanism of action" standard enunciated by Commissioner Makary. Although not yet codified, Petitioners believe the FDA can utilize its promised regulatory flexibility and prove NurOwn with a broad, confirmatory phase for study utilizing AI to further validate NurOwn's efficacy in a much larger population than could ever be assessed in a small, 200-person phase 3B trial in a vastly heterogeneous rare disease.

A. Substantial Evidence Supports NurOwn's Approval

In 1962, the FD&C Act for the first time required that a drug demonstrate evidence of efficacy and not just safety. To that end, the Act was amended to include the "substantial evidence" of effectiveness standard, which is defined as: (a) evidence consisting of adequate and well-controlled clinical investigations; and (b) **conducted by "experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect" it purports to have** under the conditions of use recommended in the proposed labeling.

1. Expert KOL Neurologists, Statisticians Opined that NurOwn Works

In both its Guidance and in its application, the FDA understandably has focused on the first prong of "adequate and well-controlled investigations." But in making its approval decisions , it seemingly ignored the second prong of the test specifying that the FDA shall rely upon opinions and conclusions of "experts qualified to evaluate the effectiveness of the drug."

No where is expert opinion more important than in rare diseases like ALS where the FDA does not possess internal expertise. Thus, Petitioners are asking that the FDA's approval decision about NurOwn **shall** include and weigh the expert opinions of researchers and treating clinicians in rare diseases with critical unmet needs. By definition, rare diseases affect smaller populations of people. As such there are few physicians and researchers with expertise in those diseases. Because of that limited pool, often the top disease experts are participating as investigators in the clinical trials, preventing them from serving on Advisory Committee panels.

Thus, it is unreasonable to expect AdComm members or FDA officials to have the same level of expertise in rare diseases as they do in common diseases like heart disease or cancer. For most physicians, often their only experience with the rare disease was one lecture in medical school or one patient they saw on rounds during their residencies. Speaking in 2023, former Commissioner Califf acknowledged this problem:

> *"[I]f we think about rare diseases as an example, show me an expert in a rare disease who's not spending time working on therapeutics for that disease. Then you automatically have what traditionally is a conflict. Yet, if you look inside the FDA the main thing that employees want out of advisory committees is expert opinion from the outside."*

As such, Petitioners suggest that the FDA give the utmost of deference to the opinions of trial investigators and sub-specialized treating physicians who offer clinical observations, opinions and real-world evidence/data about the safety and efficacy of investigational drugs developed for rare diseases le ALS. Currently there is no codified way to require that this expert testimony be considered nor how to properly weigh their evidence.

In the NurOwn AdComm, the opinions and clinical observations of the world's top ALS neurologists were not discussed and indeed were ignored – even though they have decades of experience treating thousands of people with ALS. Because the NurOwn trial has now been unblinded, we now know some of the trial participants that prompted the Principal Investigators' bold AdComm assertions about improvements that they had **never** seen in their decades-long careers as ALS neurologists.

In the NurOwn AdComm, the trial's Principal Investigator, Dr. Tony Windebank, testified that NurOwn works. Dr. Windebank conducts clinical trials at MAYO's ALS Center of Excellence – where Lou Gehrig was diagnosed in 1939. He is one of the world's foremost ALS experts who has been treating ALS patients for 40+ years and he also runs the world class Regenerative Neurobiology Lab that is a leader in stem cell research.

Dr. Windebank testified that he and other PIs observed a *"significant number"* of people who had a clinically meaningful and unprecedented benefit from NurOwn:

- SIGNIFICANT NUMBER of people were "responders' to NurOwn treatment
- Some people stabilized in a way that he had have never seen in any other ALS trial
- Some people stabilized while on NurOwn in the trial
- DETERIORATED during the interval between the trial and EAP
- Stabilized again during in the additional treatment period in EAP
- Some IMPROVED their ALSFRS-R score

Yet during the AdComm, there was not one moment of discussion about these unprecedented clinical observations by Dr. Windebank and other investigators in the trial who saw similar responses, like PI and world-renowned ALS researcher and neurologist, Dr. Bob Brown. And although Dr. Brown was present at the AdComm, he was not given time to testify or answer questions. We know he was present as he asked Josh Smith ahead of time for permission to share his EAP story. Dr. Brown has been on record since 2021 opining that NurOwn works. Shortly after the trial's topline data was shared, Dr. Brown said there were:

> *"An EXCEPTIONAL number of folks who had a VERY DRAMATIC RESPONSE….*
> *I do think there is a benefit from the stem cell therapy."*

Later he stated, "*many of us with longstanding experience in ALS therapy development agree that there was evidence of benefit from NurOwn."*

Although there were six neurologists on the 19-person AdComm panel, no one on the AdComm nor in the FDA had comparable ALS experience to Doctors Windebank and Brown.

Dr. Windebank's patients who received NurOwn included Matt Klingenberg, Roberto Muggli and Kade Simons. Josh Smith was at UMass with Dr. Brown. Eric Stevens and Phil Green were EAP participants with Dr. Namita Goyal at UC-Irvine. Every one of these people has been saying NurOwn halted their lethal ALS progression and helped them regain function from the time of their first dose.

Because there are so few researchers and clinicians with expertise in rare diseases, trial investigators' opinions and clinical observations should be given the weight commensurate with their credentials and expertise – just as required to do under the clear and unambiguous language of the FD&C Act.

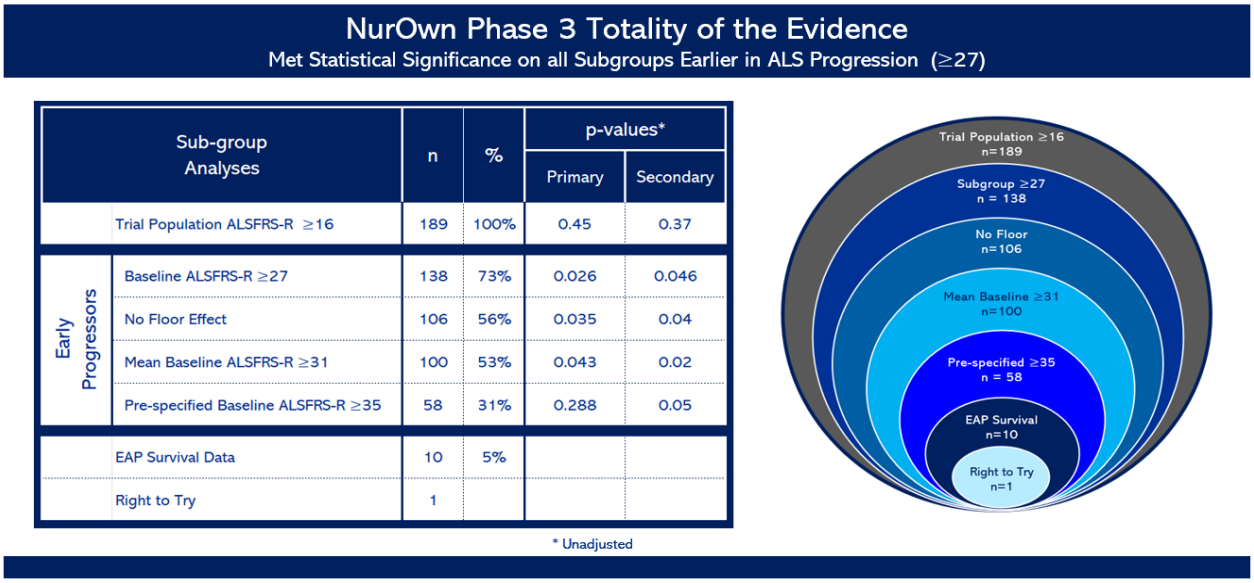
2. Existing Trial Data Supports Approval under "Totality of the Evidence" Protocol More Appropriate for Rare Disease Trials

The "totality of the evidence" methodology refers to an approach where the FDA considers a comprehensive dataset —beyond a single time in a single trial using a single endpoint—to assess a drug's efficacy for approval. This includes clinical trial data, real-world evidence, surrogate endpoints,

natural history studies, and post hoc analyses, often applied in rare diseases where traditional randomized controlled trials (RCTs) are challenging due to small patient populations and heterogeneity.

Following is a summary of the evidence that NurOwn improved how people feel, function and survive. As outlined in section "E" in the Fact section starting on page 66 above, NurOwn had a clinically meaningful and statistically significant impact on people earlier in ALS progression.

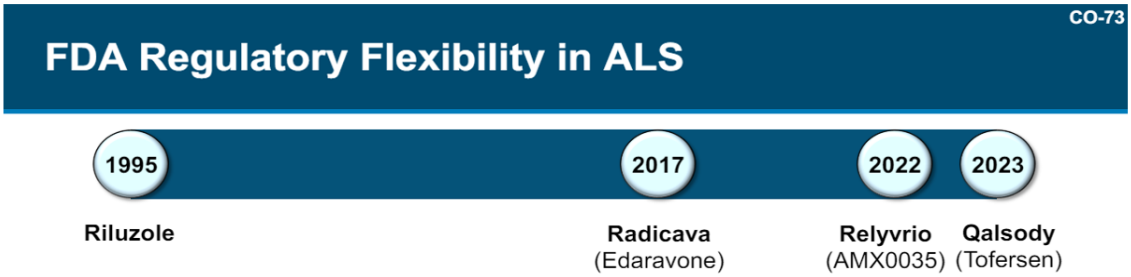
<u>Graphic</u> - NurOwn's Totality of the Evidence: p-values by endpoint and cut-point



3. <u>Post Hoc Data Can and Has Been Used to Support Drug Approvals in ALS</u>

Because they characterized it as post hoc, FDA-CBER discounted the efficacy conclusions for the subgroup of NurOwn responders earlier in progression (floor effect subgroup and those ≥27). Yet the FDA has used post hoc data as "supportive evidence" for drug approvals in other divisions – especially Oncology – and multiple times in ALS. Brainstorm's AdComm Presentation included this information showing post hoc data was used for all four ALS drug approvals:

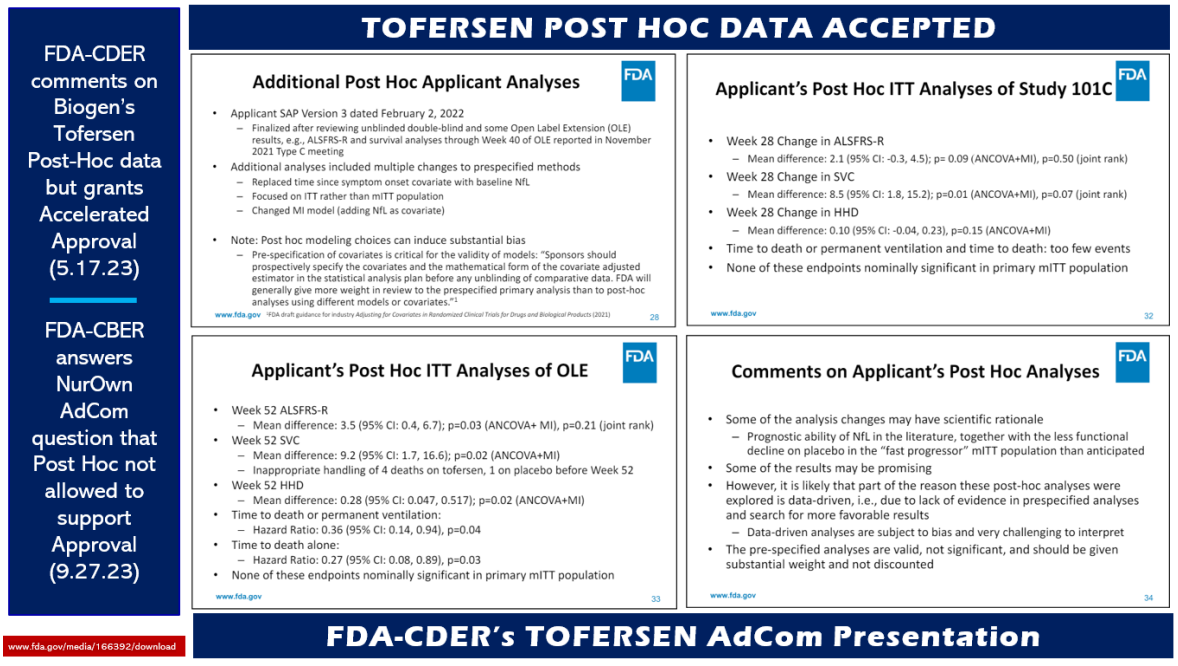
Graphic - Sponsor's Presentation Slide: Post Hoc Data Used in all Four ALS Drug Approvals



- Riluzole: post hoc analyses showed a moderate increase in survival
- Edaravone: 3 failed Phase 3 trials; followed by one study showing less decline in function on ALSFRS-R
- RELYVRIO: Phase 2 trial; post-hoc analyses suggesting longer median overall survival
- QALSODY (Tofersen): failed Phase 3 trial; accelerated approval based on post-hoc analysis of NfL biomarker data

In fact, FDA-CDER's Presentation at the Tofersen AdComm talked extensively about all the post hoc data that was not pre-specified in Biogen's statistical analysis plan (SAP). Then ultimately, CDER properly accepted that evidence of efficacy in this 100% fatal disease with a critical unmet need:

Graphic - FDA's Presentation: Tofersen Post Hoc Data Accepted



(FDA's Presentation pgs. 27-34)

Moreover, Petitioners assert that there are varying levels of reliability in post hoc data. The subgroup of responders earlier in ALS progression looked at the same data – using the same exact endpoints and the same ALSFRS-R – specified in the SPA to see if people earlier in progression responded differently than people later in progression. This is no different than asking if people with Stage I vs Stage IV cancer respond differently.

Admittedly, post hoc data is generally hypothesis-generating and is something that was not anticipated in the original trial design. Illustrating the difference, following are some hypothesis-generating examples of post hoc observations:

- Do men with concussions and repeated sub-concussive TBIs have larger magnitude functional changes on NurOwn, higher baseline inflammatory biomarkers, or stronger changes in inflammatory biomarkers?
- Do the UNC13A A/C responders indicate that carriers of other mis-splicing genes may also be responders?
- Given Tara Collazo's three-point decline each month post-COVID vaccination, is there any evidence that an inflammatory response to the vaccine might have contributed to her expedited progression?

When examining that post hoc evidence through the lens of regulatory flexibility, you can see that NurOwn works on those early in progression – just like a cancer therapy is likely to work better on those with stage I/II cancer.

B. New Respiratory Data Demonstrates a Clinically Meaningful Slowing in Time-to-NIV and is Reasonably Likely to Predict an Impact on Mortality.

The importance of respiratory function in ALS cannot be overstated. Despite ALS being a clinical diagnosis with variable genotypes, phenotypes, pathology and progression, all patients experience respiratory symptoms and most inevitably die typically from respiratory failure. As such, in this vastly heterogeneous disease, the decline in vitality capacity (VC) – both forced vitality capacity (FVC) and slow vitality capacity (SVC) -- provide an objective way to assess clinical disease progression and is associated with clinical events later in the disease such as respiratory failure, tracheostomy and death.

In the 2019 ALS Guidance Document, the FDA acknowledged that FVC was an acceptable endpoint for evaluating treatment effectiveness in ALS.

1. Typical Respiratory Decline

Decreases in vitality capacity have been directly correlated with disease progression by ALSFRS-R, tracheostomy and death. In this study published in JAMA Neurology, Dr. Jinsy Andrews of Columbia and Dr. Jeremy Shefner of Barrow studied 893 placebo-treated patients from three different datasets in the PRO-Act database. Each dataset had similar rates of SVC decline averaging –2.73 to –2.90 percentage points per month. Additionally, faster rates of SVC decline were associated with older age at onset and lower functional scores. The rate of decline in SVC was also associated with meaningful clinical events including respiratory failure, tracheostomy and death suggesting it is an important indicator of clinical disease progression. The authors concluded that ALS patients ≤ 65 years old had an average loss of 15% of VC over six months and these changes were directly related to OS.

Furthermore, the recent approval by the clinically effective drug Tofersen for SOD1 ALS failed to demonstrate a benefit based on ALSFRS at six-months in that blinded trial, although several other measures, including VC, did demonstrate beneficial change at 6 months.

2. Therapies Approved Using Vital Capacity

a. Idiopathic Pulmonary Fibrosis[201]

In 2014, the FDA approved nintedanib and pirfenidone for IPF, relying on clinical trials that demonstrated their efficacy in **SLOWING** the decline in forced vital capacity (FVC), a critical measure of lung function -- despite FVC not being an established surrogate for mortality or quality of life.

For nintedanib, the phase 3 trials showed a significant reduction in the annual rate of FVC decline, with adjusted mean declines of −114.7 mL (approximately −2.8% predicted) and −113.6 mL (approximately −2.7% predicted) in the nintedanib groups compared to −239.9 mL (approximately −5.8% predicted) and −207.3 mL (approximately −5.0% predicted) in the placebo groups, respectively, over 52 weeks (Richeldi et al., 2014).[202] This translates to a relative reduction in FVC decline of about 52%.

Additionally, **24.8% of nintedanib-treated patients had an improvement or no decline in FVC % predicted compared to 9.0% in the placebo group** (Flaherty et al., 2018).[203]

For pirfenidone, the ASCEND and CAPACITY trials demonstrated a significant reduction in FVC decline, with the trial showing a mean decline of −235 mL (approximately −5.6% predicted) in the pirfenidone group versus −428 mL (approximately −10.2% predicted) in the placebo group over 52 weeks, a relative

[201] Karimi-Shah BA, Chowdhury BA. Forced vital capacity in idiopathic pulmonary fibrosis--FDA review of pirfenidone and nintedanib. N Engl J Med. Mar 26 266 2015;372(13):1189-91; and King TE, Jr., Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. May 29 269 2014;370(22):2083-92.
[202] Richeldi, L., du Bois, R. M., Raghu, G., Azuma, A., Brown, K. K., Costabel, U., ... & Kim, D. S. (2014). Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. New England Journal of Medicine, 370(22), 2071–2082
[203] Flaherty, K. R., Brown, K. K., Wells, A. U., et al. (2018). Stability or improvement in forced vital capacity with nintedanib in patients with idiopathic pulmonary fibrosis. European Respiratory Journal, 52(Suppl 62), PA1332

reduction of about 45%.[204] The CAPACITY trials reported similar trends, with pirfenidone reducing the proportion of patients with a ≥10% decline in FVC % predicted by 50% compared to placebo (Noble et al., 2011).[205] Real-world data further supported these findings, showing FVC stabilization at 6 and 12 months, though declines of 2.5% to 4.3% in FVC % predicted were observed over 180 weeks in some cohorts.[206]

Importantly, while both drugs slowed FVC decline, **only a minority of patients (e.g., 24.8% for nintedanib) showed FVC stabilization or improvement**, and the primary effect was a reduction in the rate of decline rather than an increase in FVC. In contrast, NurOwn caused large magnitude and clinically meaningful IMPROVEMENTS in FVC ranging from 13% to 41%. These improvements are striking compared to nintedanib and pirfenidone, which primarily slow FVC decline (e.g., from −10.2% to −5.6% for pirfenidone) rather than restore lung function.

b. Nexviazyme for Pompe disease[207]

Approved on August 6, 2021, this enzyme replacement therapy addresses late-onset Pompe disease. The pivotal trial was a Phase 3 RCT with 123 patients, with a primary endpoint of 6-minute walk distance (6MWD) change at 49 weeks. The FDA used the "totality of evidence" approach, integrating the Phase 3 RCT trial data with an OLE and natural history data. The primary endpoint was forced vital capacity (FVC) % predicted.

Patients treated with Nexviazyme showed a 2.9-point improvement in FVC % predicted from baseline to Week 49, indicating improved lung function. Nexviazyme patients had a 2.4-point greater improvement in FVC % predicted compared to alglucosidase alfa (0.5% improvement) Statistical superiority was narrowly missed (p = 0.06). The 2.9-point improvement was meaningful in LOPD, where respiratory decline (e.g., 1–3% annual FVC loss in untreated patients) leads to ventilator dependence or death. Stabilization or improvement in FVC supports better respiratory outcomes, critical for survival.

Far surpassing Nexviazyme, many of the people in the NurOwn phase 3 trial and EAP have compelling respiratory data.

---

[204] King, T. E., Jr., Bradford, W. Z., Castro-Bernardini, S., Fagan, E. A., Glaspole, I., Glassberg, M. K., ... & Noble, P. W. (2014). A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. New England Journal of Medicine, 370(22), 2083–2092

[205] Noble, P. W., Albera, C., Bradford, W. Z., Costabel, U., Glassberg, M. K., Kardatzke, D., ... & du Bois, R. M. (2011). Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): Two randomized trials. Lancet, 377(9779), 1760–1769.

[206] Cameli, P., Bergantini, L., Salvini, M., Refini, R. M., Pieroni, M., Bargagli, E., & Sestini, P. (2018). Pirfenidone and nintedanib in idiopathic pulmonary fibrosis: Real-life experience in an Italian referral centre. Pulmonology, 25(3), 149–154.

[207] U.S. Food and Drug Administration. (2021, August 6). FDA approves new treatment for Pompe disease. FDA News Release.

- 10/10 people in EAP survived at least 5 years tracheostomy-free
- Josh Smith has documented RWD demonstrating a 41% improvement in FVC
- Neither Josh Smith nor Lesley Krummel are using NIV at 84 and 94 months post- symptom onset, respectively. This is 69-79 months longer than median natural history.
- Neither Roberto nor Kade used NIV before their deaths. They lived 71 and 78 months respectively (56-63 months longer than median natural history)
- RWD from Phil Green and Eric Stevens showed that they both regained 13% in 2022 after receiving their 4th dose in EAP.

Because the FDA relied upon slight changes in respiratory function to approve Nexviazyme, Petitioners submit that the FDA should likewise rely upon NurOwn's respiratory RWD and patient experiences as supporting evidence of efficacy.

C. NurOwn's Biomarker Evidence And Survival Evidence Are "Reasonably Likely To Predict A Clinically Meaningful Impact" on a Broader Population of People with ALS and thus Support Accelerated Approval with a Phase 4 Post-Marketing Biorepository.

Provisions of FDASIA in Section 506(c) of the FD&C Act provide that the FDA may grant Accelerated Approval to a product for a serious or life-threatening disease like ALS if that the product has an effect on:

- Intermediate clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is 'reasonably likely to predict an effect' on irreversible morbidity or mortality
- Surrogate endpoint such as biomarkers that are 'reasonably likely to predict clinical benefit'

The FDA Guidance for Expedited Programs provides that the decision on whether to use Accelerated Approval should take into account the *"severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."* A "reasonably likely" surrogate endpoint does not yet have sufficient evidence to be considered a validated surrogate endpoint. As such, to determine if a surrogate endpoint meets the 'reasonably likely' depends on: the biological plausibility of the relationship between the disease, the endpoint, the desired effect as well as the empirical evidence to support that relationship.

1. Intermediate Endpoint – Survival and Respiratory Data.

The NurOwn Phase 3 and EAP data meet the "reasonable likelihood" threshold for accelerated approval. If the FDA finds that the quantity of the EAP survival data (n=10) is not sufficient for traditional approval, it can find -- akin to an intermediate endpoint -- that the small cohort of EAP data is "reasonably likely to predict a clinically meaningful impact on mortality" for the larger ALS population (≈32,000).

Notably, NurOwn's survival data is unprecedented in ALS. And as outlined above, it meets or exceeds the survival data used to support accelerated approval of many cancer therapies. Similarly, Petitioners have submitted new compelling respiratory data expressed as "time-to-trach," "time-to-NIV" and improved FVC. Although it's never been used to support accelerated approval in ALS, because respiratory function is the biggest predictor of survival in ALS, we believe the profound NurOwn respiratory data is "reasonably likely to predict a clinically meaningful impact on mortality," thus justifying accelerated approval of NurOwn.

2. Surrogate Endpoint – Objective Biomarker Data is Reasonably Likely to Predict a Clinically Meaningful Benefit.

NurOwn's biomarker data also provides another basis to use accelerated approval. In 2016, Congress passed the bipartisan 21st Century Cures Act ("Cures"). In response to mandates in the 21st Century Cures Act, in December 2018, the FDA issued draft Guidance entitled *"Biomarker Qualification: Evidentiary Framework."* Notably this draft Guidance was issued after the NurOwn Phase 3 trial had begun enrolling.

In 2018, former FDA Commissioner, Scott Gottlieb, issued a Press Release introducing the FDA's new Guidance Document[208] on biomarkers and stressed that biomarkers could be a gamechanger:

> *"New medical breakthroughs are altering how diseases are treated in ways that seemed unimaginable just a decade ago. One of the most significant developments is the ability to use markers, such as proteins expressed in a person's blood, to help identify the biological activity of a disease and patient's response to therapy…. Using biomarkers in drug development can help lower development costs and improve efficiency of drug development programs, including potentially reducing the sample size needed to achieve statistical significance to demonstrate clinical effect or identifying potential safety signals earlier. This means that a drug can potentially get to market faster. Today, to advance these opportunities, we issued a new draft guidance that provides considerations for the kinds of evidence that can support qualifying biomarkers for use in drug and biologic development programs. This guidance is part of the FDA's ongoing efforts to encourage medical innovation and help make sure patients have more opportunities to access effective therapy."*

[208] "This guidance provides recommendations on general considerations to address when developing a biomarker for qualification under the 21st Century Cures Act. Qualification of a biomarker is a determination that within the stated context of use, the biomarker can be relied on to have a specific interpretation and application in drug development and regulatory review. The draft guidance describes an evidentiary framework to support qualification of a biomarker that consists of several components: describing the drug development need, defining the context of use for the biomarker, considering potential benefits if the biomarker is qualified for use and considering potential risks associated with the proposed use of the biomarker in a drug development program."

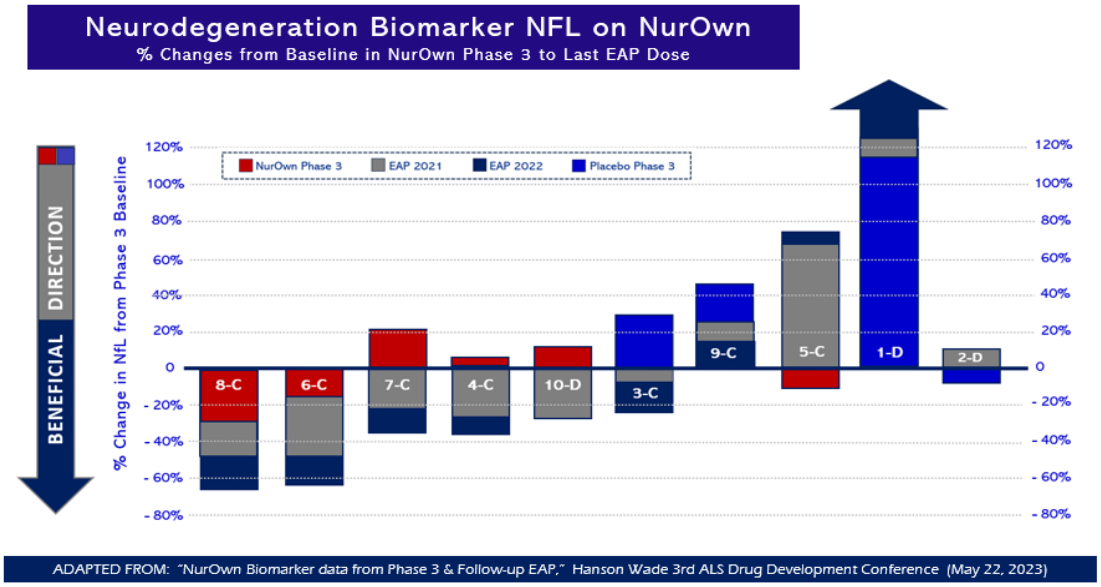
Brainstorm has three different types of biomarker evidence to support accelerated approval: (1) Neurofilament Light in EAP; (2) Two dozen CSF biomarkers om Phase 3; and (3) UNC13A biomarker data.

a. Neurofilament Light in EAP.

Based on Brainstorm's poster presentation of the EAP neurofilament light data, those who were treated early in ALS progression -- and then received the most additional doses in EAP -- experienced the largest magnitude clinically meaningful decreases in harmful NfL (≥60% from baseline). Even with long gaps in dosing, this decease from baseline NfL exceeded the changes that supported CDER's accelerated approval of Tofersen.

Recall Brainstorm's EAP-NfL data:

Graphic - NurOwn's Neurofilament Light Results - Percentage of Change - by Participant



In the graphic above, the navy bar represents the NfL levels after EAP round 2 in 2022; the gray bar represents the NfL levels after EAP round 1 in 2021. The red bar represents the NfL levels in the NurOwn arm at the end of the Phase 3 trial; and the bright blue bar represents the NfL levels in the placebo arm at the end of the Phase 3 trial. The beneficial direction is downward.

Following are some general observations from the consolidated graphic:

- 70% (7/10) = decrease in NfL levels from baseline dose #1 to last dose in EAP
- 83% (5/6) on NurOwn = decrease in NfL from baseline to last dose in EAP
- 86% (6/7) who completed EAP #2 = decrease in NfL from baseline dose #1 to last dose in EAP
- 78% (7/9) who completed EAP #1 = decrease in NfL from baseline dose #1 to last dose in EAP

- 71% (5/7) with baseline ≥ 31 mean = decrease in NfL from baseline to last dose in EAP
- 67% (4/6) with baseline ≥ 40 = decrease in NfL from baseline to last dose in EAP
- 50% (2/4) in placebo crossover group = decrease in NfL in each round of EAP
- 25% (1/4) in placebo crossover group dropped out before completion of EAP round #1

Even among those people who crossed over from placebo to the EAP, they too experienced decreases from baseline NfL levels -- despite having a multi-year delay before they received their first dose of NurOwn.

Graphic - NurOwn's Neurofilament Light Results from Phase 3 and EAP

Percent Change from Baseline NFL in NurOwn Phase 3 & EAP									
	Phase 3					EAP Round 1		EAP Round 2	
Trial Status	TOTAL Phase 3 Population		Sx to Trial Dose #1 (months)	EAP Participants in Phase 3 (2017-2020)		Gap to EAP Dose #1 (months)	EAP 1 (2021)	Gap to EAP Dose #4 (months)	EAP 2 (2022)
NurOwn P3	95	<11%>	12 - 25	6	<4%>	9 - 28	<27%>	7 - 9	<36%>
Placebo P3	94	<1.6%>		4	37%	29 - 42	17%	6 - 9	<5%>
Difference	189	9.4%		10	41%		44%		31%

b. Two Dozen First-in-Class CSF Biomarkers.

Petitioners also continue to assert that the totality of the two dozen other CSF biomarkers from Phase 3 also support the use of accelerated approval; these biomarker data demonstrate target engagement across disease pathways of neuroinflammation, neurodegeneration and neuroprotection. (See section M in the Fact section above). Commenting on the strength and consistency of this statistical analysis, Dr. Bowser remarked:

> *"The likelihood of observing this consistency in data if there's no treatment effect is very small. In fact, the p-value is less than 0.0001."*

D. RWE, RWD, PROs & Unblinded Patient Experience Buttress the "Totality of the Evidence" and are Supporting Evidence that NurOwn Works.

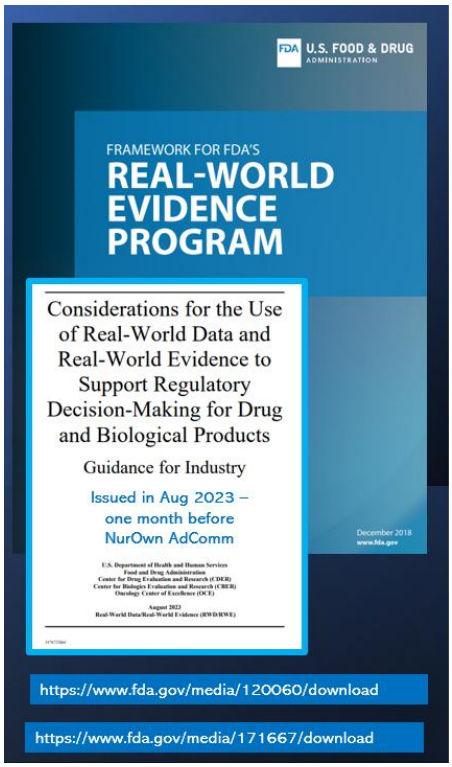
Petitioners are asking the FDA to consider real-world evidence and patient experience as supporting evidence of efficacy and/or part of the "totality of the evidence" supporting approval, pursuant to 21st Century Cures and the commitments in the Guidance Documents, which were enacted AFTER the NurOwn Phase 3 trial.

For over a decade, people in the NurOwn trial have been sharing their unprecedented response on NurOwn, only to be rebuffed that their response is anecdotal and merely a "n of 1." Others have rebuffed the EAP results as too small of a population from which to draw conclusions or challenged its

use without a control arm. But both the FDA and Congress think differently about the importance of RWE in rare diseases with critical unmet needs.

1. FDA Committed to Use RWE from EAPs and Practice Settings

Shortly after Congress passed 21st Century Cures, the FDA issued this Framework in 2018 and committed to considering RWE and RWD from expanded access programs as well as practice settings.



RWE to support efficacy determinations in Rare Diseases can consist of supportive evidence from chart reviews and "Expanded Access and other practice settings."

Definitions of Real-World Data and Real-World Evidence

Section 505F(b) of the FD&C Act defines RWE as "data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional clinical trials" (21 U.S.C. 355g(b)).[5] In developing its RWE program, FDA believes it is helpful to distinguish between the sources of RWD and the evidence derived from that data. Evaluating RWE in the context of regulatory decision-making depends not only on the evaluation of the methodologies used to generate the evidence but also on the reliability and relevance of the underlying RWD; these constructs may raise different types of considerations. For the purposes of this framework, FDA defines RWD and RWE as follows:

Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

Real-World Evidence (RWE) is the *clinical* evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Examples of RWD include data derived from electronic health records (EHRs); medical claims and billing data; data from product and disease registries; patient-generated data, including from in-home-use settings; and data gathered from other sources that can inform on health status, such as mobile devices. RWD sources (e.g., registries, collections of EHRs, administrative and medical claims databases) can be used for data collection and, in certain cases, to develop analysis infrastructure to support many types of study designs to develop RWE, including, but not limited to, randomized trials (e.g., large simple trials, pragmatic clinical trials) and observational studies (prospective or retrospective).[6]

Supporting FDA's Regulatory Decisions of Effectiveness

In limited instances, FDA has accepted RWE to support drug product approvals, primarily in the setting of oncology and rare diseases. When approval is based on a single-arm interventional trial — often when using a parallel assignment control arm is unethical or not feasible and usually when the effect size is expected to be large, based on preliminary data — the supportive RWE has consisted of data on historical response rates drawn from chart reviews, expanded access, and other practice settings.

"FDA will work with its stakeholders to understand how RWE can best be used to increase the efficiency of clinical research and answer questions that may not have been answered in the trials that led to the drug approval, for example how a drug works in populations that weren't studied prior to approval."

Janet Woodcock, M.D., Director, CDER

2. Congress Clearly Intended that the FDA Consider Both Real-world Evidence and Patient Experiences when Making Efficacy Decisions.

During the July 2021 Congressional hearing on neurodegenerative diseases, Dr. Michael Burgess framed the entire day's line of questioning around Congressional intent in codifying the 21st Century Cures Act. He asked:

> ***"How do we get some answers before everyone expires? It just seems to take so long and the whole purpose of Cures was to reduce the time from lab bench to bedside."*** [209]

One of the lead sponsors on 21st Century Cures was Congressman Fred Upton. At the E&C hearing, the former Committee Chair reminded the FDA that the 21st Century Cures Act had unanimous bipartisan support and its primary goal was to expedite getting treatments and cures into the bodies of people dying of rare terminal diseases:

> *"I want to just remind my colleagues that when we embarked on 21st Century Cures, important legislation that every one of us then on the committee supported – 53 to 0 – back in 2016. We worked with the FDA; we worked with the agencies; we worked with the patient groups; and we asked a lot of questions.* ***How do we help you approve the cures earlier so that we can deal with these folks and not have them languish and die? … The ALS community is so frustrated."***

In the past, the FDA had not used "patient experience" or "real-world evidence" in the approval decisions of several heterogeneous rare diseases.

In 2016, Congress passed the 21st Century Cures Act. Specifically, the Act discusses the use of biomarkers, surrogate measures, patient experience information, and observational data from routine clinical use or "real-world evidence" to facilitate more rapid drug and device approval. The 21st Century Cures Act defines RWE broadly and includes:

> *"**Data** regarding the usage, or the potential benefits or risks, of a drug derived from **sources other than randomized clinical trials**."*

It does not require that the data be pre-specified as that would be the antithesis of "the clear and unambiguous language of "sources other than clinical trials."

In 2022 – five years after the NurOwn AdComm – the FDA issued Draft Guidance on various aspects of using RWE and RWD to support regulatory approval. The FDA defines RWD and RWE as follows:

> *"RWD are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources; and RWE is the clinical evidence regarding a medical product's use and potential benefits or risks derived from analysis of RWD."*

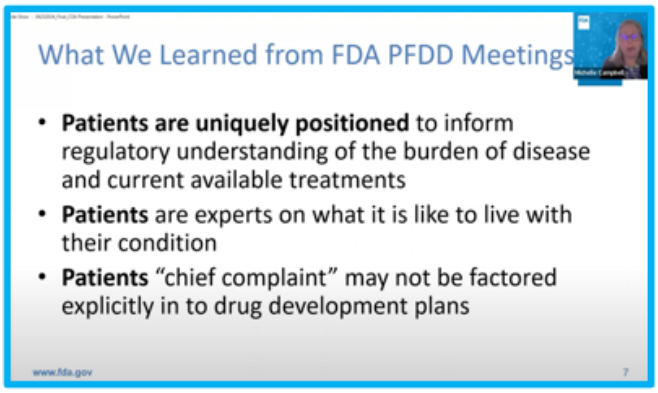
[209] *"The Path Forward: Advancing treatments and cures for neurodegenerative diseases."* Hearing before the Health Subcommittee of the Committee on Energy and Commerce, House of Representatives, 117th Cong. (2021, July 29).

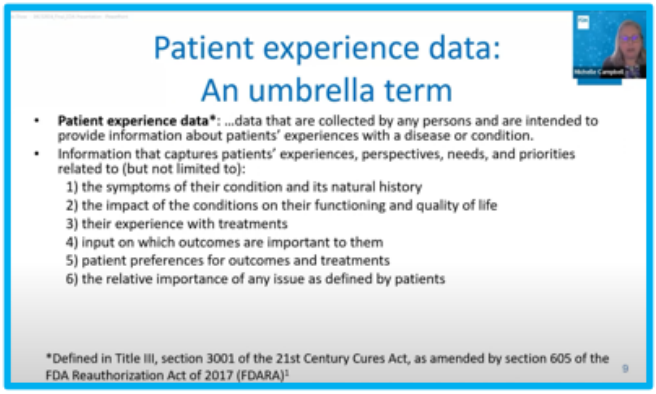
In the 21st Century Cures Act, Congress also emphasized that patients' experiences should be part of the FDA's approval process.

> **(c) PATIENT EXPERIENCE DATA**.—For purposes of this section, the term 'patient experience data' includes data that—
> (1) are **collected by any persons** (including patients, family members and caregivers of patients, patient advocacy organizations… researchers, & drug manufacturers); and
> (2) are intended to provide information about patients' experiences with a disease or condition, including—
> (A) **impact of such disease or a related therapy on patients' lives**; and
> (B) **patient preferences with respect to treatment of such disease**.

Below are excerpts of a presentation by FDA's Michelle Campbell at the Critical Path Institute's Public Discussion about ALS Clinical Outcome Assessments:

Graphic - PFDD – Patient Experience





The FDA defines real-world evidence and real-world data ("RWD") as follows:

- RWD are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. Examples of RWD include data derived from electronic health records, medical claims data, data from product or disease registries, and data gathered from other sources (such as digital health technologies) that can inform on health status.

- RWE is the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

In the August 2023 draft Guidance Document,[210] the FDA limited its consideration of RWE and RWD to only that data pre-specified in the study protocol. Real-world evidence is evidence – regardless if pre-specified – and Petitioners submit that it should be treated as such. It is nonsensical to ignore evidence of people who regained function or halted their lethal progression in a 100% fatal disease.

Rare Disease Caucus Chair Doris Matsui was emphatic in stressing that the FDA must include patient experiences in their efficacy determinations, and that patient focused drug development data shall be considered as part of FDA's benefit-risk framework for drug approval. She also commented about the recent report (required as part of 21st Century Cures) that concluded there was variability and inconsistency in the FDA's use of patient experience data.

In response to Rep. Matsui's concerns, CDER's Dr. Cavazzoni stressed that the ALS Guidance encourages drug sponsors to use validated scales that measure Patient Reported Outcome ("PRO") as endpoints. What she neglected to say is that, to this day, there are no PRO scales or any COAs that assesses ALS symptoms (i.e. "how patients feel") such as measuring changes in clonus, pain, cramping, burning tears, spasticity or fasciculations. And it takes years to investigate, create and validate any new COA so that is not an option for the ALS community dying today.

But most importantly the ALS Guidance Document was not adopted until September 2019 – nearly two years after the beginning of the NurOwn Phase 3A trial. It took the FDA 6 years to draft and adopt an 8-page document. But because the ALS community fought so hard to incorporate PRO language into the Guidance, they also knew how important it was. So they did the next best thing, they:

- Documented their PROs in before and after videos so the FDA could see for itself how trial participants' function had improved.
- Participated in the ALS-TDI's Precision Medical Program, which is a natural history study that allows patients to self-report and track their own changes in ALSFRS-R scores.
- Shared their clinical data in blogs and social media stories – as "present sense impressions" at the time those changes were occurring.
- They made extra appointments with neurologists, pulmonologists and physical therapists – outside the trial – to document the stabilization and improvements consistent with the provisions regarding RWE and RWD in 21st Century Cures.
- They contacted the members of Congress to share and document their unprecedented changes.

[210] Petitioners also refer to two other Guidance documents relevant to the discussion in this memo: (1) Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products, which provides considerations for sponsors proposing to design a registry or to use an existing registry to support regulatory decision-making about a drug's effectiveness or safety; and (2) Data Standards for Drug and Biological Product Submissions Containing Real-World Data, which addresses considerations for the use of data standards currently supported by the FDA in applicable drug submissions containing study data derived from RWD sources.

As demonstrated repeatedly in the Petitioners' section above, many patients, parents, family members and caregivers documented the changes in how the patients "feel, function and survive" when participating in the NurOwn trial and EAP. That patient experience evidence was provided in videos, photos, Public Comments, and testified about in the Open Public Hearing section of the AdComm. But that evidence was not discussed and in some cases was not even read or viewed.

In his 2022 remarks to NORD, Commissioner Califf said real-world data is ***"basically all data not collected in a specialized research environment."*** The collection and analysis of RWD can help generate real-world evidence ("RWE"), which is the clinical evidence relating to a drug's use. Commissioner Califf then commented on the importance of evidence and real-world data ("RWD") in rare diseases:

> *"The more complex the medical challenges, the more important it is that we expand the sources, quality, and types of data we use to analyze and overcome them. Nowhere is that challenge clearer than in the rare disease area…."*

There is no more complex challenge than ALS. Thus, the RWD and RWE are critical supporting evidence of NurOwn's efficacy. At the Congressional hearing, Rep. Matsui acknowledged the challenges in rare diseases and reiterated that many rare diseases can't utilize the accelerated approval pathway since they don't have biomarkers. As such, she advocated:

> *" I'm looking at the fact that many people don't have a lot of time and quite frankly some of this depends upon the particular disease you have and the pathway available, and so I would hope that we could focus a lot on how we might expedite this process more safely and **look at some of the patient type experiences** that they've had."*

At one point in the E&C hearing Chairwoman Eshoo – clearly frustrated by Dr. Cavazzoni's continual reference to lack of ALS biomarkers – interrupted the questioning and asserted:

> *"Even though you don't have the biomarkers, **you know what the outcomes are**. I think that that is an area that we need to hear more about from you; maybe it's not a leapfrogging advance, but it is an advance. **It demonstrates something, and that means a great deal to those that bear this God-awful disease**. So I just want to get that down for the record."*

3. People who Received NurOwn Repeatedly Experienced "Clinically Meaningful" Improvements in Function

As Josh Smith said in his Public Comment: *"Only a few people in the world can say they know what it feels like to have NurOwn changing how they feel and function. Believe us."*

People in the NurOwn EAP met virtually with CBER Doctors Wilson Bryan, Celia Witten and Peter Marks in October 2021 asking them to authorize a second round of EAP, which thankfully, they did. Nicole Cimbura had been communicating with Dr. Marks since 2015 when NurOwn helped her husband regain function – albeit temporarily – with just one dose in the Phase 2 trial. And of course, the Bellinas regularly communicated with the FDA about Matt's unprecedented improvements when he received 7 doses via Right to Try.

As such, when CBER issued the Refusal to File letter, these same people co-authored a Press Release in November 2022 asking CBER to grant Brainstorm Cell an Advisory Committee meeting so the trial and EAP participants could share their evidence of efficacy. In their AdComm testimony and Public Comments, NurOwn trial participants and members of the ALS community told the FDA how NurOwn had caused clinically meaningful improvements in their activities of daily living ("ADL") and quality of life ("QOL").

Many were detailed in this Joint Public Comment. In this Press Release that is part of the Public Comments, EAP participants listed changes in ADLs that were clinically meaningful to them and proved NurOwn works:

- walk without a walker, walk longer distances, walk in sand or farm field
- rise out of a chair unassisted and get up off the floor unassisted
- climb up and down stairs
- climb up into a four-wheel drive vehicle
- decreased or halted fasciculations
- improved balance and less falls when walking
- put our arms over our heads and wash our bodies and hair unassisted
- use the bathroom unassisted or hold a urinal
- open water bottles, pill bottles and food jars
- hold a pen to write
- use a cell phone to text and type
- speak more clearly without someone to translate & speak longer without bipap
- pull the throttle on a lawn mower and push the lawnmower to mow the grass
- grip a glass and lift it to drink
- operate a wheelchair with one finger
- throw a ball to the dogs or throw rocks with the kids
- swallow dense foods like fried chicken, rice, sushi
- breathe stronger, as evidenced by FVC and no more need for bipap

In their AdComm testimony, photographic and video evidence, they shared many more things that were clinically meaningful to them as a result of receiving NurOwn doses:

- Eric Stevens – ability to play with and read to his young daughter
- Josh Smith – walking up/down steps to waterfall, playing ball with the dog
- Roberto Muggli - fishing, taking batting practice with the grandkids
- Sandy Morris – regained ability to eat pizza & sushi with son during late night movies
- Lesley Krummel – play with grandkids, take cruises & attend KC Chiefs games with family
- Matt Bellina – attend sons' games & stand to dance with wife on anniversary
- Mike Cimbura - write a note to that kids that said "Love Dad"
- Terry Saenz - family vacations to Mackinac; holding new grandkids
- Bobby Forster - walked without a walker, breathing improved
- Matt Klingenberg – live long enough so his young kids remember him

Many more changes were detailed in Petitioners' section above.

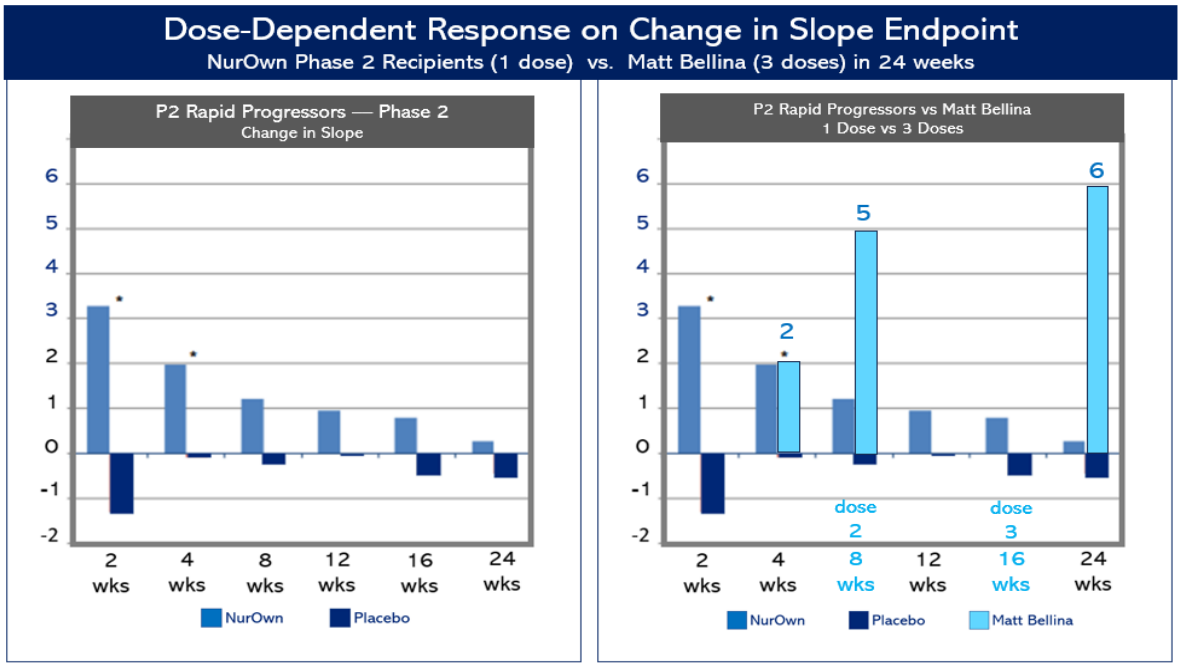
4. NurOwn Had a Dose-Dependent Response

In November 2016, Dr. Merit Cudkowicz commented on the results of the Phase 2 trial that had administered just one dose of NurOwn, and predicted that researchers would see a dose-dependent response in the future trials:

> *"We are optimistic that if we continue to administer cells that produce neurotrophic factors we will see a durable response…. NurOwn® very much is a therapy, much like a pill.* ***If you take one pill, the effect may only last one day. Almost all therapies require subsequent dosing and it is logical to believe that we will see an improved response with follow-up treatment."***

Her forecast proved true in Phase 3 where some people had a large magnitude and longer-lasting response to NurOwn. It became more apparent in EAP. But it was first obvious during Right to Try. Compare the change in slope below of fast progressors in the phase 2 trial – who only received only 1 dose -- with the change demonstrated by Matt Bellina with just 3 of his eventual 7 doses.

Graphic - Dose-Dependent Response

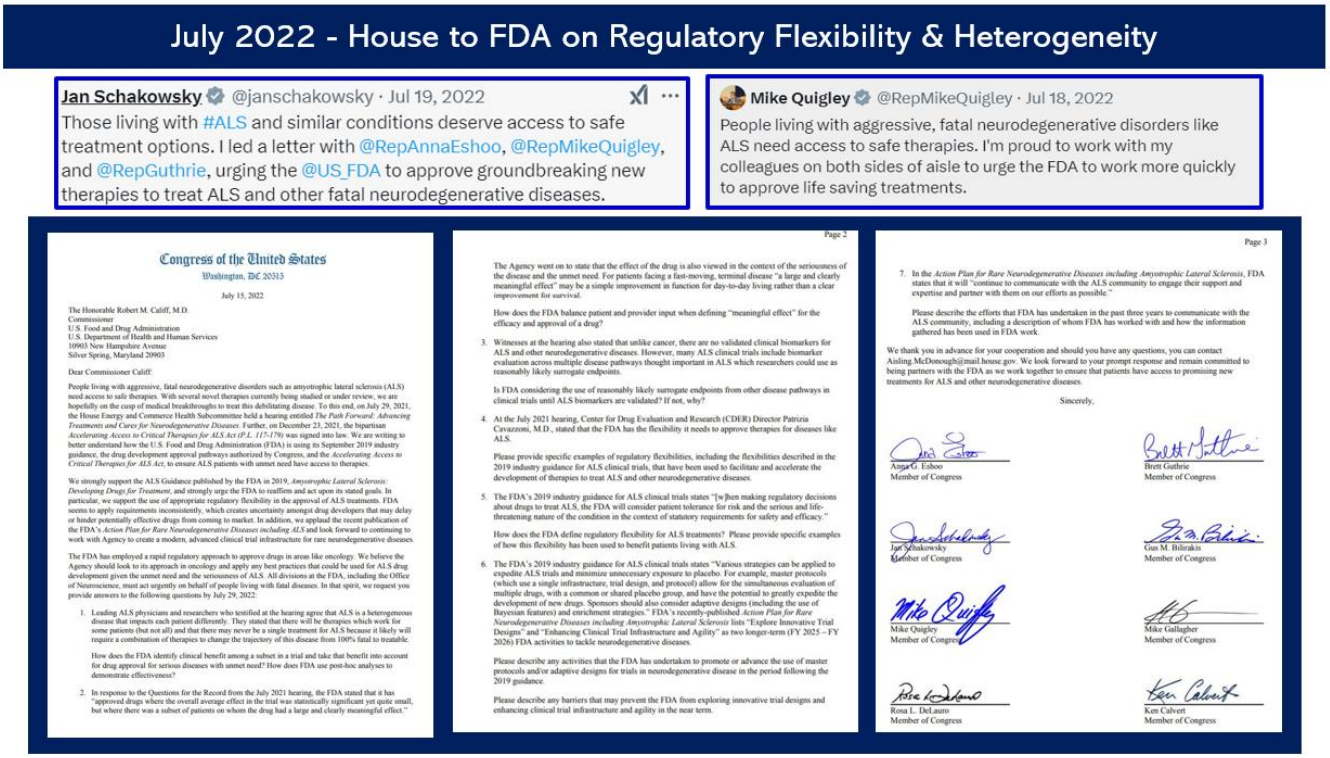


E. FDA has Repeatedly Promised to Exercise Regulatory Flexibility in ALS

Former Chair of the Rare Disease Caucus, Congressman Butterfield reminded the FDA about the "human cost of failed progress." He thought that the FDA recognized the human cost when it released its 2019 Guidance on ALS drug development and that it understood the appropriateness of "exercising regulatory flexibility for serious diseases with unmet medical needs." But now it's asking for confirmatory trials that will take 3-4 years, during which time half of the 20,000 Americans currently living with ALS will leave us.

He then asked: **"why hasn't the FDA employed this flexibility for ALS treatments to match its willingness to be flexible with emergency use authorizations in other areas?**

Below is a bi-partisan letter to the FDA, following up on the July 2021 hearing where "regulatory flexibility" was a primary focus of the E&C members' questions.

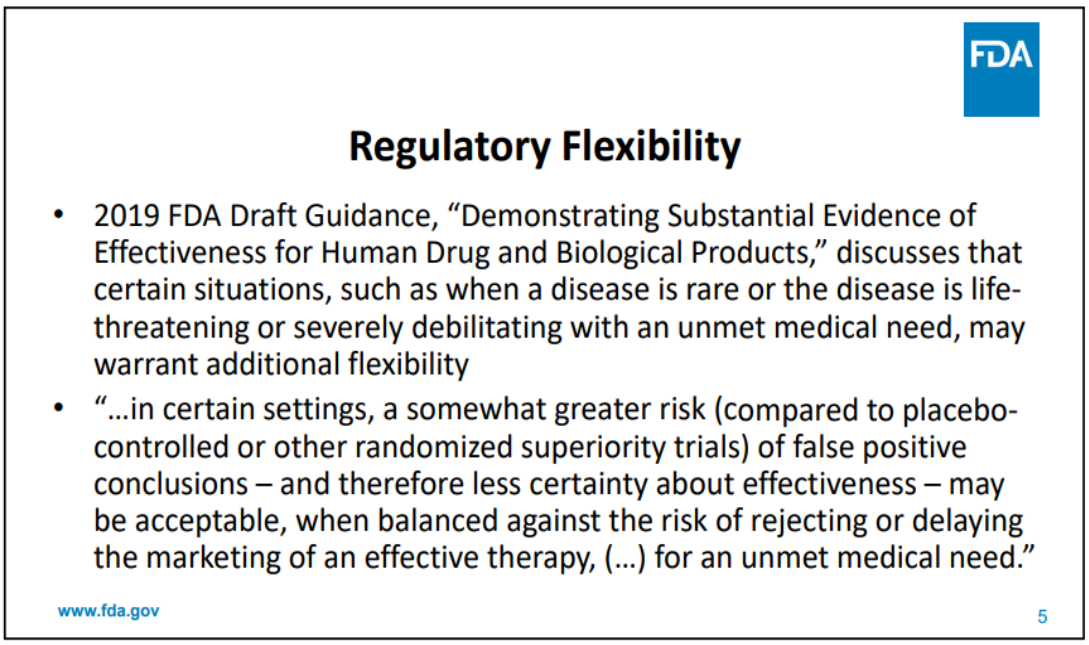


The FDA has used regulatory flexibility in other divisions for other ALS therapies. At page 62 in the Tofersen AdComm Briefing Document, FDA-CDER said:

> *"In this setting of a very rare, life-threatening disease with significant unmet need, it is appropriate to exercise regulatory flexibility in applying the statutory standards for establishing effectiveness. For example, FDA's regulation at 21 CFR 312.80 notes, "while the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand flexibility in applying the standards.*
>
> *The FDA has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness." This approach is reiterated in FDA's guidance for industry, ALS: Developing Drugs for Treatment (September 2019), which states: "The statutory standards for effectiveness apply to drugs for ALS just as the standards apply for all other drugs. However, FDA has long stressed the appropriateness of exercising regulatory flexibility in applying the statutory standards to drugs for serious diseases with unmet medical needs, while preserving appropriate assurance of safety and effectiveness."*

Similarly on page 5 in the FDA-CDER's Presentation, they framed the AdComm discussion around the concept of Regulatory Flexibility.

Graphic - FDA's Regulatory Flexibility Slide from Tofersen AdComm



No similar slide or discussion was in the NurOwn AdComm or Briefing documents.

F. NurOwn Meets Conditional Approval Threshold of a "Plausible Mechanism of Action" in a Heterogeneous Terminal Rare Disease with a Critical Unmet Need

Commissioner Makary has proposed a novel conditional approval pathway for rare disease drugs, focusing on a "plausible mechanism of action" to expedite access for patients with rare diseases with a critical unmet need. This pathway targets diseases affecting small populations where traditional randomized controlled trials are often infeasible or efficacy analyses are difficult due to limited patient numbers. Makary emphasized the need for flexibility, stating, *"If there is an investigational drug that makes sense physiologically—the mechanism is scientifically plausible that this treatment would help these individuals—we could approve that therapy on a conditional basis"* (Makary, as cited in BioSpace, 2025). The approach includes robust post-approval surveillance to monitor patient outcomes, aiming to balance early access with safety. CBER Director Vinay Prasad, supports this initiative, aligning it with the goal of empowering patient choice. He stated, "The goal is to empower patients to make choices right for them," emphasizing the use of real-world data to assess treatment effects post-approval. The proposal's success hinges on defining "plausible mechanism" and ensuring robust surveillance, with potential legislative action needed for implementation (BioSpace, 2025).[211]

Both Dr. Makary and Dr. Prasad have committed to using a new Conditional Approval pathway for rare, terminal diseases with dire or critical unmet needs. In the confirmation hearings, Senator Lisa Murkowski specifically asked Dr. Makary about his approach to diseases like ALS. She stated that:

> "*The FDA's Accelerated Approval pathway has really been important and I think very promising for treatments for ALS and some other rare diseases. You have advocated for using "common sense" alongside science. Very briefly, how do we define "common sense" as it applies to the regulatory decisions of the FDA? How do we make sure as* ***ALS patients again, who are looking at a very very limited time frame, they can't wait for the regular approval process****. Give me a Little bit of your view here on how you would like to proceed using these accelerated approval pathways."*

Commissioner Makary responded:

> ***"We have to customize the regulatory approval process to the condition that we're hoping to be able to offer hope for…. We cannot require two randomized controlled trials if our goal Is to provide safe and effective therapies****. I do believe firmly in that approach and I think we can use some common sense to ask some big questions we've never asked before at the FDA."*

Even though the new conditional approval pathway has not yet been codified, the FDA can exercise its regulatory flexibility and approve NurOwn based on a "plausible mechanism of action."

[211] BioSpace. (2025, June 4). FDA's Prasad vows to make rare disease drugs available at 'first sign of promise'. https://www.biospace.com

G. Mesenchymal Stem Cells & Neurotrophic Factors Demonstrate A Plausible Mechanism of Action to Treat ALS, and NurOwn Uses a Plausible Method Of Delivery to Avoid Blood Brain Barrier Hurdles.

Mesenchymal stem cells & neurotrophic factors have two decades of evidence demonstrating plausible mechanisms of action, but NurOwn uniquely combines the two to exemplify an amplified impact and plausible method of delivery. For over 25 years, both stem cells and neurotrophic factors have shown promise, albeit unfulfilled. NurOwn changes that. It uses the stem cells to deliver those supercharged neurotrophic factors directly to the site of the damage: the brain and dying motor neurons.

And as Dr. Windebank clarified during the AdComm, MSCs are safe.

> *"Let me take a brief moment to address the overall safety of MSCs . First, they have been resourced for more than 30 years in the US alone . A meta-analysis over the past 15 years showed the safe and different populations is a formal systematic review. MSCs were isolated from several tissues across 62 randomized clinical trials covering 3,546 patients. No serious safety events other than transient fever, administration site adverse events, sleepiness and constipation."*

Petitioners believe the FDA can exercise its promised regulatory flexibility and grant conditional approval to NurOwn with a broad Phase 4 biorepository.

1. Neurotrophic Growth Factors have a Plausible Mechanism of Action if the Method of Delivery Can Avoid the Problems with the Blood Brain Barrier.

As discussed in the Fact section above, neurotrophic factors exert their proposed mechanism of action on neurons by promoting survival, reducing inflammation, and inhibiting apoptosis – all of which are critical in mitigating the progressive degeneration seen in ALS and other neuro- degenerative diseases.

Admittedly, past trials of CNTF (Myotrophin) and BDNF failed. Researchers hypothesize that challenges in delivery – particularly the inability to effectively cross the blood-brain barrier – are the reasons for the failures. Subcutaneous administration, used in both trials, resulted in poor CNS penetration because neurotrophic factors are large polypeptides with short half-lives, rapidly degrading or being cleared systemically before reaching motor neurons in sufficient concentrations. This led to limited efficacy. Intrathecal delivery trials aimed to bypass the BBB by directly targeting the CNS, but still showed limited success, possibly due to rapid clearance from the CSF or insufficient dosing frequency, highlighting the need for advanced delivery methods to achieve therapeutic concentrations at the neuronal level.

Comparatively, NurOwn possesses the "plausible mechanism of action" demonstrated in the multiple stem cell therapies mentioned below, but it supercharges the effect of those MSCs with the benefits of neurotrophic factors using its proprietary advanced delivery method to ensure therapeutic concentrations at the neuronal level.

Additionally, demonstrating the importance of the method of delivery is a brand new study in Parkinson's disease, which is validating the neurorestorative capabilities of glial cell line-derived neurotrophic factor (GDNF). The Phase 2 trial, published in Movement Disorders,[212] investigated the delivery of GDNF into the brains of 41 Parkinson's disease (PD) patients. The trial used an implantable catheter system called a convection-enhanced delivery (CED) system to bypass the blood-brain barrier (BBB) and deliver a high-dose infusion of AAV2-GDNF directly into the putamen of people with mild to moderate Parkinson's disease. AAV2 carries the gene for GDNF into brain cells, so your brain cells can start making GDNF themselves.

GDNF is a protein that supports survival of dopaminergic neurons. Unlike dopamine-based drugs, this therapy aims to **protect or even restore damaged brain cells by delivering neurotrophic support** in the striatum. The striatum is an area where this support could be helpful for Parkinson's.

Over 9 months, monthly infusions of GDNF showed:

- significant 3.5-point improvement in UPDRS Part III OFF score vs. placebo
- 25% increase in putamenal 18F-DOPA uptake indicating enhanced dopamine function.
- Three moderate PD patients showed promising outcomes with an approximate 20-point improvement in motor scores (MDS-UPDRS Part III), reduced OFF time, less dyskinesia, and lowered levodopa. Four mild PD patients appeared stable.
- Safety was confirmed with no serious adverse events linked to GDNF itself, but there were catheter-related issues occurring in 10 patients.

This trial demonstrates the ability to deliver GDNF directly to the brain can overcome the BBB's limitation—a key reason for past neurotrophic factor trial failures. Michael Okun, the medical director of the Parkinson's Foundation said on X:

> *"These are early-phase results. The results have however paved the way for the REGENERATE PD Phase 2 trial, now underway (NCT06285643). If you're following Parkinson's gene therapy or* ***curious about neurorestorative strategies, this is one to watch****. Remember,* ***'ab uno disce omnes' – from this one example learn all the rest."***

The NurOwn trial in ALS shares both similarities and differences with the PD study. Both use neurotrophic factors to enhance motor neuron survival and function in their respective diseases. Both methods address the BBB challenge innovatively. NurOwn's approach is different in that it supercharges multiple neurotrophic factors and uses mesenchymal stem cells as a delivery vehicle to bypass the BBB and those MSCs then secrete GDNF locally throughout the CNS. And NurOwn's cellular approach likely offers broader neurotrophic support as it secretes multiple neurotrophic factors like BDNF, VEGF, GDNF and others, whereas the PD study focused solely on GDNF, potentially limiting its mechanistic scope.

[212] Roch, G., Whone, A. L., Luz, M., Nakabayashi, K., Campbell, P., Barber, T., ... & Gill, S. S. (2025). Randomized placebo-controlled trial of convection-enhanced delivery of glial cell line-derived neurotrophic factor in Parkinson's disease. Movement Disorders, 39(10), 1802–1812

Nonetheless, the PD-GDNF study is more validation of Petitioners' assertion that NurOwn's MSC-NTF neurorestorative strategy is a "plausible mechanism of action" to treat 100% fatal ALS.

2. Stem Cell Research has Demonstrated a Plausible Mechanism of Action in Multiple Neurological Diseases and Conditions with Critical Unmet Needs.

For over two decades, stem cells have demonstrated a promising mechanism of action in animal models at Commissioner Makary's own Johns Hopkins; in human studies in ALS and other neurodegenerative diseases; and in spinal cord injuries. Now NurOwn has demonstrated a plausible mechanism of action in both MS and ALS. In the documentary *"Die Trying,"* Dr. Tony Windebank explained in simple terms how the NurOwn stem cells work:

> *"The cells come out of the bone marrow and then they're treated in a way that makes them protective for nerve cells, so they're kind of enhanced stem cells. … When you have an injury anywhere in your body those stem cells will move out of the bone marrow and they go to the area that's injured and they aid the healing process. Now we're taking these healing cells and we're putting them into the nervous system."*

a. Stem Cell Research in ALS Showed Some Efficacy in Animal Models and Demonstrated a Plausible Mechanism of Action Two Decades Ago.

In her February 2000 interview with Charlie Rose, Project ALS co-founder Jenifer Estess famously said:

> *"The thought that other people can get a heart transplant or a liver transplant or kidney transplant, and there's nothing that we can do for the nervous system seems, in this day and age, completely ludicrous to me."*

Jenifer's neurologist told her that stem cell transplants were science fiction. But ten years later, Jenifer's science fiction fantasy became scientific fact. That same skeptical neurologist, Jeff Rothstein of Johns Hopkins, credited Project ALS as the *"driving force"* behind ALS stem cell research in the US. As a result of their funding, Dr. Rothstein spoke about the early promising results his lab discovered when using transplanted fetal stem cells in SOD1 animal models.

> *"We've used this rat to begin to investigate stem cells and we've actually hit some pay dirt in those experiments. Quite excitingly when we put these cells in, these **animals actually start getting better**. When we inject these cells and we watch them over the next 1 to 3 months and we clearly see that **some** of these rats actually **regain some of their strength**. **Not all**. We're not curing these animals by any means. But there's **no question that a paralyzed animal regains some motor function** in their hind limbs."*

(Watch the rats that regained function in the "*Three Sisters*" documentary at 33:38). These animal models are compelling as obviously rats don't know what a placebo effect is.

b. Stem Cells Showed Efficacy in Some People with ALS

One of the first studies to show preliminary signs of efficacy in MSCs was a seven-person study out of Italy in 2003 – 22 years ago. Over a four-year follow-up, some patients showed temporary improvements in ALSFRS scores.[213] In long-term follow-up (up to 9 years), again some patients showed slower decline in ALSFRS and forced vital capacity (FVC), with evidence of increased motor neuron survival, supporting MSCs' potential as a disease-modifying therapy.[214]

Recently, Clive Svendsen, PhD conducted a trial at Cedars-Sinai, combining GDNF (one of the neurotrophic factors in NurOwn) with stem cells. Then he surgically implanted the stem cells. Dr. Svendsen commented:[215]

> *"Using stem cells is a powerful way to deliver important proteins to the brain or spinal cord that can't otherwise get through the blood-brain barrier."*

Besides NurOwn, a variety of different types of stem cell studies corroborate a "plausible mechanism of action" to treat ALS. The studies use autologous mesenchymal stem cells derived from bone marrow like NurOwn or adipose tissue like a Phase 1 study at Mayo. Other studies use allogeneic stem cells derived from umbilical cord or from fetal spinal cord (also called neural stem cells). The method of delivery varies: intra-surgical (IS), intravenous (IV), or intrathecal (IT) like NurOwn. Almost all showed some temporary stabilization or slowing in decline.

Though benefits were variable and not universal, these studies highlight that stem cells offer a plausible mechanism of action to treat ALS.

None have enrolled and completed a Phase 3 trial like NurOwn. If approved, Brainstorm Cell would be first-to-market with the first disease-modifying therapy in sporadic ALS. This aligns with President Trump's "America First" agenda.

[213] Mazzini, L., Fagioli, F., Boccaletti, R., Mareschi, K., Oliveri, G., Olivieri, C., ... & Madon, E. (2003). Stem cell therapy in amyotrophic lateral sclerosis: A methodological approach in humans. Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders, 4(3), 158–161.

[214] Mazzini, L., Mareschi, K., Ferrero, I., Vassallo, E., Oliveri, G., Nasuelli, N., ... & Fagioli, F. (2010). Mesenchymal stem cell transplantation in amyotrophic lateral sclerosis: A Phase I clinical trial. Experimental Neurology, 223(1), 229–237.

[215] Cedars-Sinai. (2022, September 5). Stem cell-gene therapy shows promise in ALS safety trial. Cedars-Sinai.

Graphic - Plausible MOA: Stem Cell Trials in ALS

Country	Disease	Phase	Type	Autologous or Allogeneic	Source	Method of Delivery	# Trial Participants	ALSFRS-R Change	FVC Change	Authors' Names	ClinicalTrials.gov Number	PubMed Cite
USA	ALS	I	MSC	Autologous	Adipose	IT	8	Stable or improved in some	Stable in some	Staff & Windebank	NCT03268603	
Poland	ALS	I	MSC	Autologous	Adipose	IS	(small cohort)	Stabilized in some	Reduced decline in some	Kuzma-Kozakiewicz & Madei	Not reported	
USA	ALS	I/IIa	NSC	Allogeneic	Fetal spinal cord	IS	18	Trend toward improvement in treated limb	Not reported	Svendsen & Johnson	NCT02943850	
USA	ALS	I	NSC	Allogeneic	Fetal spinal cord	IS	12	Stable in some	Stable in some	Glass & Rothstein	NCT01348451	
USA	ALS	I/II	NSC	Allogeneic	Fetal spinal cord	IS	18	Stable in some	Stable in some	Feldman & Glass	NCT01348451	
USA	ALS	II	NSC	Allogeneic	Fetal spinal cord	IS	15	Slowed decline in some	Slowed decline in some	Glass & Feldman	NCT01730716	
Italy	ALS	I	MSC	Autologous	BMA	IT	7	Temporary improvement in some	Stable in some	Mazzini & Madon	Not reported	
Italy	ALS	I	MSC	Autologous	BMA	IT	9	Slower decline in some	Slower decline in some	Mazzini & Fagioli	Not reported	
South Korea	ALS	I	MSC	Autologous	BMA	IT	8	Stable in some	Stable in some	Oh & Kim	NCT01363401	
India	ALS	Pilot	MSC	Autologous	BMA	IT + IV	10	Slower deterioration	Stable for ~6 months	Prabhakar & Khandelwal	Not reported	
Iran	ALS	I	MSC	Autologous	BMA	IT + IV	6	Significant improvemt at 3 months	Significant improvemt at 3 months	Nabavi & Ebrahimi	Not reported	
Spain	ALS	Pilot	MSC	Autologous	BMA	IS	11	(histological focus)	NR	Blanquer & Martinez	Not reported	
Belarus	ALS	Pilot	MSC	Autologous	BMA	IT + IV	(small cohort)	Slower deterioration	NR	Rushkevich & Alekseeva	Not reported	
Poland	ALS	Pilot	MSC	Autologous	BMA	IT	(small cohort)	Improved in some	NR	Pawlukowska & Machaliński	Not reported	
Australia	ALS	I	MSC	Allogeneic	Umbilical cord	IV	20	No significant change	No significant change	Goutman & Feldman	NCT02881476	
China	ALS	I/II	MSC	Allogeneic	Umbilical cord	IT	15	Stable or improved in some	Stable in some	Zhao & Zhang	NCT01494480	

c. Stem Cells Showed Efficacy in Some Human Studies in Neurodegenerative Diseases

Stem cell therapies are showing similar promise in other neurodegenerative diseases like Multiple Sclerosis (MS) and Parkinson's Disease (PD). Indeed, Michael Okun of the Parkinson's Foundation said: *"Of all the potential therapies being pondered & developed for PD over the previous two decades, none has garnered more hope and attention than stem cell transplantation."*

In April 2025, Nature published two new papers about the use of stem cells in PD. On X, Michael Okun summarized those results as follows:

- One study used induced pluripotent stem cells (iPSCs)[216] from adult cells and one used human embryonic stem cells (hESCs)[217].
- Both aimed to make and implant dopaminergic neurons.
- Autologous cell iPSC study likely has less risk of rejection compared to hESCs that may require immunosuppression drugs.
- Both small studies: 7 vs 12 patients.
- Both approaches require neurosurgery for insertion of cells.
- Even with surgical implantation, both approaches were reasonably safe.
- Both revealed some signal for improvement in clinical outcomes.
- Larger prospective L/T trials needed to compare performance relative to Parkinson's medications, DBS & pump therapies

[216] Schweitzer, J. S., Song, B., Herrington, T. M., Park, T.-Y., Lee, N., Ko, S., ... & Kim, K.-S. (2025). Transplantation of human embryonic stem cell-derived dopamine neurons in Parkinson's disease: 2-year outcomes of a first-in-human clinical trial. Nature, 634(8032), 140–149.

[217] Barker, R. A., Björklund, A., Gash, D. M., Kirik, D., Thompson, L. H., & Brundin, P. (2025). Dopamine neurons derived from human embryonic stem cells substantially improve motor function in a model of Parkinson's disease. Nature, 634(8032), 131–139.

But these two studies aren't the only approaches demonstrating a "plausible mechanism of action" for the use of stem cells in neurodegenerative diseases. The following table outlines some stem cell trials in PD, MS and even one in Huntington's Disease, which is an inherited neurodegenerative disease.

Graphic - Plausible MOA: Stem Cell Trials in Other Neurodegenerative Diseases

Country	Disease	Phase	Type	Autologous or Allogeneic	Source	Method of Delivery	# Trial Participants	ALSFRS-R Change	Authors' Names	ClinicalTrials.gov Number
USA	MS	II	MSC-NP	Autologous	BMA	IT	54	48% improved EDSS Plus (EDSS, T25FW, or 9-HPT)	Harris & Sadiq	NCT03355365
USA	MS	I	MSC-NP	Autologous	BMA	IT	20	40% improved EDSS, 30% improved T25FW	Harris & Sadiq	NCT01933802
USA	MS	I	MSC	Allogeneic	Umbilical cord	IV	18	83.3% had inactive MRI lesions at 1 year	Riordan & Morales	NCT02034188
Israel	MS	IIb	MSC	Autologous	BMA	IT	80	Ongoing, results pending (prior trial: 60% halted progression)	Karussis	Not reported
Italy	MS	I/II	NSC	Allogeneic	Fetal spinal cord	IT	12	Ongoing, results pending	Uccelli & Mancardi	NCT03269071
Italy	MS	I/II	NSC	Allogeneic	Fetal spinal cord	ICV (Intra-cerebroventricular)	24	Ongoing, results pending	Uccelli & Mancardi	NCT03282760
USA	PD	I	MSC	Allogeneic	BMA	IV	20	Reduced UPDRS OFF state score	Schiess & Stowe	Not reported
USA	PD	II	MSC	Allogeneic	BMA	IV	45	Results pending (expected 2025)	Schiess & Stowe	Not reported
India	PD	I	MSC	Allogeneic	BMA	IS (Subventricular)	5	Improved UPDRS score at 12 months	Venkataramana & Pal	Not reported
Belarus	PD	I	MSC	Autologous	BMA	IT	5	Improved motor and nonmotor symptoms	Boika & Ponomarev	Not reported
Italy	PD	I	MSC	Autologous	BMA	IT	5	No significant H&Y score change	Storch & Eggert	Not reported
Italy	PSP - PD	I	MSC	Autologous	BMA	IA (Intra-arterial)	5	Stabilized UPDRS, H&Y, PSP-RS scores	Canesi & Pezzoli	Not reported
France	HD	II	FSC	Allogeneic	Fetal tissue	IS (Intracerebral)	45	No significant motor improvement	Bachoud-Lévi & Remy	Not reported

d. Stem Cells Showed Efficacy in Human Studies of Spinal Cord Injuries, Demonstrating a Plausible Mechanism of Action.

Just last year, the Mayo Clinic News Network[218] published a story entitled ***"Study documents safety, improvements from stem cell therapy after spinal cord injury."***[219] Notably, Dr. Anthony Windebank – a NurOwn Phase 2 and Phase 3 principal investigator – was also an author on this stem cell paper.

The study reported on a Phase 1 clinical trial where stem cells derived from patients' own fat (adipose-derived mesenchymal stem cells). The MSCs were injected intrathecally to treat patients with traumatic Spinal Cord Injuries (SCIs). Using the American Spinal Injury Association (ASIA) Impairment Scale, 7 of 10 participants demonstrated improvements, including increased sensation (pinprick and light touch tests), improved muscle strength, and recovery of voluntary anal contraction aiding bowel function. Notably, two of three patients with complete thoracic injuries regained some sensation and movement below the injury level, a significant outcome given only 5% of such patients naturally recover function. The story emphasizes the potential of stem cell therapy to improve – not just stabilize -- SCI outcomes, challenging the historical assumptions of limited recovery.

[218] Mayo Clinic News Network. (2024, April 1). Study documents safety, improvements from stem cell therapy after spinal cord injury.

[219] Bydon, M., Qu, W., Windebank A.J. et al. Intrathecal delivery of adipose-derived mesenchymal stem cells in traumatic spinal cord injury: Phase I trial. Nat Commun 15, 2201 (2024).

In 2021, Yale News[220] published a story entitled: "***Yale scientists repair injured spinal cords using patients' own stem cells.***" In this study,[221] IV injection of autologous bone marrow-derived stem cells led to significant motor function improvements in SCI patients. Conducted with Sapporo Medical University in Japan, the study involved patients with non-penetrating injuries who had lost motor function, coordination, and sensory abilities due to falls or minor trauma. After receiving their own cultured stem cells, over half of the patients showed substantial recovery within weeks, including improved walking ability and coordination. The story highlights the potential of this approach for broader clinical use.

3. NurOwn's Plausible Mechanism of Action Demonstrated in MS

NurOwn's plausible mechanism of action in ALS was discussed in the Fact section above. Additionally, it has shown potential in other neurodegenerative diseases and neuro-inflammatory diseases like Progressive MS.

Dr. Jeffrey Cohen[222] is a leading MS clinician researcher from Cleveland Clinic with over 40 years of experience. He was also the principal investigator in the NurOwn Phase 2 MS trial as well as the lead author on the resulting publication.[223] In his interview in Neurology Live,[224] Dr Cohen said one of the biggest unmet needs in Progressive Multiple Sclerosis is for treatments that "promote repair, reverse damage, and improve neurologic function." While more than 20 medications are available for treating MS, they are primarily helpful for relapsing-remitting disease.

In contrast, people with progressive MS have already experienced inflammatory destruction, so they need therapy that can also repair damage. No disease-modifying treatments exist for progressive MS.

---

[220] Yale News. (2021, February 22). Yale scientists repair injured spinal cords using patients' own stem cells.

[221] Honmou, O., Yamashita, T., Morita, T., Oshigiri, T., Hirota, R., Iyama, S., ... & Kocsis, J. D. (2021). Intravenous infusion of auto serum-expanded autologous mesenchymal stem cells in spinal cord injury patients: 13 case series. Clinical Neurology and Neurosurgery, 203, 106565

[222] Jeffrey Cohen, MD is Professor of Neurology in the Cleveland Clinic Lerner College of Medicine and holds the Hazel prior Hostetler Endowed Chair. He has worked at Cleveland Clinic's Mellen Center for Multiple Sclerosis Treatment and Research since 1994 and was Director in 2014-2017. Dr. Cohen has a large clinical practice devoted primarily to the care of patients with multiple sclerosis. He is Director of the Experimental Therapeutics Program and has been involved in various capacities in a large number of clinical trials developing new therapies for MS. Dr. Cohen has served on a large number grant review committees, advisory groups and national and international task forces. Practicing for over 40 years, he has over 300 publications concerning immunologic, clinical and research aspects of MS. He has been cited over 72,000 times. As of May 2025, he has an i-10 index of 440 and an h-index of 111.

[223] Cohen, J. A., Lublin, F. D., Lock, C., Pelletier, D., Chitnis, T., Mehra, M., Gothelf, Y., Aricha, R., Lindborg, S., Lebovits, C., Levy, Y., Motamed Khorasani, A., & Kern, R. (2023). Evaluation of neurotrophic factor secreting mesenchymal stem cells in progressive multiple sclerosis. Multiple Sclerosis, 29(1), 92–106.

[224] Cohen, J. (2021, August 11). NeuroVoices: Jeffery Cohen on alternative methods to tackling progressive MS. Neurology Live.

While stem cells offer a potential treatment to repair damage in progressive MS, earlier trials have not met expectations.[225] Applying lessons from those trials, Dr. Cohen suggested that MSCs may be more effective when: (1) modified to augment production of neurotrophic factors; (2) delivered directly via intrathecal injection instead of IV; (3) repeated in multiple doses. That is precisely what NurOwn does.

While telling Neurology Live that results of the NurOwn small Phase 2 open-label trial should be interpreted with caution, Dr. Cohen acknowledged that the results were also "encouraging." Cleveland Clinic reported:

> *"For the timed walking speed and peg tests, none or substantially fewer of the matched controls achieved these improvements — in fact, controls worsened slightly on many of the measures during comparable follow-up."*

With just 3 doses over the 28-week trial, approximately one-third of patients showed a "clinically meaningful" response in several objective neurologic assessments of efficacy:

- **12-item MS Walking Scale** (self-reported COA re impact on mobility): Mean improvement of 4.17 points, with 38% achieving at least a 10-point improvement
- **Timed 25-foot walking speed:** 19% of participants achieving ≥25% improvement
- **9-Hole Peg Test** (assesses finger dexterity): 13% achieving ≥25% improvement
- **Low-contrast letter acuity test,** (assesses visual dysfunction): Mean improvement of 3.3 letters, with 27% of participants improving by at least eight letters
- **Symbol Digit Modalities Test** (assesses cognitive function): Mean improvement of 3.8 points, with 67% of participants improving by at least 3 points

Efficacy data was not limited to functional improvements but included objective biomarker changes as well. Like the NurOwn ALS trial, the MS trial focused uniquely on first-in-class CSF biomarkers.

Dr. Cohen remarked that NurOwn: *"showed quite promising results."* As reported in the MS Journal,[226] NurOwn resulted in consistent increases in CSF neuroprotective factors (VEGF-A, HGF, NCAM1, Follistatin, LIF, and fetuin-A) and a consistent reduction in immunomodulatory inflammatory biomarkers (MCP-1, SDF-1, Osteopontin, and CD27).[227]

Additionally, even though ALS and MS are two distinct diseases, Dr. Cohen testified at the ALS AdComm that NurOwn demonstrated "encouraging results" and has the potential to address the unmet need in MS as well as ALS. As such, Dr. Cohen closed by advising the AdComm that based on the NurOwn Phase 2 trial, his MS center would "enthusiastically agree" to participate in future studies. He obviously would not agree to such a commitment if there were not a "plausible mechanism of action" for his patients.

---

[225] Smith, J. A., Nicaise, A. M., Ionescu, R.-B., Hamel, R., Peruzzotti-Jametti, L., & Pluchino, S. (2021). Stem cell therapies for progressive multiple sclerosis. Frontiers in Cell and Developmental Biology, 9, 696434.
[226] Picher-Martel, V., & Dupré, N. (2023). Juvenile amyotrophic lateral sclerosis. Frontiers in Neurology, 13, 1055266.
[227] Cohen JA, Lublin FD, … Gothelf Y, Aricha R, Lindborg S, Lebovits C, Levy Y, Motamed Khorasani A, Kern R. Evaluation of neurotrophic factor secreting mesenchymal stem cells in progressive multiple sclerosis. Mult Scler. 2023 Jan;29(1):92-106.

III. Petitioners are Asking the FDA to Consider Additional Risks In Its Risk-Benefit Assessment.

Petitioners assert that ALS is one of the worst diseases with which people can be diagnosed.

> *"I believe that the FDA's risk-benefit calculation in ALS must be different than it is for therapies developed for non-life-threatening conditions. There is almost no risk worse than imminent death from ALS."*

(Public Comment - Dr. Mallory Feng, MD, Psychiatrist).

A. Risk Assessment must include the Risk of Type II Errors that Cause Irreparable Harm to People with ALS.

We are asking the FDA to reconsider its Benefit-Risk assessment and contemplate the "risk" of a statistical Type II error -- failing to approve or delaying approval of a drug that does work in an imminently fatal, heterogeneous rare disease like ALS. In ALS, any delay or a denial in approving a drug creates irreparable harm. Type II errors hasten disability, paralysis, and death allowing people to die waiting for a drug that could have helped them live.

Graphic - Risk-Benefit: Risk of Type II Errors

		FDA DECISION ALS: Fatal Disease with Critical Unmet Need		
		Approve	**Deny**	**Delay**
REALITY	**Therapy is Safe**	Correct Decision - Patient Benefits	TYPE II ERROR FDA EXPEDITES Paralysis & Death	TYPE II ERROR FDA EXPEDITES Paralysis & Death
	Therapy is NOT Safe	TYPE I ERROR Patients Suffer Physical Harm But is it worse than Disease?	Perhaps Correct Decision - FDA Prevents Physical Harm But is Harm worse than Disease?	Perhaps Correct Decision - FDA Prevents Physical Harm But is Harm worse than Disease?
	Therapy is Effective	Correct Decision - Patient Benefits	TYPE II ERROR FDA EXPEDITES Paralysis & Death = NurOwn	TYPE II ERROR FDA EXPEDITES Paralysis & Death = NurOwn
	Therapy is NOT Effective	TYPE I ERROR Patients Suffer Financial Harm	Correct Decision - FDA Prevents Financial Harm	Correct Decision - FDA Prevents Financial Harm

Historically the FDA's paramount concern has been the risk of a Type I safety error – putting an unsafe drug on the market like thalidomide. That risk is part of the FDA's analysis before it approves a drug. But in rare, heterogeneous life-threatening diseases with a critical unmet need like ALS, any delay or denial of a drug's approval can have even worse repercussions than a Type I safety error.

In a story published in Biocentury, Janet Woodcock's Chief of Staff shared how Dr. Woodcock would weigh in on the risk of Type II errors by instructing FDA reviewers to: ***"consider the risk of NOT approving a drug that DOES work."*** But today any such discussion is discretionary and thus subject to inconsistent and arbitrary application.

Petitioners request the risk of Type II errors be codified in the ALS and Rare Disease Guidance Documents and that both the FDA and AdComm members should be instructed about that risk.

In his Public Comment to the NurOwn AdComm, Shah's other brother, Ardalan Minokadeh MD, PhD proposed the following checklist to assess the risks of Type II errors. He suggested the FDA should exercise more, not less, regulatory flexibility when the following factors are present as they increase the chances of a Type II statistical error.

1. Seriously debilitating and imminently life-threatening diseases
2. Rare diseases with critical unmet needs
3. Heterogeneous diseases where a drug may work on some
4. Rare Disease without validated, objective biomarkers
5. Subjective COAs with acknowledged flaws
6. Hypothesis doesn't accurately assess if drug works
7. Real-world data and real-world evidence demonstrate efficacy

Indeed Zelia Bowman MD was one of the hundreds of unaffiliated physicians who submitted Public Comments in support of approval. She is an attending Hematologist/Oncologist:

> *"ALS … is in my opinion one of the most devastating diagnoses, much worse than several cancers that I treat. Time is of the absolute essence with this diagnosis with half the patients not living past 3 years with much morbidity following the time of diagnosis. Hence it would not be wise to await large phase 3 data to come to fruition on potential agents; 30,000 patients would die waiting if we wait another 5 years on more robust data. Please consider the existing trial data and permit a phase 4 post marketing study, which would provide the efficacy data while granting access to the drug. One should also consider statistical Type II error – not approving or delaying approval of a drug that does work. Those patients would die or progress which is more harmful than a Type I safety error of approving an unsafe drug."*

Delays did cause a deadly Type II error. As you recall, Kandy Simons lost her 26-year-old son to ALS. In Kandy's Public Comment, she quoted Dr. Marks' presentation discussing the need for urgency, a comment he made when speaking about gene therapies for children with terminal diseases:

> *"Right now, we have this need for access. And if you're the parent of a young child who has a rare genetic disease that is going to kill them in the first years of life… you want the technology now, not years from now."*

Agreed. But it doesn't matter if your child is 1 or 21, like Kade Simons… if their disease is genetic or sporadic, like Kade Simons … if they are going to die in the first years or the first decades of life, like Kade Simons. When your child has a disease that is going to kill them before they live the lives they deserve to live, you want treatments now, not years from now.

Kade was one such precious life. He died at 26 years old because the FDA didn't believe him when he told them NurOwn worked on him when he was 21 years old.

Delaying approval until there is yet another efficacy trial will not only cost another $40-60 million dollars; but more importantly, it will cost tens of thousands of lives. Please keep Dr. Mary Porter's Public Comment in mind:

> *"In the military, when confronting an enemy … we always strive to equip our men and women with every possible weapon in the arsenal to enable them to complete the mission … to beat the enemy. In the military, if we make mistakes, people die. Similarly, if the FDA makes a mistake about NurOwn, people will die. Don't let a Type II error change our futures."*

As Dr. Prasad recently said, " time equals money" for pharmaceutical manufacturers. But he also reminded everyone that time has bigger implications for patients. And as Dr. Michelle RENGARAJAN, a Duchenne mom and endocrinologist at the Broad Institute recently said at the Gene & Cell therapy roundtable:

> *"For patients and families, the single most important commodity is time. As you think about improving efficiency and advancing therapeutic products, I hope you remember for many patients time is muscle. time is brain. And time is life."*

B. Risk Assessment must be Adjusted in 100% Fatal Rare Diseases

At the 2021 E&C hearing CDER Director Cavazzoni committed to the Chair of the Rare Disease Caucus:

> *Our Guidance and the way we operate recognizes that, first and foremost, there is a higher threshold for risk in patients who are suffering from diseases such as ALS because they are so rapidly progressive and lethal. We also as we look at how to guide developers and how we interpret the data that they put in front of us we take into consideration the fact that we there has to be a higher threshold for risk and also that we may be in situations where we may have to accept some degree of uncertainty around the benefit.*

In the documentary *"Die Trying,"* Wassam's brother said that he is willing to accept the risk, to which Wassam responded. *"What risk? There is none. But even if there was, what do I have to lose? Nothing. The FDA is protecting me to death."*

At the inaugural I AM ALS flag event in 2022, Patty Manhardt implored the FDA to consider the risk-benefit like it's the ALS battlefield:

> *"Let me paint a picture for you of our lives. We have all found ourselves on the ALS battlefield along with 30,000 other Americans…. We are stuck out on the battlefield where every day we lose a piece of the person we used to be…. We have no ammunition and no weapons. This isn't a battle, it's a slaughter. We are being invaded. We have no defenses. We cannot run for cover and we cannot fight. Can you imagine walking into a war zone knowing that you have a 100% chance of death because no one even gave you a Kevlar vest to protect you. You would have nothing, not even hope. With ALS, we need hope. You need a chance – even if it's a 1% chance, even if you only have one Kevlar vest to hand out. If one life can be saved, it is worth it. Not only will that one person be saved but 30,000 others will now have hope.*
>
> *We are here today asking the FDA to give us the weapons. Give us the ammunition to fight this horrible disease. We are worth it. Just do the right thing, the humane thing. And do it quickly with regulatory flexibility and urgency. There's a critical unmet need. Please encourage drug companies to request approval. Be swift in approving Brainstorm's NurOwn, Neuvivo's NP001, and Biogen's Tofersen. Give us a fighting chance because we are dying waiting.. We need drugs in bodies and hope in souls."*

Perhaps the most complete recitation of the risk-benefit tolerance among the ALS community can be found in the 2000+ Public Comments, almost all filed in support of NurOwn's approval. One compelling Public Comment was led by Petitioner Dr. Shahriar Minokadeh's brother, Anush Minokadeh MD, who like Shah is also a Johns Hopkins-trained anesthesiologist. Today, Anush is on faculty and works in the Neuro ICU at UC San Diego. First he shared his professional opinion about how he balances risk-benefit decisions in his daily critical care practice:

"I frequently make risk-benefit assessments for treatment of patients in life-threatening situations … where the outcome – without intervention – is certain death. You would want the ER physician to give you a chance even if the chance of benefit is low…. Similarly, against a backdrop of certain paralysis and death in ALS, it's hard to fathom that ANY chance of efficacy isn't worth the risk of approving a therapy."

Anush went on to discuss how he's had to stand by helplessly and watch the personal devastation – both emotional and physical suffering – that has befallen his brother. He shared that when patients and loved ones tell us that ***"no risk is worse than ALS, we must believe them."***

"We must honor the wishes of people who understand what it is like to die of ALS a little more each day… what it's like to be trapped inside your own body with a brilliant mind like my brother's. At just 39, my brother lost the career and identity that he strived to achieve from the time he was a small boy. And like many families, he also lost his spouse, who was unwilling to deal with the devastation that ALS leaves in its wake.

No one can understand the loss of intimacy and human touch until you cannot hug a loved one. No one can imagine the inability to scream in pain or to pull your hand out of a bowl of scalding water being used to loosen your clonus and cramping. No one understands the pain of lying in a bed or sitting in a chair every day without moving, the pain of strictures contracting your every muscle. As if ALS isn't tragic enough, it's even more cruel that your sensory neurons stay intact. What we were taught in medical school is wholly inaccurate. ALS is a physically painful disease.

No one can fathom that utter fear and desperation when you're choking on your own saliva… or gasping for breath when the power fails on your ventilator … or can't cough up a small morsel of food. This is the hopeless deterioration and suffering that befalls everyone diagnosed with ALS."

Another physician's perspective was from Dr. Ajay Sampat MD, a neurology faculty member at UC Davis. He also had submitted an application to be an AdComm Patient Representative believing his perspective as a neurologist with ALS would provide unique value. He was not chosen. So instead, Dr. Sampat submitted a Public Comment and testified during the Open Public Hearing.

Indeed at 7:01 into the Energy & Commerce hearing, now-Senator John Curtis reminded the FDA: ***"Patients are not exactly worried about their safety; they're worried about living."***

One of Dr. Ajay Sampat's colleagues, Kinga Skowron Olortegui, MD, a surgeon from the University of Chicago, submitted a Public Comment imploring the FDA to use the same risk-benefit flexibility that it does for cancer treatments:

"As a physician, I urge you to consider the approval of debamestrocel…. Perhaps the most disheartening part of this illness is the paucity of medications to slow its progression. Now, we have hope with the arrival of debamestrocel. In my work, ***I see many patients undergo high risk operations or extensive treatments for cancer which have much more risk for even smaller potential gain than debamestrocel. Patients with ALS deserve the opportunity to give their lives and their families hope.****"*

A board-certified neurologist and neuromuscular medicine specialist, **Hamza Malek, MD,** submitted a Public Comment.

"I constantly navigate the delicate balance between assessing risks and making decisions in the best interest of my patients, particularly when dealing with life-threatening conditions like ALS. In situations where limited treatment options exist, such as ALS, the decision-making process becomes even more challenging. When considering a new drug with an unclear benefit, my deliberation centers on the safety profile and potential for even modest improvements in the patient's quality of life. In such cases, the paramount goal is to provide hope and a chance for a better outcome, despite the uncertainties, as there are often no viable alternatives. The well-being and comfort of my patients remain at the forefront of these difficult decisions, emphasizing the importance of compassionate and evidence-based care. In the face of a devastating disease like ALS, where each day without effective treatment is a day lost, we implore you to consider the approval of Debamestrocel. It has shown substantial evidence of a clinically meaningful effect, and we believe it could change the narrative for ALS patients worldwide. Please continue the FDA's pattern of regulatory flexibility of ALS therapies, so more people can live longer with ALS as we work towards a cure."

C. Risk Assessment must include the Risk of People Going Outside the US to get Treatments.

While dying patients demand faster approvals, regulators prioritize long-term data. This leaves thousands of people dying of ALS feeling trapped in their own bodies and then being tortured even more by a slow process against a fast-moving disease. For so many, no risk is worse than the cruel and inevitable death from ALS.

Thus, Petitioners request that researchers and regulators be cognizant of and weigh the incredible risks that dying patients will take if they cannot get access to approved therapies in the US.

Frustrated with the pace of clinical research and regulatory approval process, people with ALS are trying off-label drugs, makeshift investigational drugs, and traveling to get stem cell transplants at far away clinics. During the 2021 E&C Congressional hearing, North Carolina Congressman Butterfield shared Dr. Bedlack's warning about the risk that patients – out of desperation – are self-experimenting with both promising products and unproven snake oil manufactured by unregulated, underground compounders in far away countries. Not only are these patients likely suffering medical and financial harms from self-experimentation, but the research community suffers because it loses the opportunity to study this population of people with ALS who desperately need help with proven therapies.

1. Medical Tourism to Stem Cell Clinics Abroad

People with ALS are also traveling outside the US to seek stem cell treatments. Indeed in a recent podcast, Secretary Kennedy acknowledged the problems with Americans who must travel outside the US to get options for seriously debilitating or lethal diseases.

> *"You shouldn't have to go to Antigua to get stem cells, which I had to do for my throat, and they helped me enormously. Why did I have to go to Antigua for that?"*

In the PALS video, Eric Stevens tells us:

> *"It's crazy that there's something out there that has actually helped people and you can't get it. It's crazy… We're raised in this country that is, you know, supposedly the best. The best in medicine. The best in health care. Yet you find yourself and everyone with ALS searching outside the country for help."*

That very thing was shared in the documentary, *"Die Trying: the battle for ALS treatments."* ALS patient Wissam Majid shares that he was left with no other option than to go abroad to Beirut, Lebanon to seek treatment. His brother commented:

> *"Bureaucracy is getting in the way right now. The FDA is worried about safety. I mean the side-effect of ALS is death. It's not right. Every day that passes, he's losing more of himself and that goes for every ALS patient. He's willing to take the risk….* if there were options here in America, we'd prefer to do it here, but there are no options right now."

Wissam's family and friends raised $30,000 to send him to Lebanon for an experimental stem cell treatment that the clinic falsely asserted would work in a similar way as NurOwn. We'll never know if the stem cell therapy helped. On June 15, 2022, Wissam died waiting for the FDA.

At the June 2019 PFDD meeting, Dr. Bob Sinnott told the FDA he traveled to South Korea for stem cells. In this advocacy video at 5:56, he also shared that he had qualified for and dropped out of the NurOwn Phase 3 trial. Instead, he and several other people with financial means chose not to risk getting a placebo in the NurOwn trial and instead chose to travel to Asia to get Corestem's Neuro-Nata, a stem cell treatment licensed in South Korea.[228]

At 7:01 into the Energy & Commerce hearing,[229] now-Senator John Curtis spoke about the number of constituents that have contacted the offices expressing the inability to access drugs using EAP or Right to Try. Then he shared the story of his friend and constituent with ALS who traveled the world trying a variety of unproven stem cell therapies.

> *"ALS has ravaged – ravaged -- my neighborhood. I currently have a very, very good friend suffering from ALS. he's been fortunate because of some of his resources, he's been able to travel worldwide to receive some of these treatments that so many are not. He frequently discusses how patients are unable to receive many treatments under right to try that are under clinical investigation for which he can if he's willing to travel and spend more than the average person is able to do."*

All four men with ALS traveled to China to get stem cells. All are now deceased. They all died waiting for NurOwn.

[228] Of all the people Petitioners know who received stem cells in South Korea, all are deceased, trached or "locked in" with no remaining motor function to move or communicate. Petitioners are aware of no one whose function comes anywhere close to the bulbar or respiratory function as people in the NurOwn trial and EAP.

[229]"The Path Forward: Advancing treatments and cures for neurodegenerative diseases," Hearing before the Subcommittee on Health of the Committee on Energy and Commerce, House of Representatives, 117th Cong. (2021, July 29). https://www.youtube.com/live/42rmmKTd3lE[](https://www.youtube.com/live)

In this 2022 review about International stem cell tourism, the authors warn:

> *"Stem cell tourism is an emerging area of medical tourism activity. Frustrated by the slow translation of stem cell research into clinical practice, patients with debilitating conditions often seek therapeutic options that are not appropriately regulated…. The leading countries in the international stem cell tourism market are the USA, China, India, Thailand and Mexico. As the majority of clinics offering stem cell therapies are based in low- and-middle-income countries, stem cell tourists place themselves at risk of receiving an unproven treatment. In addition to often being ineffective, stem cell therapies are associated with complications such as infection, rejection and tumorigenesis."*

Those risks can result in life-threatening adverse events. In this Neurology article[230] titled '*Complications from 'Stem Cell Tourism'", the* authors examine the serious risks associated with unproven stem cell therapies. The authors conducted a retrospective analysis of 13 patients with neurological conditions, including ALS, MS and stroke. The patients experienced complications after receiving stem cell treatments at unregulated clinics abroad – primarily in China, Mexico, and Russia. Ultimately 80% of patients required hospitalization and significant neurological worsening (e.g., seizures, paralysis). And tragically, in 2 of the 13 cases, the "complication" was death.

These stem cell "clinics" abroad often use inadequately characterized stem cell products, (or no stem cell products at all), and many use risky methods lacking sterile protocols, training and expertise. But the harm is not just medically related. Patients often drain their life savings hoping for a chance at something to save their lives.

2. NP001 Story, Sodium Chlorite Substitute and Two Decades of Delays

The NP001 saga can teach us many regulatory lessons. The science underlying NP001 began in 2001. The first trial that showed efficacy was in 2011. The drug company, Neuraltus, went out of business; Neuvivo bought the assets and began the laborious process of reanalyzing the NP001 trial data. Neuvivo then published survival data in 2024 that validated what the trial participants have been saying since 2011. NP001 worked – especially on respiratory and bulbar function. And now we also know, it extends survival. In the 14 years that have passed, 84,000 Americans with ALS have died waiting.

[230] Julian, K., Yuhasz, N., Rai, S., Salerno, J. A., & Imitola, J. (2020). Complications from "stem cell tourism" in neurology. Annals of Neurology, 88(4), 661–668. https://doi.org/10.1002/ana.25842

a. The Trial Participants' Experience & RWD on Patients Like Me

The NP001 story started with the story of three scientists – Ben Harris, a physicist, Rob Tison, a mechanical engineer; and Eric Valor, an automotive research scientist with Mercedes Benz. Ben and Rob were enrolled in the NP001 trial in 2011. They like many others including Petitioner Shah Minokadeh – felt it working in his body. Ben reported:

> *"A few minutes into his second infusion … he distractedly reached for his coffee and found the cup empty. For Ben, drinking without choking took great concentration, and he had just downed an entire beverage without thinking about it. Instantly, he knew that he was getting the drug—and that it was working. That afternoon, Ben began testing himself. He tilted his head back further and took bigger gulps of water with no problems. Then he decided to really push the limit: he fixed his gaze on a ceiling tile and chugged. "It felt like jumping off a cliff," he wrote to Rob in an email that afternoon. "To my utter amazement I chugged the liquid easily!" Over subsequent hours and days, Ben's muscle twitches began to subside, and his speech improved slightly. He was drooling less, he could move his tongue more, and it took less concentration to eat solid foods. The changes were unmistakable. Just as Rob had experienced, the drug wasn't simply stalling Ben's progression, it was reversing it."*

Excitement erupted online as Ben and Rob shared their experiences. Trying to encourage trial enrollment, Ben told the San Francisco Business Times,[231] *"NP001 stopped my ALS, and it will probably stop yours."* But many people couldn't qualify for the trial. And when the trial was over, neither Rob nor Ben could get more. Expanded Access wasn't an option because of the start-up company's financial constraints.[232] Neuraltus CEO Bob Casey discussed those constraints in the documentary "*Die Trying: the Battle for ALS Treatments*."

The book, "Personal Trials" details how these three scientists joined dozens of other patients in dosing themselves with a chemical substitute for NP001.[233] Petitioner Dr. Shah Minokadeh did not take the makeshift compound, but he understands the motivation of those who did. "*Facing a frustratingly slow and opaque biomedical research and regulatory system,"* this group of dying patients took treatments into their own hands, ***"fighting not just for their lives, but for a disease community that for years has struggled to be heard."***[234]

---

[231] Grabowski, C. (2011, September 2). Patients enlist in fight against ALS. San Francisco Business Times.
[232] This is the same trial that Petitioner, Dr. Shahriar Minokadeh, believes slowed his ALS progression.
[233] Sodium chlorite is a compound used in water treatment plants; and people with ALS were eager to try it – without waiting for three more trials to meander their way through the FDA's regulatory maze. This sodium chlorite is not the same as NP001, which is a pH-adjusted IV formulation of purified sodium chlorite.
[234] Akst, J. (2016). Personal trials: How terminally ill ALS patients took medical treatment into their own hands. CreateSpace Independent Publishing Platform.

Eric Valor joined Rob and Ben in importing a compounded version of sodium chlorite (trying to duplicate NP001) from the underground market.[235] Sadly, all three died waiting for the approval of the real thing. Rob died in 2012. Ben died in 2013. Eric died in 2019 but he was trached by the time they made the "Die Trying" documentary in 2016. These are the real life implications of a Type II error. In contrast, people like Shah and others who did not import the makeshift drug are still alive today.

The cost of importing the compounded sodium chlorite from Europe was approximately $10,000 per month. We will never know if the imported makeshift compound expedited or slowed their ALS progression. Petitioners are aware of one person who was importing the makeshift compound, went into anaphylactic shock and had to have his heart shocked to resuscitate him. These are the risks people with ALS are willing to take, and Petitioners believe that these are the risks the FDA must consider in its risk-benefit analysis.

No similar SAEs were reported in the NP001 study when the product was manufactured under all stringent GMP principles and practices.

b. NP001 - The Science and Regulatory Saga

The other moral to the NP0001 story is how the financial hardships, the FDA's failure to accept post hoc data, and regulatory delays in rare diseases can destroy a small pharma company – keeping potentially disease-modifying drugs out of dying patients' bodies. The timeline below of published studies tells the story of the clinical trial conundrum that has kept NP001 out of the hands of patients who need it most.

- 2004 - Evidence for systemic immune system alterations in sporadic ALS [236]
- 2014 - NP001 regulation of macrophage activation markers in ALS: a phase 1 clinical and biomarker study[237]
- 2015 - Randomized phase 2 trial of NP001, a novel immune regulator: safety and early efficacy in ALS[238]
- 2017 - Serum C-Reactive Protein as a Prognostic Biomarker in ALS[239]

[235] Park, M. (2012, May 17). Lou Gehrig's disease: Patients research with their own hands. ABC News.
[236] Zhang, R., Gascon, R., Miller, R. G., Gelinas, D. F., Mass, J., Hadlock, K., Jin, X., Reis, J., Narvaez, A., & McGrath, M. S. (2005). Evidence for systemic immune system alterations in sporadic amyotrophic lateral sclerosis (sALS). Journal of Neuroimmunology, 159(1-2), 215–224.
[237] Miller RG, Zhang R, Block G, Katz J, Barohn R, Kasarskis E, Forshew D, Gopalakrishnan V, McGrath MS. NP001 regulation of macrophage activation markers in ALS: a phase I clinical and biomarker study. Amyotroph Lateral Scler Frontotemporal Degener. 2014 Dec;15(7-8):601-9.
[238] Miller RG, Block G, Katz JS, Barohn RJ, Gopalakrishnan V, Cudkowicz M, Zhang JR, McGrath MS, Ludington E, Appel SH, Azhir A; Phase 2 Trial NP001 Investigators. Randomized phase 2 trial of NP001-a novel immune regulator: Safety and early efficacy in ALS. Neurol Neuroimmunol Neuroinflamm. 2015 Apr 9;2(3):e100.
[239] Lunetta C, Lizio A, Maestri E, et al. Serum C-Reactive Protein as a Prognostic Biomarker in Amyotrophic Lateral Sclerosis. JAMA Neurol. 2017;74(6):660–667.

- 2022 - Phase 2B randomized controlled trial of NP001 in amyotrophic lateral sclerosis: Pre-specified and post hoc analyses[240]
- 2022 - Macrophage-Targeted Sodium Chlorite (NP001) Slows Progression of ALS through Regulation of Microbial Translocation[241]
- 2024 - Systemic Innate Immune System Restoration as a Therapeutic Approach for Neurodegenerative Disease: Effects of NP001 on ALS Progression[242]
- 2024 - The Effectiveness of NP001 on the Long-Term Survival of Patients with ALS[243]
- 2025 - Respiratory Function Improvement and Lifespan Extension Following Immunotherapy with NP001 Support the Concept That ALS Is an Immuno-Neurologic Disease

NP001, was originally developed by Mike McGrath MD PhD in 2001. His lab at UCSF specializes in studying the role of macrophages in the pathogenesis of a wide variety of diseases, including neurodegenerative diseases and cancer.[244] McGrath took lessons learned from his studies on AIDS and applied them to ALS. For example, AIDS-related dementia is a macrophage inflammatory disease and prior to effective combination anti-retroviral therapy (cART), there were dementia hospices filled with patients who had "lost" neurons because of AIDS. With effective cART, AIDS-dementia patients went back to work, having cleared the effects of inflammation that caused dysfunction, but not death, of neurons.

In an attempt to determine whether non-AIDS neurodegenerative diseases might have a similar pattern with inflammation driving dysfunction, McGrath began a collaboration with KOL Robert Miller, MD at the Forbes-Norris ALS Center at California Pacific Medical Center (CPMC). Together, they published a study implicating inflammation in the pathogenesis of ALS (Zhang 2005),[245] which found

[240] Miller RG, Zhang R, Bracci PM, Azhir A, Barohn R, Bedlack R, Benatar M, Berry JD, Cudkowicz M, Kasarskis EJ, Mitsumoto H, Manousakis G, Walk D, Oskarsson B, Shefner J, McGrath MS. Phase 2B randomized controlled trial of NP001 in amyotrophic lateral sclerosis: Pre-specified and post hoc analyses. Muscle Nerve. 2022 Jul;66(1):39-49.
[241] Zhang R, Bracci PM, Azhir A, Forrest BD, McGrath MS. Macrophage-Targeted Sodium Chlorite (NP001) Slows Progression of Amyotrophic Lateral Sclerosis (ALS) through Regulation of Microbial Translocation. Biomedicines. 2022 Nov 12;10(11):2907.
[242] McGrath MS, Zhang R, Bracci PM, Azhir A, Forrest BD. Systemic Innate Immune System Restoration as a Therapeutic Approach for Neurodegenerative Disease: Effects of NP001 on Amyotrophic Lateral Sclerosis (ALS) Progression. Biomedicines. 2024 Oct 16;12(10):2362.
[243] Forrest BD, Goyal NA, Fleming TR, Bracci PM, Brett NR, Khan Z, Robinson M, Azhir A, McGrath M. The Effectiveness of NP001 on the Long-Term Survival of Patients with Amyotrophic Lateral Sclerosis. Biomedicines. 2024 Oct 16;12(10):2367.
[244] According to this Press Release, Neuraltus was a privately held company that began operations in 2009 based on a technology portfolio and IP assembled by the company founders, Ari Azhir, PhD, Neuraltus' COO; Michael McGrath, MD, PhD, Professor of Laboratory Medicine at UCSF; and Edgar Engleman, MD, Professor of Medicine at Stanford School of Medicine. In March 2009 Neuraltus closed a $17M Series A financing with leading venture groups. In a subsequent Press Release in 2013, Rich Casey was named as President & CEO. In 2015, the ALS Association awarded Neuraltus a $1.5 million grant to help fund the Phase 2 trial. The last Press Release from Neuraltus was January 2018, announcing it had completed enrollment of the Phase 2B trial.
[245] Zhang, R., Gascon, R., Miller, R. G., Gelinas, D. F., Mass, J., Hadlock, K., Jin, X., Reis, J., Narvaez, A., & McGrath, M. S. (2005). Evidence for systemic immune system alterations in sporadic amyotrophic lateral sclerosis (sALS). Journal of Neuroimmunology, 159(1-2), 215–224.

that the degree of inflammation was directly related to progression rate of ALS. With the confirmation of ALS as an inflammatory disease, McGrath and current CEO of Neuvivo, Ari Azhir, discovered a manufacturing process to produce pure sodium chlorite, a molecule known to regulate macrophage activation (McGrath 2002). They named it NP001.

Neuraltus conducted the phase 2a trial of NP001 in 136 people. It was a randomized, double-blind, placebo-controlled clinical trial of people with ALS from January 2011 through November 2012 (NCT01281631). NP001 was given 5 days in a row in the first month and three days in a row thereafter on a monthly basis as 30-minute IV infusions. There were two doses of NP001 tested and they confirmed a dose-dependent halting of disease progression in a subset of patients with higher baseline levels of inflammation (Miller 2015).[246]

Patients were randomized in a 1:1:1 manner to receive placebo, the low dose of 1 mg/kg of NP001, or the higher dose of 2 mg/kg of NP001. The endpoint was "change from baseline" ALSFRS-R. The study suggested that NP001 might slow or stop the progression of ALS in a subgroup of patients with high levels of neuroinflammation. Neuraltus then conducted a Phase 2b trial (NCT02794857) but the trial failed to meet both the primary and secondary endpoints . However, it did work on a subgroup in this heterogeneous disease.[247]

In 2017, ALS KOLs Robert Miller, Stanley Appel, and Adriano Chiò published a review in JAMA Neurology that concluded: ALS patients with elevated serum CRP levels progress more rapidly than do those with lower CRP levels and "this elevation may reflect a neuroinflammatory state potentially responsive to the immune regulators such as NP001."[248] Although the overall results of the NP001 trials were negative, they showed an efficacy signal in a subgroup that was not pre-specified.

In 2024, Neuvivo published survival data that validated what the trial participants had been saying since 2011. NP001 worked – especially on respiratory and bulbar function. The findings from this study suggest that a six-month course of NP001 resulted in a five-month increase in overall survival.[249]

[246] Miller RG, Block G, Katz JS, Barohn RJ, Gopalakrishnan V, Cudkowicz M, Zhang JR, McGrath MS, Ludington E, Appel SH, Azhir A; Phase 2 Trial NP001 Investigators. Randomized phase 2 trial of NP001-a novel immune regulator: Safety and early efficacy in ALS. Neurol Neuroimmunol Neuroinflamm. 2015 Apr 9;2(3):e100.
[247] Miller RG, Zhang R, Bracci PM, Azhir A, Barohn R, Bedlack R, Benatar M, Berry JD, Cudkowicz M, Kasarskis EJ, Mitsumoto H, Manousakis G, Walk D, Oskarsson B, Shefner J, McGrath MS. Phase 2B randomized controlled trial of NP001 in amyotrophic lateral sclerosis: Pre-specified and post hoc analyses. Muscle Nerve. 2022 Jul;66(1):39-49.
[248] Lunetta C, Lizio A, Maestri E, Sansone VA, Mora G, Miller RG, Appel SH, Chiò A. Serum C-Reactive Protein as a Prognostic Biomarker in Amyotrophic Lateral Sclerosis. JAMA Neurol. 2017 Jun 1;74(6):660-667. doi: 10.1001/jamaneurol.2016.6179.
[249] Forrest BD, Goyal NA, Fleming TR, Bracci PM, Brett NR, Khan Z, Robinson M, Azhir A, McGrath M. The Effectiveness of NP001 on the Long-Term Survival of Patients with Amyotrophic Lateral Sclerosis. Biomedicines. 2024 Oct 16;12(10):2367.

Today, the FDA has asked Neuvivo to conduct yet another Phase 3 trial to confirm what trial participants have known since 2011. NP001 worked. In fact, just as with NurOwn, one of Dr. Bedlack's confirmed "reversals" was someone who participated in the early NP001 trial.

In the 14 years that have passed since people regained function back in 2011, 84,000 Americans with ALS have died waiting. This type of regulatory morass is precisely what caused Ben Harris, Rob Tison, and Eric Valor, to import an unknown compound from an unknown lab over a decade earlier. Petitioners submit that this is a risk that the FDA should consider in its risk-benefit analysis.[250]

Although beyond the scope of this Petition, Petitioners believe that CDER should reconsider the NP001 efficacy data and put NP001 on the market with a Phase 4 post-marketing study.

D. FDA should Exercise the Utmost of Regulatory Flexibility when the Investigational Therapy is to Treat a Terminal, Service-Related Disease that Veterans Get from Risking Their Lives to Serve our Country.

Anytime the FDA is considering approving a drug for a service-related disease, military men and women should be given a seat at the table. They should not only be given a voice in how they assess risk, but also a vote in whether the drug shows sufficient efficacy for approval. The men and the women in our military risked their lives to protect us. It's the least we can do to let them make their own decisions about what risks they're willing to accept.

In the documentary "Die Trying: the battle for ALS treatments," Navy pilot Matt Bellina said:

> *"It's ridiculous. A guy like me, I've been, you know on and off, risking my life for ten years. Let me try some drugs that are gonna potentially help. I'll take the risk."*

When they were fighting to pass Right to Try, the Bellinas produced a video with the National Right to Try movement. In it, Matt Bellina's wife Caitlin spoke of the irony in how the DOD and FDA differently view risks to our service members:

> *"It's a slap in the face, especially since he's a veteran. You wanted him to strap a rocket to his back and go fly to defend the country. But now that it's his turn, and something's wrong with him, you're like 'sorry, it's too dangerous for you to try that.' "*

At the NurOwn AdComm and in a Public Comment, the daughter of a veteran, Mandi Bailey presented the story about veterans with ALS.

[250] Petitioners also believe that there is ample evidence to approve NP001 with a Phase 4 post-marketing study.

> *"From the moment we raise our right hand, we promise to defend our great nation until our last breath. We are willing to sacrifice our lives for our country. We are not, however, willing to forfeit our voices. This is why we implore the FDA to honor the country's promise to care for us in our time of need. As research into the cause of ALS in veterans continues, the incidence rate has climbed from 2 to 10 times that of the general population. Thus, the urgency rises now that we must fight, not in defense of our nation, but in defense of our lives. Although no longer on the battlefield, our need for weapons in this fight is critical…. NurOwn is such a weapon."*

Many other veterans, family and friends shared their voices in Public Comments begging for access to NurOwn. USN veteran Shelley Hoover; Army veteran Dr. Mary Grace Porter; US Navy Lieutenant & USMC veteran Kate Peters; USAF medic Juan Reyes; Carol Manning, widow of USN veteran Jerry Manning; John McCormack, Jessica Shortall on behalf of USN doctor Capt. Jason Rice; Shelley Baumgartner, Army Nurse Corps veteran; and Deb Bellina, mother of USN pilot Matt Bellina.

Besides pilots, the other military occupations with the highest risk are doctors and health care professionals like Dr. Mary Porter who was awarded a Bronze Star for her service in Iraq. With a 6x risk of getting ALS, Dr. Mary Porter's Public Comment made a compelling plea for access to NurOwn – both as a physician and a veteran:

> *"Selfless service. Duty. Honor. Respect. Loyalty. Those values were forged in me as a young Army physician. I worked tireless hours serving our nation's heroes and their families. Now I am asking our country to respect and honor my sacrifice by giving me access to a mesenchymal stem cell therapy, NurOwn (aka Debamestrocel) that can help me fight this insidious disease."*

The men and women in our military are getting ALS at an alarmingly high rate. They deserve access to every weapon in the medical arsenal to help them fight this insidious disease. Petitioners are asking the FDA to exercise the utmost in regulatory flexibility when considering whether to approve a drug for a service-related disease like ALS. Unfortunately, neither the FDA nor AdComm members had one moment of discussion about veterans who wanted access to NurOwn. Not one discussed the sacrifice veterans made for our country, how it caused their ALS, and our moral obligation to give them access to every possible weapon in the medical arsenal.

IV. Petitioners are Asking FDA-CBER to Consider Additional Benefit of a Broad Phase 4 Biorepository and Natural History Database To Advance ALS Research & Drug Development

Petitioners are asking the FDA to consider how significantly a broad biorepository of CSF biomarkers and DNA samples could benefit scientific research -- not just of ALS -- but because of the halo effect, it could also benefit other neurodegenerative diseases. In ALS, that benefit could change the trajectory of drug development of this most heinous of diseases with a critical unmet need.

In a Washington Post podcast on Rare Disease Day 2024, former Commissioner Califf acknowledged that one of the ongoing challenges in rare diseases is the paucity of medical data. In his 2016 presentation to NORD, Commissioner Califf said:

> *"Natural history studies and registries … can form the basis for an evidence base to make progress. This need for an evidence base does not stop when a drug or device gets on the market—careful post-market studies and measurement of the quality of healthcare delivery can make a huge difference."*

At the July 2021 hearing before the Energy & Commerce Health subcommittee, both FDA and NIH officials discussed the need for biomarkers in fatal neurodegenerative diseases like ALS, Parkinson's, Huntington's, and Alzheimer's. Former CDER Director Patrizia Cavazzoni said:

> *In ALS and many other neurodegenerative diseases there are no easily measured biomarkers that are reliable predictors or surrogates for the rate of disease progression in individual patients. Such tools could improve the precision with which drug response could be evaluated leading to more robust and earlier insight to distinguish the more promising drugs from those that are less likely to succeed.*

In his 2022 comments at NORD, former Commissioner Califf again reiterated the importance of identifying biomarkers:

> *"I want to spend a few minutes focusing on one important area that advances rare disease drug development -- when we get it right – biomarker development. As many of you know, biomarkers are powerful tools in our armamentarium for facilitating the discovery and development of new cures, and real-world data may help us connect biomarkers to clinical outcomes that matter to patients. ….*
> *Good biomarkers can help us tell more quickly whether or not a drug is engaging the right target, and what the best dose might be. The best biomarkers are backed by solid translational science programs in development and are reasonably likely to predict clinical outcomes. Developing useful biomarkers is hard work and it takes extensive collaboration and attention to detail to get it right."*

Nearly a decade after Dr. Califf's speech about the importance of validated biomarkers, ALS still has none. This Administration has the power to make transformative and disruptive changes.

A. CSF Biomarkers

By creating a Phase 4 post-marketing biorepository, the FDA has a unique opportunity to change the future of ALS. When NurOwn is administered intrathecally, the physician removes 5 ml (approximately one teaspoon) of CSF and replaces it with NurOwn. That CSF is a goldmine for researchers.

The quantity of CSF samples in biorepositories is much lower than blood and urine samples. People aren't excited to go get a lumbar puncture to donate CSF – especially not longitudinally. In contrast, thousands would be excited to get NurOwn and donate that teaspoon of CSF every few months.

Recall that Dr. Windebank said he had nearly 1000 people on a waiting list for the 16 slots in the NurOwn Phase 2 trial in 2015. That was before Matt Bellina's videos went viral in the ALS community in 2019 and before the dozens of people in the Phase 3 trial and EAP halted their lethal progression and regained function. Petitioners believe that thousands upon thousands would want NurOwn.

Thus, an independent ALS biorepository would be the beneficiary of NurOwn's accelerated approval. Mandatory participation in a Phase 4 biorepository would exponentially increase the number of CSF samples available for researchers to study. This is the most obvious benefit but there are so many more.

B. Heterogeneity

A Phase 4 Biorepository will help us decipher the complex heterogeneity of ALS. Despite tremendous efforts in basic research, a growing number of clinical trials, and promises from clinicians that this is the most hopeful time in ALS, the outcomes haven't changed since Lou Gehrig was first diagnosed back in 1939.

> *"One possible reason for the lack of effective causative treatment options is that ALS may not be a single disease entity but rather may represent a clinical syndrome, with diverse genetic and molecular causes, histopathological alterations, and subsequent clinical presentations contributing to its complexity and variability among individuals. Defining a way to subcluster ALS patients is becoming a central endeavor in the field."*[251]

[251] Tzeplaeff, L., Jürs, A. V., Wohnrade, C., & Demleitner, A. F. (2024). Unraveling the heterogeneity of ALS—A call to redefine patient stratification for better outcomes in clinical trials. Cells, 13(5), 452.

In this video, MIT Computational biologist, Dr. Ernest Frankel,[252] suggested that AI and machine learning could help us overcome the problems plaguing ALS drug development and approvals:

> *"It's possible that some of these previous clinical trials – that were deemed to have failed – would have actually succeeded if we had been able to separately study the results for different subtypes of the disease, different clinical patterns of decline."*

That's the computational biology explanation. In lay terms, this is why Petitioners believe when an ALS therapy shows some impact on some people in a 100% fatal heterogeneous disease, "some must be enough." Drugs that have plausible mechanisms of action and evidence of efficacy in some subgroups should be approved with a broad Phase 4 post-marketing study where computational biologists like Dr. Fraenkel can then decipher the scientific reason that some people in the trial responded differently than others. However, we cannot continue to allow people to die while scientists figure out the science.

In this review entitled *"Unraveling the Heterogeneity of ALS: a Call to Redefine Patient Stratification for Better Outcomes in Clinical Trials,"* the authors discuss the heterogeneous nature across genetic, molecular, and clinical dimensions and advocate for integrative research combining multi-omics, biomarkers, and clinical data to develop targeted treatments and improve patient outcomes. -

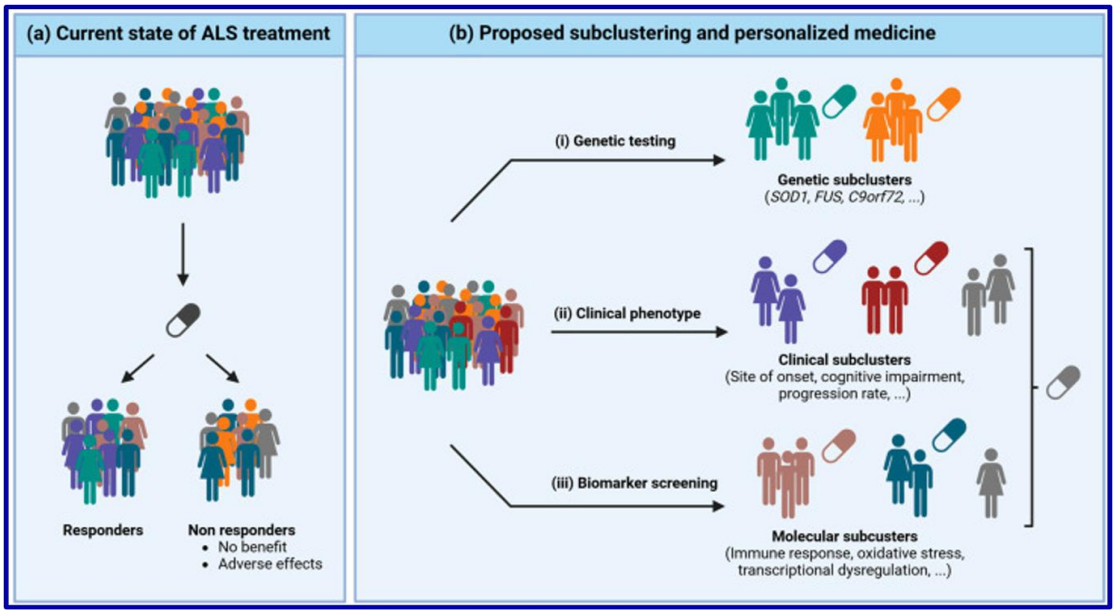
While cluster identification based on postmortem tissue is only possible postmortem, and while blood mainly gives access to peripheral information, the authors assert that ALS research community would:

> *"greatly benefit from further studies based on CSF samples…. Moreover, cluster analyses of brain-derived EVs (e.g., proteins, miRNA, lipids, and metabolites) would offer potential insights into the pathological states of the brains of ALS patients via CSF collection or simple blood or tear fluid collection. All these new discoveries mark the beginning of molecular-based patient classification in clinical trials … to better identify suitable ALS clusters and responders."*

The following graphic from the review illustrates the difficulty of conducting a clinical trial in a rare heterogeneous disease with small trial sizes.

[252] Dr. Fraenkel commented that "If you start with the wrong hypothesis, you're not going to get very far." "The goal of systems biology is to systematically measure as many cellular changes as possible, integrate this data, and let the data guide you to the most promising hypotheses." So the Fraenkel Lab is approaching the ALS problem in a new way. To account for the vast heterogeneity in ALS, they measure many cellular changes — including transcription of genes, protein-DNA interactions, of thousands of chemical compounds and of protein modifications — and can apply artificial intelligence and machine learning to those measurements.

Graphic - Heterogeneity in ALS Trials and Impact on Trial Outcomes



And as Dr. Hande Ozdinler suggested in her Public Comment, ALS needs a personalized medicine approach and more biomarkers:

> *"As you know ALS is a very heterogeneous and rare disease…. I think our goal should not be to find the one magical drug or solution that is going to cure them all (the science shows us that this in fact may not be possible) but rather* ***develop a more personalized medicine approach*** *that would address the needs of individual patients,* ***determined by the underlying cause of the disease for each patient****. I suggest that we* ***focus on identifying biomarkers*** *that would help us understand the underlying cause of the disease, so that we can have better inclusion criteria for clinical trials, and we should* ***identify pharmacokinetic biomarkers so that we tell the response to treatment in a more quantitative and reproducible way."***

To speed up drug development and take a personalized medicine approach to ALS, we need to identify and understand the subtypes, and we need to understand some of those subtypes may respond differently to therapeutics based on their exposome and pathology. But to do that in a vastly heterogeneous disease, we need tens of thousands of samples, not hundreds in a Phase 3b trial.

We will never unravel the complexities of this heterogeneous disease if we are basing our conclusions on studies of hundreds of people instead of biosamples from tens of thousands. A NurOwn Phase biorepository could be a gamechanger for ALS researchers.

C. GWAS and Variants of Uncertain Significance

DNA Samples from tens of thousands in a Phase 4 biorepository will help identify disease-causing mutations, oligogenic risk factors, genetic modifiers, and Variants of Uncertain Significance (VUS), that today are understudied. Likewise, an enormous number of polygenic risk factors have not yet even been identified.

As such, we need a population-wide database to discover and validate these genetic risk factors across the diverse, heterogeneous ALS population. Large-scale genetic studies, including genome-wide association studies (GWAS), are needed to evaluate the frequency of these VUS in the ALS population versus controls, to assess their impact on clinical outcomes, and hopefully to develop drugs that target these variants.

In the NurOwn trial, 124 people consented to have genetic testing of 31 pre-specified ALS-related genes and SNPs. Even with that very small sample size, several people learned they had a VUS in suspicious ALS genes that merit further investigation, such as MAPT, TARDBP (fast progressors); and SETX (juvenile onset, not ALS4).

If NurOwn were approved with a mandatory Phase 4 biorepository, we could collect, not hundreds, but thousands of DNA samples and do full GWAS. Then using AI, we could learn so much more about the genetics of this lethal heterogeneous disease.

1. Example: SETX Variants Possibly Associated with ALS

Approximately 10% of people develop ALS before the age of 40 and only ~1% before the age of 25. Little has been done to investigate the cause of juvenile- and early-onset ALS, and it is mostly unclear what factors influence the age of onset.[253]

But when your child is in that 1%, it is 100% of your world and your motivation. In her Public Comment to the NurOwn AdComm, Kandy Simons got permission from the family members of all these young people to use their photos. (See Exhibits). These are the forgotten ones…. the faces of these young people whose lives are being cut short by ALS. They and their families deserve answers.

As discussed above, Petitioners Shah Minokadeh, Mayuri Saxena and Kade Simons all have a VUS in the SETX gene, and all were diagnosed decades earlier than normal – Shah at 35; Mayuri at 32 and Kade at 21. Although there is a pathogenic variant of SETX that causes a subtype of juvenile ALS called ALS4, their variants do not match that ALS4 phenotype.

While one variant of the SETX gene is associated with juvenile onset ALS, other variants of the SETX gene may also contribute to ALS by altering immune regulation during viral infections. Senataxin, encoded by SETX, modulates RNA polymerase II activity to prevent excessive transcription of antiviral

[253] Suzuki, N., Nishiyama, A., Warita, H., & Aoki, M. (2023). Genetics of amyotrophic lateral sclerosis: Seeking therapeutic targets in the era of gene therapy. Journal of Human Genetics, 68(3), 131–152.

genes, such as IFN-β, thus maintaining immune homeostasis.[254] SETX variants, including gain-of-function mutations associated with ALS4, disrupt R-loop resolution and transcriptional control, leading to heightened antiviral mediator expression and chronic neuroinflammation. [255]

This dysregulated response to viral pathogens can exacerbate motor neuron degeneration, as persistent inflammation may trigger or accelerate ALS pathology. For instance, SETX variants that impair senataxin's interaction with RNA metabolism pathways could amplify inflammatory cascades following viral exposure, contributing to ALS progression. [256] These findings suggest that diverse SETX variants, beyond those in ALS4 may predispose individuals to ALS by compromising antiviral response regulation, warranting further investigation into their mechanistic roles.

When Mayuri and Shah asked researchers to investigate their SETX variants, uniformly researchers said they needed more SETX samples to eliminate or confirm a pathogenic or modifying role in ALS. Accordingly, Mayuri became a "citizen scientist." She made a simple post on some ALS social media groups and multiple people responded. Not surprisingly, many SETX-US carriers had juvenile onset (<25 years) or early onset (<40 years old). One has 8 family members affected and no one has investigated this proband. People also had a variety of viruses ranging from EBV, COVID, herpes, chicken pox etc.

Graphic – Heterogeneity Example: SETX-VUS

Age Dx	fALS	VUS	Clin Var	DNA Change	Base Change	Amino Acid Change	Pathogenic?	Onset	Speed	Deceased	Survival (mos)	Trial	Other Genes	Ethnicity	Exposome History	Clinical History	Occupation	Comments
21	N	Y	N	c.3187	A>G	p.Lys1063Glu		UL LL	Fast	26	78	NurOwn		Caucasian	Repeated subconcussive hits; & Multiple concussions; football baseball & wrestling; Herbicides on ballfields; Pb exposure in utero?	EBV; Asthma; Immune probs; dozens fxs	College Student	preserved breathing & bulbar fx, sleeps laying flat w/o breathing devices & eats everything he wants.BIO sample in NurOwn trial. Highest allele frequency in South Asian populaton
35	N	Y	N	c.907	T>A	p.Ala969Ala			Slow	N		NP001		Iranian			MD	
32	N	Y	N	c.4663	C>G	p.Leu1555Val		LL	Slow	N			SOD1	Indian	Traveled internationally a lot		Govt Policy	Blood & CSF at Columbia. Dad died young so not known if a carrier
24	N							LL		MAiD 27				Caucasian				
36	N	Y	N	c.3456	T>G	p.Phe1152Leu		UL		40	56		ALS2		pesticides & herbicdes	Familly: PD & Schizophrenia	Landscaper	ALS2 c.2108 G>C (p.Arg703Thr) = AR (one copy) NIH Fischbeck did GWAS on decedent & 3/4 siblings. Grew up on farm in rural NY.
33	N	Y	Y	C.7427	C>A	p.Gly172-Gly175 del.	VUS	LL		N			FUS	Caucasian	Repeated subconcussive hits; concussions; hockey player			two SETX c.7427 VUS listed on ClinVar with different protein changes.
42	Y	N	Y	c.6838	A>G	p.Asn2280Asp	VUS	UL-LH LL-LL	Slow	N				Caucasian	Repeated concussions and sub-concussive hits in football and baseball. Heavy Metal exposure as A/C tech	PTSD-abuse. Severe foraminal stenosis	Metal Fab A/C duct company	8 maternal family members w ALS - 7 dx'd in 50s & died in 50s. Mother not sx. Grandfather had ALS but died of MI. 2 aunt 1 uncle, . GG & 3 siblings died of ALS. No one has studied the family.
59	N	Y	Y	c.7860	C>A	p.Ser2620Arg	VUS	LL		N				Caucasian				Speech, swallowing & breathing not initially affected

[254] Miller, M. S., Rialdi, A., Ho, J. S. Y., Tilove, M., Martinez-Gil, L., Moshkina, N. P., Peralta, Z., Noel, J., Melegari, C., Maestre, A. M., Mitsopoulos, P., Madrenas, J., Heinz, S., Benner, C., Young, J. A. T., Feagins, A. R., Basler, C. F., Fernandez-Sesma, A., Becherel, O. J., ... Marazzi, I. (2015). Senataxin suppresses the antiviral transcriptional response and controls viral biogenesis. Nature Immunology, 16(5), 485–494.

[255] Bennett, C. L., Dastidar, S. G., Ling, S. C., Malik, B., Ashe, T., Wadhwa, M., Miller, D. B., Lee, C., Mitchell, M. B., van Es, M. A., Grunseich, C., Chen, Y., Sopher, B. L., Greensmith, L., Cleveland, D. W., & La Spada, A. R. (2018). Senataxin mutations elicit motor neuron degeneration phenotypes and yield TDP-43 mislocalization in ALS4 mice and human patients. Acta Neuropathologica, 136(3), 425–443.

[256] Giannini, M., & Porrua, O. (2024). Senataxin: A key actor in RNA metabolism, genome integrity and neurodegeneration. Biochimie, 217, 10–19.

As such, a NurOwn Phase 4 biorepository is a win–win for researchers and patients alike. The ALS community needs a broad Phase 4 biorepository so researchers can explore the genetic variants that cause or contribute to early onset ALS. For those people with ALS who are still with us today, they also deserve a chance to live longer. With NurOwn, they can.

2. ALS VUS not Submitted to ClinVar

As in Mayuri's case above, some people with ALS are refused genetic testing because they don't have a known family history. Others get the genetic testing and find out that they have a Variant of Uncertain Significance (VUS). But that VUS often isn't reported to ClinVar by the testing company or by the neurologist who ordered the test. As such, Petitioners suspect researchers are missing the opportunity to evaluate whether a gene is pathogenic solely because it was never reported.

For example, someone in the NurOwn trial had an MAPT mutation classified as a VUS, but this variant is not listed on ClinVar as being associated with ALS. MAPT has been associated with a spectrum of related autosomal dominant neurodegenerative disorders including frontotemporal dementia (FTD), Pick disease, progressive supranuclear palsy 1 (PSNP1), collectively known as MAPT-related tauopathies. Additionally, this MAPT gene has preliminary evidence supporting a correlation with susceptibility to late-onset Parkinson's disease, and to many individuals with frontotemporal dementia (FTD) and Alzheimer's disease (AD). Most troubling is that it has been reported as associated with FTD, yet no one was compelled to report this person's results despite the concurrence of ALS and FTD.[257] A Phase 4 biorepository would no longer put the onus on an individual to remember to report the VUS.

3. Polygenic Risk Factors, VUS and Repurposed Therapies

Despite identifying over 40 ALS-associated genes, much of the heritability in sporadic ALS remains unexplained, requiring larger GWAS and multi-omics studies to change the future. A broad Phase 4 biorepository could help us identify VUS and polygenic risk factors that contribute to ALS and eventually may lead to the discovery of new or off-label therapies to treat ALS.

While approximately 10% of ALS cases are familial, linked to specific monogenic mutations, the majority are sporadic, with growing evidence suggesting a polygenic contribution, where multiple genetic variants collectively increase disease risk or modify ALS phenotype. Exposome factors may also interact with genetic predispositions to increase risk.[258]

---

[257] FTD co-occurs with ALS in approximately 10-15% of cases. About 5-25% of ALS patients develop full-blown FTD, while up to 50% may exhibit milder cognitive or behavioral symptoms associated with FTD. The prevalence varies due to genetic factors, particularly C9orf72 gene mutations, which are linked to 40% of familial ALS and 25% of familial FTD cases. In sporadic ALS, FTD is less common, affecting roughly 6-7% of patients.

[258] Bandres-Ciga, S., , ... & Singleton, A. B. (2019). Shared polygenic risk and causal inferences in amyotrophic lateral sclerosis. Annals of Neurology, 85(4), 470–481.

In this study led by Eva Feldman and Stephen Goutman of University of Michigan, the authors demonstrated that combining oligogenic (few large-effect variants) and polygenic (many small-effect variants) risk scores improves ALS prediction, highlighting the cumulative effect of multiple genetic variants alongside environmental exposures.[259]

Polygenic risk scoring (PRS) can help capture the complex genetic architecture of ALS -and support the integration of genetic and phenotypic data for early detection, as well as drug development and utilization of existing off-label therapies. Jonathan Cooper-Knock's recent study supports a model where ALS risk arises from the cumulative effect of common and rare variants across multiple genes, with pathways converging on motor neuron degeneration. It also notes that people with sporadic ALS often carry multiple low-frequency variants, contributing to disease heterogeneity.[260]

D. A Phase 4 Biorepository could Collect Exposome and Toxicology Data Missed by the old CDC Registry

Exposome data is not routinely collected in interventional drug trials and because it's not medically actionable, and the exposome is almost never discussed at ALS clinics unless you happen to be at University of Michigan, Dartmouth or Miami. Currently not enough is being done to investigate the exposome that plays a role in the six unique factors causing or contributing to each person's ALS. A Phase 4 biorepository would allow us to collect exposome data on thousands that researchers could then use AI to explore.

The possible causes of ALS are as heterogeneous as the genotypes and phenotypes. Professor Ammar Al-Chalabi of the UK has proposed the widely accepted six-factor Gene-Time-Environment hypothesis.[261] Derived from the Armitage-Doll model in cancer epidemiology research, he posits that ALS is a multistep process, requiring approximately six sequential biological events to trigger ALS onset.

This model suggests that ALS results from a combination of genetic and environmental factors accumulating over time, with incidence increasing exponentially with age. For familial ALS cases with large-effect mutations (e.g., C9ORF72, SOD1), fewer steps are needed, as these mutations may account for one or more steps. This hypothesis highlights the complex interplay of genetic predisposition, environmental exposures, and aging in ALS pathogenesis, suggesting that identifying these steps could guide targeted therapies.

[259] Jin, W., Boss, J., Bakulski, K. M., Goutman, S. A., Feldman, E. L., Fritsche, L. G., & Mukherjee, B. (2024). Improving prediction models of amyotrophic lateral sclerosis (ALS) using polygenic, pre-existing conditions, and survey-based risk scores in the UK Biobank. medRxiv.

[260] Zhang, S., Cooper-Knock, J., Shaw, P. J., et al. (2022). Genome-wide identification of the genetic basis of amyotrophic lateral sclerosis. Neuron, 110(6), 992–1008.e11.

[261] Al-Chalabi, A., Calvo, A., Chiò, A., Colville, S., Ellis, C. M., Hardiman, O., ... & Veldink, J. H. (2014). Analysis of amyotrophic lateral sclerosis as a multistep process: A population-based modelling study. The Lancet Neurology, 13(11), 1108–1113.

Recently in their OpEd for JAMA Viewpoint, Commissioner Makary and Dr. Prasad outlined five FDA priorities, one of which is exposome research.[262]

> *"Fresh new ideas are needed to address root causes and develop innovative approaches. At the FDA, we will examine the role of … environmental toxins, the introduction of which has paralleled the epidemic of chronic diseases… We will transition from a purely reactionary healthcare system to one that is proactive, intellectually curious about underlying causes, and financially aligned to promote health -- not just treat sickness."*

Two of the others relate to using big data and artificial intelligence. The approval of NurOwn with a mandatory post-marketing biorepository and exposome registry could be the innovative approach Dr. Makary referenced to advance the scientific understanding of ALS.

This 2017 study published in NeuroToxicology reviewed environmental risk factors associated with ALS.[263] It synthesizes epidemiological and experimental evidence linking ALS to factors such as heavy metals (e.g., lead, mercury), pesticides, electromagnetic fields, and physical trauma, including repetitive head injuries from activities like contact sports. The authors highlight that ALS is a multifactorial disease, with environmental exposures interacting with genetic and lifestyle factors to increase disease risk. These exposures may induce oxidative stress, mitochondrial dysfunction, and protein misfolding (e.g., TDP-43 aggregates), which are hallmarks of ALS pathology. The authors propose that these environmental insults may trigger or accelerate motor neuron degeneration in susceptible individuals.

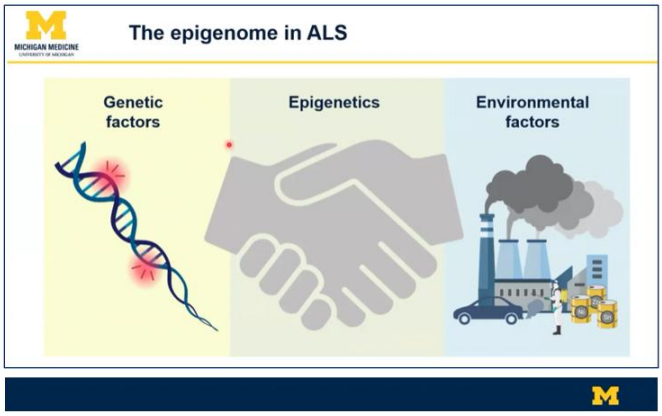
Three ALS clinics have led the exposome research in ALS: Elijah Stommel at Dartmouth; Walter Bradley at Miami; and Eva Feldman and Stephen Goutman of the University of Michigan. Recently, Dr. Goutman presented the exposome hypothesis on a recent NEALS webinar entitled *"Exposome and Epigenetic ALS Insights: How Exposures Alter ALS Risk and Progression."*

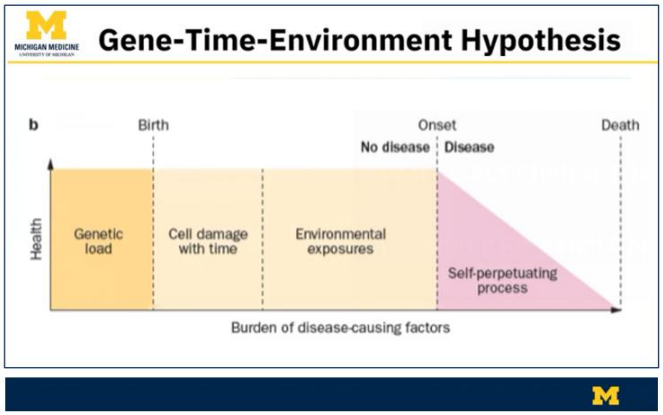
1. Gene-Time-Environment (GTE) Hypothesis

Al-Chalabi's GTE hypothesis posits that ALS results from the cumulative burden of disease-causing factors over an individual's lifetime, integrating genetic predisposition, environmental exposures, and the passage of time.

[262] Makary, M. A.; Prasad, V. (2025, June 10). Priorities for a New FDA. JAMA Viewpoints, 329(24), 2117–2118.
[263] Wang, M.-D., Little, J., Gomes, J., Cashman, N. R., & Krewski, D. (2017). Environmental insults: Critical triggers for amyotrophic lateral sclerosis. NeuroToxicology, 58, 110–123.

Graphic - Gene-Time-Environment Hypothesis





The model divides the disease process into distinct phases leading from health to disease onset and eventual death.

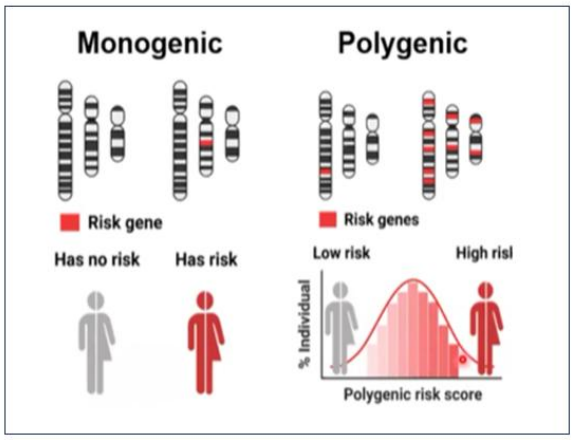
- Genetic Load (Birth to Early Life): At birth, individuals carry a baseline genetic susceptibility to ALS, represented by inherent genetic variants. This phase involves no immediate disease but establishes a foundational risk.

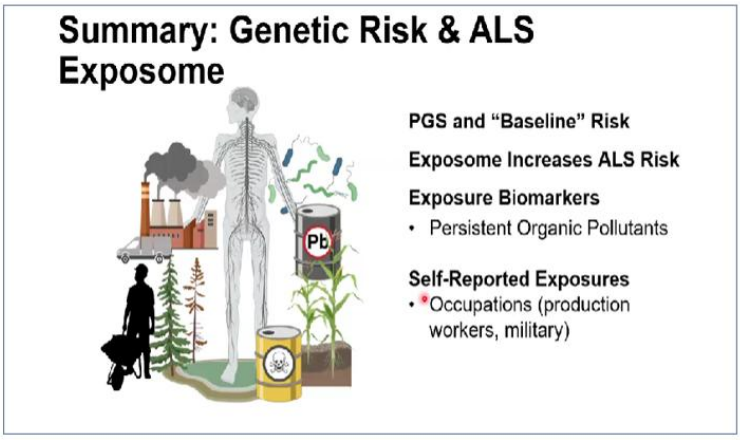
- Cell Damage with Time (Pre-Onset): Over time, cellular damage accumulates due to aging and other intrinsic factors, increasing the burden of disease-causing elements without yet triggering clinical disease.

- Environmental Exposures (Pre-Onset): Environmental factors (e.g., toxins, lifestyle, or infections) add to the burden, further elevating risk. The model suggests these exposures interact with genetic load over decades.

- Self-Perpetuating Process (Onset to Death): Once a threshold is crossed (disease onset), a self-sustaining pathological process begins, characterized by rapid neurodegeneration. This phase leads to a steep decline in health, culminating in death.

Graphic - Genetic Risk and ALS Exposome





2. ALS Clusters across the US

Currently there is no mechanism to report or track possible clusters of ALS. The CDC Registry does not track them. Likewise, there is no way to cross-match those clusters with the exposome to help identify factors that may be causing or contributing to ALS. So people in the ALS community started tracking communities, schools, industries and occupations with higher than normal incidence or prevalence.

These are some of the possible correlations discovered by Petitioners and other citizen scientists working with geospatial engineers and databases from the USGS and EPA.

- Petitioner Lesley Krummel - Walnut, IA
  Five unrelated people in her small IA farming town of 769 people had ALS. Mostly corn and soybean crops in the area. 1M; 4F. All diagnosed in their 50s. 1 bulbar and 4 limb onset. Four people lived within a few blocks of each other when growing up. All diagnosed before Lesley. All deceased but Lesley. (650/100,000)

- Petitioner Justin Rogers - Schaumburg, IL
  Two of approximately 500 high school classmates/teammates were diagnosed with early-onset ALS. Both died at 39 years old. (400/100,000)

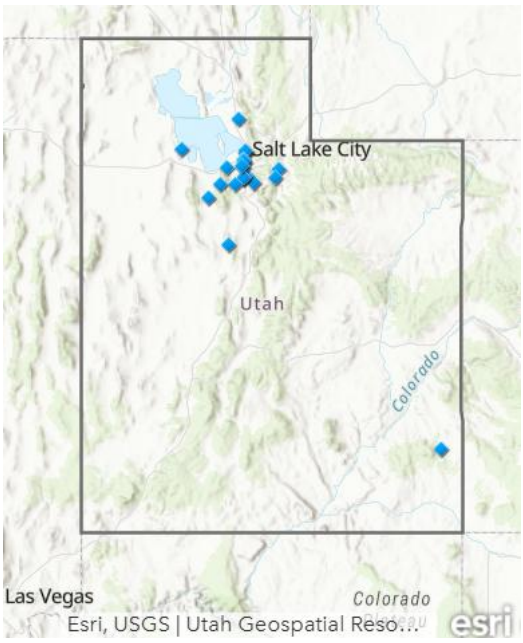
- Petitioner Jamie Berry - New Almaden, CA
  Mercury exposure from New Almaden mercury mines near San Jose, California. (See discussion below under Jamie's Berry's case study).

- Williams, CA - Six people in a town of 5,123 people were diagnosed with ALS. The town is in the Sacramento Valley, just downstream from the old mercury mines. It's an agricultural town that used to grow rice and row crops but has now shifted to orchards with almonds and walnuts mostly. (117/100,000)

- Hendersonville, NC - 7 people within a 1 mile radius have ALS. Town population of 15,500, but appx 840 people/sq mile. 19 Apple orchards. Apples are sprayed with a copper-based fungicide. Copper - zinc ratio is associated with SOD1 ALS. Three pesticides commonly used on apples: diphenylamine, Captan, and chlorpyrifos.[264]
- Scottsdale, AZ - 7 childhood classmates; 4 lived on same street. Attended Hohokam Elementary school and played in irrigated playgrounds. Hohokam was a Superfund site with TCE exposure in the groundwater from microchip plant. (1400/100,000)
- South Houston, TX - Two next door neighbors for 2 decades diagnosed with ALS. One born in 1946 with bulbar onset died in 2022; one born in the early 70s has limb onset just diagnosed. Superfund Site in the neighborhood was Brio refinery, whose primary toxic release was TCE.
- Boonton township, NJ - two neighbors who attended Boonton High in a Township population of 4,375. Boonton has several iron manufacturers and a Superfund site, the Pepe landfill (46/100,000)
- Hanover, PA - 7 people (4F, 3M) diagnosed with ALS in the small town including staff physician Annie Quinn. All live within 2 miles with a golf course in between. Town is 15,000 but population density is 4100/sq mile. (170/100,000)
- Petitioner Kade Simons - Cottonwood Canyon, and Salt Lake City, Utah
  Possible exposure to neurotoxins like lead from Emma Mine and associated smelters. Utah Senator John Curtis of Utah also mentioned the large number of constituents near SLC with ALS. Below is an EPA map showing Superfund sites in reuse in Utah.[265]

[264] Pesticides with the largest positive statistically significant associations in both the discovery and the validation studies and evidence of neurotoxicity in the literature were the insecticides carbaryl (OR 1.32 95 %CI 1.23–1.42) and chlorpyrifos (OR 1.25 95 %CI 1.17–1.33).

[265] U.S. Environmental Protection Agency. (n.d.). Superfund sites in reuse in Utah. https://19january2021snapshot.epa.gov/superfund-redevelopment-initiative/superfund-sites-reuse-utah_.html



Petitioners have identified over a hundred ALS clusters but no one has investigated them. Thus, we are asking the HHS for four things:

1) Make ALS a mandatorily reported disease;
2) Work with the CDC and EPA to establish a reporting system like VAERS so people with rare diseases can report possible clusters to be investigated;
3) Develop a mandatory exposome questionnaire and biorepository for anyone who gets access to an ALS therapy via accelerated or conditional approval
4) Fund a broad sibling study to investigate the Gene-Time-Environment hypothesis in people with juvenile or early onset ALS

3. ALS Clusters in the Military

Petitioners have identified several ALS clusters in the military. The ALS community has identified many other clusters in certain units and at certain bases that are discussed in the Exposome section below.

During their service, veterans are often exposed to environmental hazards such as burn pits, jet fuel, or cartridge-activated device (CAD) smoke; herbicides like Agent Orange; cyano-bacteria BMAA in waterways and Middle East soil;[266] neurotoxic chemicals like TCE; heavy metals like lead used in Red Lead paint; and other Superfund related toxins – leading to ALS being a presumptive "service-

[266] Metcalf JS, Richer R, Cox PA, Codd GA. Cyanotoxins in desert environments may present a risk to human health. Sci Total Environ. 2012 Apr 1;421-422:118-23.

connected" disease. Similarly, Gulf War Veterans have recounted their exposures to Congress:

> *"Gulf War troops were exposed to a host of toxic exposures often in combination including multiple low-level exposures to chemical warfare agents including from bombed munitions factories and detonated munitions bunkers. Experimental drugs mandated without informed consent like Pyridostigmine Bromide pills intended to help survive nerve agent exposure; inhalation of incredibly high levels of micro-fine particulate matter from the Kuwaiti oil well fire plumes; experimental vaccines like Anthrax, botulinum, and others; inhaled and ingested depleted uranium particulate matter; smoke from the daily burning of trash and feces; multiple pesticides; petroleum products and byproducts."*

Elijah Stommel's team at Dartmouth et al (2022) has advocated for the urgent need to act upon modifiable risk factors for military personnel who deserve enhanced protection during their years of service, not only for their short-term, but also long-term health:[267]

> *"There is a paucity of studies investigating environmental factors contributing to ALS in veterans and even fewer assessing their exposure using biomarkers. Herein, we discuss ALS pathogenesis in relation to a series of persistent neurotoxicants (often emitted as mixtures) including chemical elements, nanoparticles and lipophilic toxicants such as dioxins, polycyclic aromatic hydrocarbons and polychlorinated biphenyls. We propose these toxicants should be directly measured in veteran central nervous system tissue, where they may have accumulated for decades. Specific toxicants (or mixtures thereof) may accelerate ALS development following a multistep hypothesis or act synergistically with other service-linked exposures (e.g. head trauma/concussions). Such possibilities could explain the lower age of onset observed in veterans compared to civilians*."

The Gulf War serves as a notable case study when examining the connection between military service and ALS. Haley observed that 8 years postwar, 85% of the incident cases in Gulf War veterans were < 45 years of age.[268] **The observed incidence in young veterans increased from 1 to 5 cases per year** and was not explained by "a change in the interval from onset to diagnosis or by a change in the US population death rate of ALS in those aged < 45 years." The Military Medicine study also recognizes that these post 9/11 veterans are experiencing ALS onset at much younger ages.

[267] Re DB, Yan B, Calderón-Garciduenas L, Andrew AS, Tischbein M, Stommel EW. A perspective on persistent toxicants in veterans and amyotrophic lateral sclerosis: identifying exposures determining higher ALS risk. J Neurol. 2022 May;269(5):2359-2377.

[268] Haley RW. Excess incidence of ALS in young Gulf War veterans. Neurology. 2003;61(6):750–756.

Exemplifying the real-life implications of this early-onset statistic that no one is investigating:

- USN Prowler pilot Matt Bellina was diagnosed at 30 and medically retired at just 32 years old
- USN P-3 pilot Nick Warack was diagnosed at just 37 years old
- USAF F-15 fighter pilot Captain Cole Hollway was diagnosed at 27 years[269]
- USNA graduate & USMC Iraq War veteran, Tyler Tidwell, was diagnosed at 38 and died at 41 years old[270]

Additionally, Stommel (2022) discussed the increased risk among pilots and flight crew.

> *"The literature suggests that civilian airline flight attendants, pilots and navigators likewise have higher rates of this disease. Given that ALS prevalence has been found higher for Air Force service members relative to other military branches by certain studies, we speculate that exposure to jet exhaust may serve as a contributing factor."*

Because of the higher incidence among pilots, Petitioners also posit that hypoxia[271] during flights may also be a risk factor. In fact, one of the first ALS military clusters that the ALS community identified was in Gen. Mik's own squadron. USAF Academy graduate General Mik died of ALS in 2010. Less than a decade later, other C-141 pilots -- several who flew in his same squadron from Charleston (and Altus AFB) -- also died of ALS: USAF Academy graduate Major General Kip Self, Lt Col. Doug Hetzel, USAF Academy graduate Lt Col. Kreg Palko; Lt Col. Jim Howard; USAF Academy graduate Lt Col. Rick Nickel. Several other people working on their flight crews have also been diagnosed with ALS.

In his 2007 Congressional testimony General Mik first asked Congress to start investigating the causes for the marked increase in ALS among veterans. And When Congressman Henry Brown introduced General Mik for his VA testimony in 2007, he said General Mik served as:

> *"**We need an agency to step up to the plate and lead federal research into the cause of ALS** and how we can better improve its treatment. Most importantly, we need to begin these efforts now before more veterans, including General Mik, succumb to ALS."*

Over 17 years later and little progress has been made.

---

[269] Dunham, W. (2019, October 17). Resilience in the face of the reaper. U.S. Department of Defense. https://www.defense.gov/News/Feature-Stories/story/Article/1958302/resilience-in-the-face-of-the-reaper/

[270] Slater, C. (2020, December 11). Navy football's Tyler Tidwell fights ALS with toughness he learned on the field. The New York Times. https://www.nytimes.com/athletic/2247385/2020/12/11/tyler-tidwell-navy-football-als/

[271] Hypoxia can impair cognitive and motor performance, posing significant safety risks in aviation (Shaw et al., 2021). Training typically occurs in controlled environments to simulate high-altitude conditions (e.g., 18,000–25,000 ft) by reducing air pressure, or causing pilots breathe low-oxygen gas mixtures (e.g., 6–11.4% O_2) at sea level to mimic altitudes up to 25,000 ft (Leinonen et al., 2024; Varis et al., 2019). Evidence linking hypoxia to motor neuron damage is primarily from animal models. They suggest that prolonged or severe oxygen deprivation can disrupt motor neuron structure and function, particularly through demyelination or axonal damage. However, no direct studies link hypoxia tto motor neuron damage.

4. Concussions and Repeated Sub-concussive TBIs

A Phase 4 biorepository and AI could explore the possible connection between ALS and traumatic brain injuries. Many young athletes who have had concussions or repeated sub-concussive hits have been diagnosed with ALS including Petitioners Eric Stevens (28-NFL and NCAA football); Kade Simons (21-NCAA baseball; high school football and wrestling); Josh Smith (29-HS football); Matt Klingenberg (32-HS football and wrestling); Ryan May (21-NCAA soccer); Thurman Maynard (36-HS football and motorcycles); Justin Rogers (35-NCAA hockey and HS football); Tyler Tidwell (34-USNA football) and Petitioner Nick Warack (37-HS football & Navy rugby). As you can see, their ALS diagnoses occurred decades earlier than normal.

The CDC estimates that 1.6 to 3.8 million concussions occur each year in the United States, primarily from sports and recreational activities.[272] In 2020, approximately 214,110 TBI-related hospitalizations were recorded, with concussions being the most common form of mild TBI.[273] Sports-related concussions are significant, with around 300,000 occurring annually among high school and collegiate athletes, particularly in contact sports like football.[274]

In a 2021 study published by Dan Daneshvar of Harvard, Thor Stein of the VA, along with Chris Nowinski and Robert Cantu of the Concussion Legacy Foundation, and Ann McKee of BU's CTE Center, the authors concluded that NFL players had a 4x higher risk of ALS.[275] The researchers hypothesize that repetitive sub-concussive head impacts and traumatic brain injuries, common in NFL play, may contribute to this elevated risk, though clinical data on such exposures were unavailable.
This population-based study confirmed that 38 NFL players were diagnosed with ALS, and 28 died, primarily from ALS-related complications. Players with ALS had longer NFL careers than those without, suggesting an association between duration of play and ALS risk. Several well-known NFL players have been diagnosed or died of ALS: Steve Gleason (S), Tim Green (LB/DE), OJ Brigance (LB); Tunch Ilkin (OL); Dwight Clark (WR); Rickey Dixon (DB); Sonny Gordon (DB); Matt Hazeltine (LB); Steve McMichael (DT); Fred McNeill (LB); Tim Shaw (LB); Kevin Turner (FB); Bob Waters (QB); and of course, Lou Gehrig played fullback with Columbia before signing with the Yankees.

Similarly professional rugby players have a 15x increased risk. A study in The BMJ[276] analyzed health outcomes of 412 former Scottish international male rugby players compared to 1,236 matched controls over an average of 32 years. The study found that former rugby players had a risk of developing MND up to **15 times higher** and attributed this increased risk to repetitive head impacts

[272] Centers for Disease Control and Prevention. (2011). The epidemiology of sport-related concussion. Clinics in Sports Medicine, 30(1), 1–18.
[273] Centers for Disease Control and Prevention. (2023). Get the facts about TBI. https://www.cdc.gov/traumatic-brain-injury/data-research/facts-stats/
[274] Gessel, L. M., Fields, S. K., Collins, C. L., Dick, R. W., & Comstock, R. D. (2007). Concussions among United States high school and collegiate athletes. Journal of Athletic Training, 42(4), 495–503.
[275] Daneshvar, D. H., Mez, J., Alosco, M. L., Baucom, Z. H., Mahar, I., Baugh, C. M., Valle, J. P., Weuve, J., Paganoni, S., Cantu, R. C., Zafonte, R. D., Stern, R. A., Stein, T. D., Tripodis, Y., Nowinski, C. J., & McKee, A. C. (2021). Incidence of and mortality from amyotrophic lateral sclerosis in National Football League athletes. JAMA Network Open, 4(12), Article e2138801.
[276] Russell, E. R., Mackay, D. F., Stewart, K., MacLean, J. A., Pell, J. P., & Stewart, W. (2022). Neurodegenerative disease risk among former international rugby union players. Journal of Neurology, Neurosurgery & Psychiatry, 93(12), 1262–1268.

and traumatic brain injuries (TBIs) inherent in rugby. The authors called for "dramatic changes" in the sport, such as reducing contact training and match frequency to mitigate brain injury risks.

In a recent twin study of two collegiate soccer players made an interesting observation about concussions and the ERBB pathway. (Stahl 2022).[277] Collegiate soccer player with TBI. The authors used PBMCs to measure transcriptional changes/differences with twins with and without TBIs.
A pair of monozygotic twins were enrolled as part of a larger study of concussion biomarkers among collegiate athletes. During the study, Twin A sustained a sports-related concussion (SRC), allowing comparison of mRNA expression to the non-concussed Twin B. Twin A clinically recovered by Day 7. mRNA expression was measured pre-injury and at 6 hours and 7 days post-injury.

> *"Among 38,000 analyzed genes, important changes were identified in 153 genes. The ErbB (epidermal growth factor receptor) signaling pathway was identified as the top transcriptional network from pre-injury to 7 days postinjury. Genes in this pathway with important transcriptional changes included epidermal growth factor (2.41), epiregulin (1.73), neuregulin 1 (1.54) and mechanistic target of rapamycin (1.51). In conclusion, the ErbB signaling pathway was identified as a potential regulator of clinical recovery in a MZ twin pair discordant for SRC*."

(See detailed discussion about the ERBB pathways in Jamie Berry's case study below).

No one in the US is routinely collecting this concussion data for ALS researchers to study. It sits in a silo. A Phase 4 biorepository could help remedy that by collecting medical history data on thousands of people with ALS; and thus, it could help explore the hypothesis about the connections between ALS and repeated sub-concussive hits.

5. Case Study: Kade Simons

Petitioner Kade Simons exemplifies the urgent need for a robust Phase 4 biorepository to investigate the Gene-Time-Environment role in causing his ALS. Kade defied the "time" portion of the hypothesis because he was diagnosed with ALS at just 21 years old. Did his SETX-VUS play a role in modifying his expression? Because he never had his full genome sequenced, it is unknown what other polygenic risk factors he may have had.

As discussed above, Kade had multiple concussions early in life along with repeated sub-concussive exposures throughout his athletic career. He also had possible in utero exposure to neurotoxins like lead and arsenic from Emma Mine and associated Flagstaff and Davenport smelters. Not knowing of the risk, the Simons family lived near the Superfund site when Kandy was in her 2nd & 3rd trimester with Kade. Kade had dozens of broken bones throughout his life affirming likely osteoporotic fractures from lead exposure

277

The EPA's Superfund site profile confirms the Davenport and Flagstaff Smelters site, located 15 miles southeast of Salt Lake City at the mouth of Little Cottonwood Canyon, was contaminated with lead and arsenic from smelting operations in the 1870s. The cleanup efforts included the removal of 33,000 cubic yards of lead- and arsenic-impacted soils from residential properties and 7,100 tons from commercial and undeveloped land in 2011. The site was deleted from the National Priorities List (NPL) in 2018, with ongoing monitoring. The EPA notes lead's health risks to sensitive populations, including pregnant women and children under 7, and updated lead screening levels in January 2024. **Petitioners are aware of no study that has investigated the correlation between possible in utero exposures and ALS.**[278]

Kade's other hypothesized exposures in his young life may have included: exposures to pesticides and herbicides as a child when rolling around in the grass at minor league ballparks; in utero exposure to jet fumes when his mom was working as a flight attendant; and contracting the Epstein-Barr virus. Kade's mom reported that Kade had a lifetime of immune dysregulation.

-

The Epstein-Barr virus (EBV) is a ubiquitous virus that has been hypothesized to contribute to neurodegenerative diseases like Parkinson's and ALS through mechanisms involving immune dysregulation and neuroinflammation. A study by Caggiu et al. (2016) suggested that EBV's latent infection may trigger autoimmune responses, potentially leading to neuronal damage in susceptible individuals, with molecular mimicry between EBV proteins and neuronal components as a proposed pathway. Similarly, research by Ferraccioli et al. (2010) indicated that EBV reactivation could exacerbate inflammatory processes in the central nervous system, potentially accelerating neurodegenerative processes in diseases like ALS.[279] While these studies provide compelling hypotheses, definitive causal links remain elusive, necessitating further research to elucidate EBV's role in ALS pathogenesis.

A Phase 4 biorepository and exposome database could help researchers identify ALS clusters, then use AI to investigate possible causal links, and then study the iPSCs of people with possible subtypes associated with those heterogenous exposomes.

[278] Agency for Toxic Substances and Disease Registry. (2005, April 5). Public health assessment: Davenport and Flagstaff smelters, Bauer, Salt Lake County, Utah. https://www.atsdr.cdc.gov/HAC/pha/DavenportFlagstaff040505-UT/DavenportFlagstaff040505-UT_pt1.pdf

[279] Ferraccioli, G., Mecchia, M., & Zanusso, G. (2010). Epstein-Barr virus and neurological diseases. Journal of Neurovirology, 16(3), 189–196.

6. Case Study: Jamie Rose Berry

Petitioner Jamie Berry exemplifies the urgent need for a robust Phase 4 biorepository to identify polygenic and oligogenic risk factors in ALS, as well as the exposome contributing to ALS.[280] Jamie was diagnosed with sporadic ALS and carries two low-frequency variants of uncertain significance (VUS) identified by Invitae: ERBB4 and HFE.[281] These variants are not currently listed in ClinVar as associated with ALS, and their potential pathogenic role remains unconfirmed.

Petitioners hypothesize that Jamie's case also exemplifies the possible Gene-Time-Environment theory. Jamie's HFE mutation, her high levels of manganese, coupled with her seventeen years of childhood exposure living downstream from the New Almaden mercury mines and her persistent exposure to pesticides such as 2-4D should have warranted an investigation into how or if her exposome may have contributed to her ALS.

While a theoretical connection exists—possibly through disrupted metal transport or increased oxidative stress—we can't draw any conclusions without robust data and detailed studies. But if "citizen scientists" could find these hypothesized connections, imagine what we could discover with AI analyzing a disease-wide database with GWAS, biorepository, exposome history and geospatial mapping.

a. Jamie's Exposure to Mercury Mines and Smelters

Stommel (2022) summarized that mercury (Hg) exposure is potentially a risk factor for ALS.

- Hg was elevated in the brain of seven ALS patients compared to controls
- Higher toenail Hg levels in ALS patients compared to controls
- Hg is associated with increased risk in several studies
- Case reports of Hg poisoning demonstrated convincing ALS-like, clinical symptoms
- In mutant SOD1 ALS mice, Hg accumulates in spinal neurons
- Rats exposed to methylmercury (2 mg/kg/day) exhibited ALS-like neurological effects
- In vitro proteomics studies reveal that methylmercury exposure causes electron transport chain dysfunction, oxidative stress and ubiquitin proteasome system impairment
- Methylmercury neurotoxicity may also involve glutamate dys-homeostasis and excitotoxicity an ALS-linked mechanisms that could be relevant to the multi-stage hypothesis of ALS

In this study, Bailey (2017) found that chronic low-dose methylmercury exposure significantly accelerated the onset of ALS-like phenotypes, including motor neuron degeneration and paralysis.

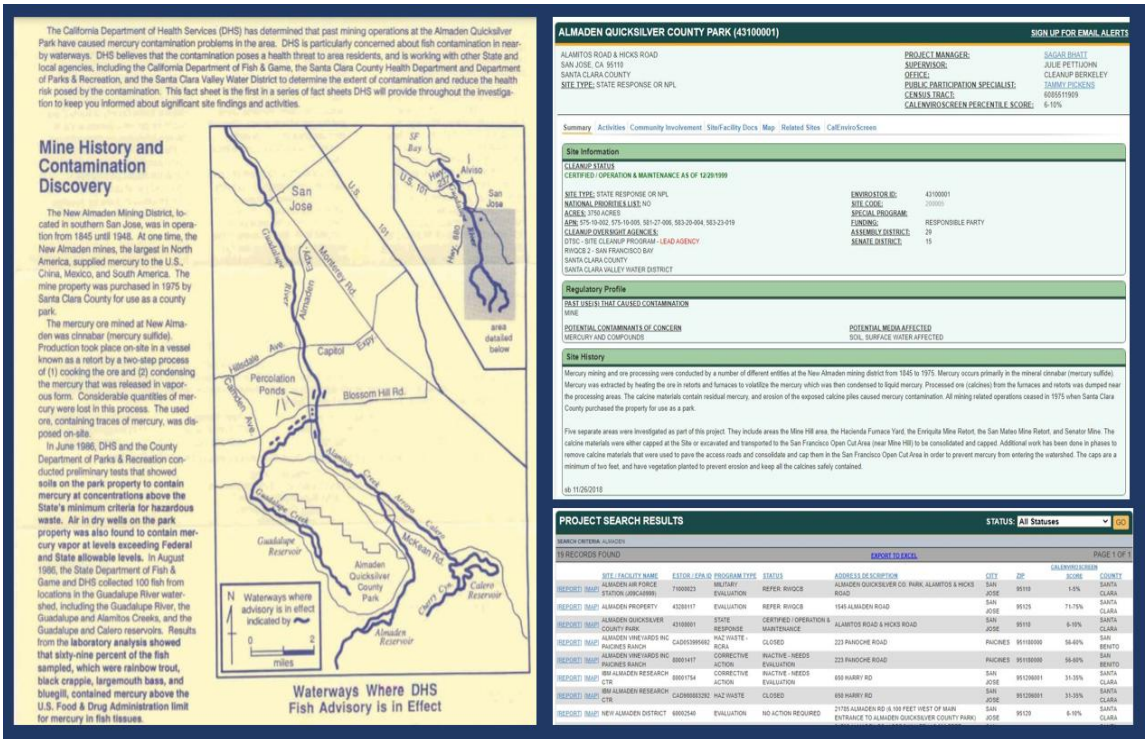
---

[280] Iacoangeli, A., Dilliott, A. A., Al Khleifat, A., Andersen, P. …. Glass, J. D., Gotkine, M., Lerner, Y., Hardiman, O.,… Pinto, S., … Farhan, S. M. K. (2025). Oligogenic structure of amyotrophic lateral sclerosis has genetic testing, counselling and therapeutic implications. Journal of Neurology, Neurosurgery & Psychiatry. Advance online publication.

[281] Feldman, E. L., Goutman, S. A., Petri, S., Mazzini, L., Savelieff, M. G., Shaw, P. J., & Sobue, G. (2022). Amyotrophic lateral sclerosis. The Lancet, 400(10360), 1363–1380.

The study highlights mechanisms like calcium-mediated glutamate excitotoxicity, where methylmercury disrupts calcium homeostasis, leading to neuronal damage.

Jamie Berry believed mercury exposure from New Almaden mercury mines near San Jose, California.[282] Throughout her childhood, she played in mercury-contaminated reservoirs and creeks and drank well water also contaminated by the mines. The New Almaden Quicksilver mine had been active since 1846 and produced 84 million pounds of mercury, making it the largest mercury-producing mine site in the US. In the 1980s, the mine and smelters were declared a California Superfund site, with cleanup beginning in the 1990s. But that ongoing mercury poisoning persisted for decades as mercury leached into the water supply including into the Guadalupe River watershed and San Francisco Bay.[283] Jamie moved back to her beloved ranch in 2018 and her ALS symptoms started in late 2019.



[282] The New Almaden mines, operational from the 1840s to 1976, produced over 83 million pounds of mercury, making them one of the most productive mercury mines in the U.S. Miners faced hazardous conditions, with exposure to mercury vapors during cinnabar roasting and poor ventilation leading to symptoms like tremors, cognitive decline, and respiratory issues. The New Almaden site, now part of Almaden Quicksilver County Park, is a designated Superfund site due to extensive mercury contamination in soil, sediments, and water. Studies by the USGS and the EPA confirmed that mercury from mine tailings continues to pollute the Guadalupe River watershed and San Francisco Bay, with sediment mercury levels in some areas reaching 10 ppm after heavy rains—five times higher than typical bay levels. Methylmercury bioaccumulation in fish has led to consumption advisories, with warning signs posted along affected waterways.

[283] Fagan, K. (2007, Feb 1). Tracking a toxic trail: Long-closed mine in Santa Clara County is still polluting waterways. SFGate.

b. Jamie's HFE Mutation, Manganese and Heavy Metal Exposures

The HFE mutation is significantly associated with hemochromatosis, which may also be associated with ALS and other neurodegenerative diseases. Interestingly, Petitioner Jamie Berry's functional medicine doctor noted her extremely high levels of manganese.

The HFE mutation is strongly linked to hemochromatosis (an iron overload disorder), and extremely high levels of manganese could involve disruptions in metal homeostasis that exacerbate neurodegenerative processes.[284] The HFE gene, particularly the H63D variant, is known to influence iron regulation, and research suggests it may also affect the handling of other metals like manganese due to shared transport mechanisms in the brain.[285] Manganese, a neurotoxic metal, can accumulate in neural tissues when its uptake or efflux is impaired, potentially worsened by HFE mutations that alter cellular metal balance. Studies have indicated that HFE mutations might increase susceptibility to manganese accumulation, as seen in animal models where mice showed altered manganese distribution after exposure, hinting at a possible link to oxidative stress and neuronal damage—key features in ALS pathology.[286]

Imagine using AI to create a Heat Map of the ALS exposome. That's when we can start proactively identifying the causes of ALS to minimize those exposures, but also to test hypotheses if different exposome groups respond differently to drugs targeting different biological pathways.

c. The Science of ErbB4 and NRG1

Jamie identified another person with ALS who carries a different ERBB4 variant and a CHCHD10 variant, as identified by Prevention Genetics; the latter encodes a mitochondrial protein potentially linked to ALS2, though this specific variant is not represented in Project MinE data.[287] Both cases suggest a possible oligogenic contribution to ALS risk, highlighting the need for expanded GWAS to validate these variants' pathogenicity and inform future therapeutic strategies.

- Jamie - ERBB4 c.3416 G>A (p.Arg1139Gln) and HFE c.187C>G (p.His53Asp)[288]
  46 yr old Caucasian female of Irish & Portuguese descent. (Invitae).
- Brian - ERBB4 c.1088A>G (p.Asn363Ser) & CHCHD10 c.221G>A (p.Ser74Asn)
  45 yr old Caucasian Male. (Prevention Genetics).

[284] Wang, D., & Connor, J. R. (2017). The role of HFE gene mutations in neurodegenerative diseases: A review. Neurological Sciences, 38(10), 1755–1762.
[285] Nandar, W.. (2011). HFE gene variants affect iron in the brain. Journal of Neurochemistry, 116(2), 293–300.
[286] Wang, X., Li, G. J., & Zheng, W. (2015). Manganese-induced oxidative stress and neurotoxicity: Implications for neurodegenerative diseases. Environmental Toxicology and Pharmacology, 39(2), 645–654.
[287] Bannwarth, S., Ait-El-Mkadem, S., Chaussenot, A., Genin, E. C., Lacas-Gervais, S., Fragaki, K., … & Paquis-Flucklinger, V. (2014). A mitochondrial origin for frontotemporal dementia and amyotrophic lateral sclerosis through CHCHD10 involvement. Brain, 137(Pt 8), 2329–2345.
[288] Li M, Wang L, Wang W, Qi XL, Tang ZY. Mutations in the HFE gene and sporadic amyotrophic lateral sclerosis risk: a meta-analysis of observational studies. Braz J Med Biol Res. 2014 Feb;47(3):215-22. doi: 10.1590/1414-431X20133296

In this 2022 study, Al Khleifat and Al-Chalabi found that ErbB4 was associated with not just an increased risk of ALS but specific genotypic patterns of expression. Over 71% of people with respiratory onset ALS & 46% of people with limb onset had an ErbB4 insertion compared with 25% of the general population.[289]

ErbB4 is a predominant receptor for Neuregulin-1 (NRG1) that plays a significant role in the pathogenesis of ALS. **NRG1 is a neurotrophic factor critical for the development, maintenance, and repair of the nervous system, particularly at motor neurons and neuromuscular junctions (NMJs). It belongs to the epidermal growth factor (EGF)-like family with ERBB4 (designated ALS19 in familial ALS) being its predominant receptor.**

ERBB proteins are in the cell membrane and transmit signals into the cell. The ERBB pathway regulates cell proliferation, migration, differentiation, apoptosis, cell motility, and neuronal development. The ERBB pathway is also related to several other neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and multiple sclerosis.[290] Several papers have reported that ERBB4 mutations are related to ALS pathogenesis. ErbB4 and NRG1 regulate synaptic structure and function. ErbB4 is expressed in interneurons, and less abundantly, in cortical pyramidal cells and in spines. ErbB4 overexpression increases spine density, area, and excitatory synaptic transmission.[291]

Reduced levels of NRG1 have been found in ALS patients. In a study related to the therapeutic role of NRG1 in SOD1 ALS, the authors wrote that NRG1 is a neurotrophic factor highly expressed in motor neurons and neuromuscular junctions which support axonal and neuromuscular development and maintenance. Thus, **increasing NRG at the spinal cord is a promising approach for promoting motor neuron protection & functional improvement in ALS**.[292]

It's not lost on Petitioners that yet another study unrelated to NurOwn has found that upregulating neurotrophic growth factors could be helpful to treat ALS.

i. Zonisamide Therapy for Rare ErbB4 Mutation?

Obviously there are no therapies in development targeting the rare ERBB4 mutations. But this 2013 study regarding ERBB4 suggested that NRG agonists might be off-label options:

---

[289] Al Khleifat, A., Iacoangeli, A., Jones, A. R., van Vugt, J. J. F. A., Moisse, M., Shaw, P. J., ... Al-Chalabi, A. (2022). Structural variation analysis of 6,500 whole genome sequences in amyotrophic lateral sclerosis. Genomic Medicine, 7(1), 8.
[290] Kwon Y, Kang M, Jeon YM, Lee S, Lee HW, Park JS, Kim HJ. Identification and characterization of novel ERBB4 variant associated with sporadic amyotrophic lateral sclerosis (ALS). J Neurol Sci 2024;457:122885. doi:10.1016/j.jns.2024.122885
[291] Li, B., Woo, R.-S., Mei, L., & Malinow, R. (2007). The neuregulin-1 receptor ErbB4 regulates dendritic spine density and excitatory synaptic transmission. Neuron, 54(4), 583–597.
[292] Modol-Caballero, G., Garcia-Lareu, B., Verdaguer, E., Sánchez-Brualla, I., Navarro, X., Pallàs, M., & Camins, A. (2021). Neurotrophic factor NRG1 mitigates motor deficits and pathology in the female SOD1G93A mouse model of ALS via multiple molecular mechanisms. Molecular Therapy - Methods & Clinical Development, 20, 138–150.

"The disruption of the neuregulin-ErbB4 pathway is involved in the pathogenesis of ALS and potentially paves the way for the development of innovative therapeutic strategies such as using NRGs or their agonists to upregulate ErbB4 functions."

(Takahashi, et al 2013).[293] Al-Chalabi (2022) found that a growth factor, NRG1 was implicated in ALS pathogenesis:

*"Pathological axoglial signaling by the glial **growth factor** neuregulin-1 leads to slow propagation of neuroinflammation resulting in neurodegeneration up and down the spinal cord; **drugs that block neuregulin-1 signaling could slow or halt the disease**.*

Parkinson's drug, zonisamide, upregulates NRG1. It's been on the market for 20 years for both epileptic seizures & now Parkinson's. Thus, it has a long safety profile and a low cost of $6.99 per month.

A 2015 Japanese study found that zonisamide upregulates NRG1, enhances neurite elongation and regeneration in the primary spinal motor neurons. Additionally, zonisamide induced mRNA expression of nerve growth factors (BDNF, NGF, and neurotrophin-4/5), and their receptors. And, post sciatic nerve graft, zonisamide was protective against denervation-induced muscle degeneration and increased gene expression at the neuromuscular junction. Plus, zonisamide was also protective against oxidative stress-induced cell death of primary motor neurons.[294]

Based on these studies, Jamie reached out to top ALS researchers in the US and the UK to see if zonisamide could help her. One responded immediately and offered to forward the information to his colleague who runs the ALSoD website that collates the various mutations reported in ALS genes.

"Thank you for this very detailed, thoughtful and thought-provoking email. In terms of Zonisamide, that is a fascinating idea. As you say, it upregulates the NRG1/ERB pathway. The difficulty is knowing if the ERBB4 mutations result in a loss of function and if that is what is driving the disease. Every dominant ALS mutation so far seems to work by gain of a novel function rather than a loss of function.
Thus, upregulating ERBB4 might then have the reverse effect to what is intended since you would potentially be increasing levels of the mutated protein with its aberrant function. … If ERBB4 is indeed an ALS risk gene (our structural variant analysis strongly suggests it is), any scientific work needs replication and support from other methods as you know."

[293] Takahashi Y, Fukuda Y, Yoshimura J,... Elenius K, Rouleau GA, Fujiyama A, Morishita S, Goto J, Tsuji S. ERBB4 mutations that disrupt the neuregulin-ErbB4 pathway cause amyotrophic lateral sclerosis type 19. Am J Hum Genet. 2013 Nov 7;93(5):900-5. doi: 10.1016/j.ajhg.2013.09.00

[294] Yagi, H., Ohkawara, B., Nakashima, H., Ito, K., Tsushima, M., Ishii, H., ... Tani, J. (2015). Zonisamide enhances neurite elongation of primary motor neurons and facilitates peripheral nerve regeneration after nerve injury. Experimental Neurology, 274(Pt B), 181–190.

Another geneticist said:

> *"ErbB4 is a very large gene so it is hard to say if these particular variants are disease causing or how they might affect the protein. Because I don't know levels of neuregulin signaling that are potentially impacted by these variants, I can't say if zonisamide would be effective or not. I am interested in ErbB4 and there is an interesting new study connecting this gene to respiratory onset ALS. My lab has found that this gene is expressed in the diaphragm innervating motor neurons."*

ii. ErbB4 - Loss of Function Variants

When Jamie reached out to see if zonisamide could help her, she was told: (a) first they needed to verify if her mutation was pathogenic; (b) then they needed to see if Jamie's variant related to a toxic loss of function or toxic gain of function; and then (c) they could test if zonisamide would work in double-blinded randomized controlled clinical trials. Until then, they couldn't determine if zonisamide would help or hurt Jamie. All of that would have taken YEARS that Jamie didn't have. On November 9, 2022, Jamie died waiting for the science to catch up with the destruction ALS was imposing on her body.

Then in 2024 and 2025, two studies found that ErbB4 was caused by a toxic loss of function, which means zonisamide MIGHT be helpful for some people with rare ErbB4 variants.

In 2024, Kwon reported the case of a 53-year-old Korean man with ALS with a novel highly pathogenic variant, c.2116 A > G, p.Asn706Asp (N706D) in the ERBB4 gene. Researchers found that the ERBB4 mutation showed reduced phosphorylation in the membrane fraction, meaning that **this ERBB4 mutation causes loss of function.** Additionally, knock-down of ERBB4 caused cellular toxicity in primary cortical neurons. These findings suggest that **mutations in ERBB4 lead to loss of ERBB4 function and motor neuron death in ALS**.[295]

The 2025 study[296] by Shen et al. investigated the prevalence and clinical significance of ERBB4 gene variants in Chinese patients with ALS. The authors identified 14 missense variants and 6 splice region variants in 23 unrelated patients, with four variants classified as damaging (p.R782P, p.M799T, p.R847C, and p.S997R). The splice variant c.1490-3C > T, associated with a 50% reduction in ERBB4 mRNA expression, was maternally inherited by a male ALS patient, while its presence in his asymptomatic mother suggested the involvement of potential genetic modifiers.

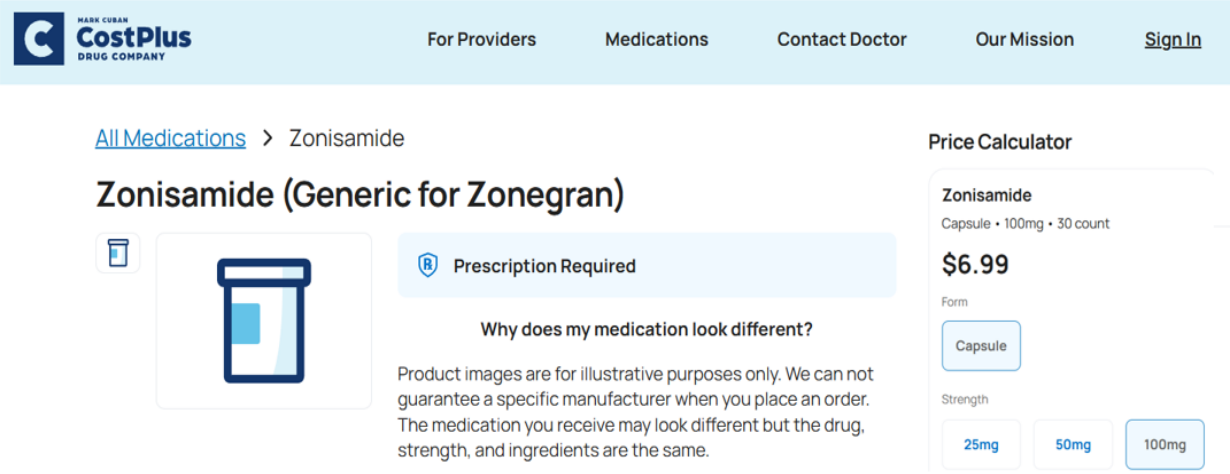
The authors concluded that ERBB4 variant carriers demonstrated earlier disease onset compared to non-carriers (46.9 vs. 52.6 years)(p = 0.015), though survival duration remained comparable. Meta-

[295] Kwon Y, Kang M, Jeon YM, Lee S, Lee HW, Park JS, Kim HJ. Identification and characterization of novel ERBB4 variant associated with sporadic amyotrophic lateral sclerosis (ALS). J Neurol Sci 2024;457:122885.
[296] Shen D, Yang X, He D, Zhang K, Liu S, Sun X, Li J, Cai Z, Liu M, Zhang X, Liu Q, Cui L. Genetic analysis of ERBB4 gene in Chinese patients with amyotrophic lateral sclerosis: a single-center study and systematic review of published literature. Front Aging Neurosci 2025;17:1584541.

analysis revealed a pooled variant frequency of 0.83% in ALS patients globally, with notable ethnic differences (1.36% in Chinese, 0.66% in European, and 1.44% in American populations.

The findings establish the prevalence of ERBB4 variants in ALS across different populations and suggest their potential role as disease modifiers, particularly affecting the age of onset. The study also highlights the need for advanced genetic and functional studies to inform precision medicine approaches for this devastating disease – especially those with rare variants that are unlikely to be investigated by Big Pharma because of the small disease population.

The cost of the generic drug that may have helped Jamie live longer is just $6.99 per month. Who will fund that study? Who would agree to be on a placebo instead of just buying it?



Jamie's tragic story reminds us why we cannot continue to let it take a decade or more to corroborate whether a rare variant is pathogenic. We must use AI to analyze data from a large GWAS biorepository. Our regulatory system must find a way to discover and expedite investigation of off-label and repurposed drugs. Then we should be able to quickly test repurposed therapies on iPSCs from that heterogeneous ALS population.

Petitioners imagine a personalized medicine world where Jamie's iPSCs could have been grown into a motor neuron along with other iPSCs from other ErbB4 mutation-carrying ALS patients. Then zonisamide could have been tested in the dish to see how or if it slowed or arrested the progression of their ALS.

A NurOwn Phase 4 biorepository could be the first step to making that personalized medicine approach a reality by collecting data and performing GWAS on tens of thousands of Americans with ALS.; Petitioners ask the FDA to consider this benefit when deciding whether to approve NurOwn with a mandatory Phase 4 biorepository.

7. Prospective Studies

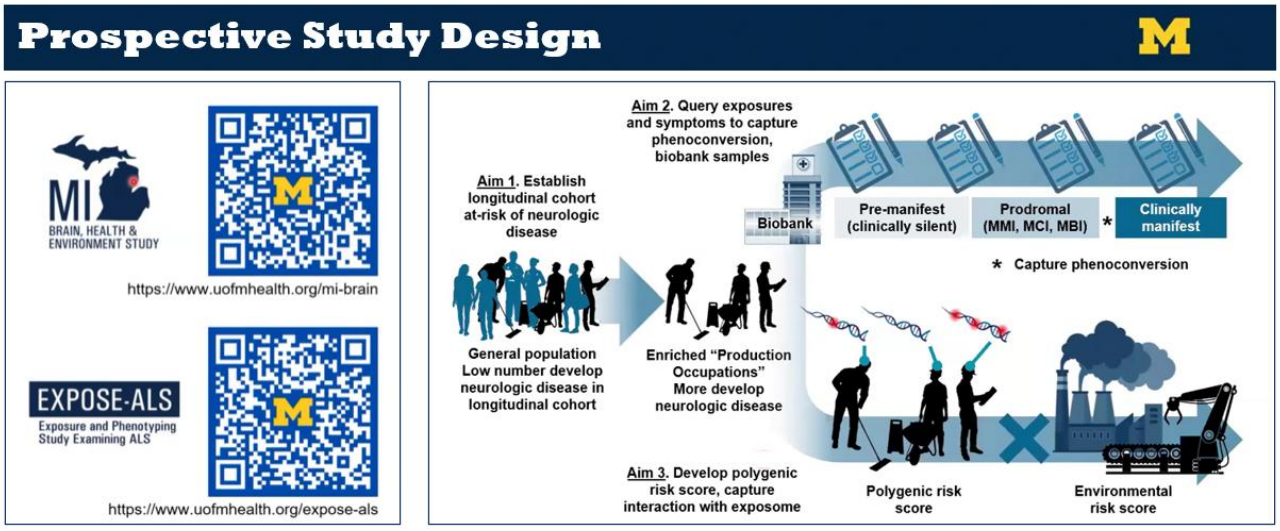
Retrospective studies are important to help generate hypotheses about the possible environmental exposures causing or contributing to ALS. But as Dr. Goutman and Dr. James Berry discussed in the NEALS webinar above, those studies are impacted by recall bias. One way to overcome that is with geospatial studies that collect data from people with ALS and use AI to compare it to databases that track environmental toxins like the EPA's Toxic Release Inventory or Superfund sites.

As such, to ensure researchers are drawing conclusions based on gold standard science, we need to create and fund prospective longitudinal studies that track thousands, not just hundreds, of people with ALS. A broad Phase 4 biorepository could do just that. With Accelerated Approval, the FDA could stipulate that people who receive NurOwn must participate in a mandatory biorepository and exposome database.

From those databases, the goal would be to allow researchers to use artificial intelligence and machine learning, along with geospatial mapping, to identify other ALS clusters and cross-match them to EPA Superfund sites and TRI database sites to develop possible exposome hypotheses. What is unique about the people who got ALS compared to those who didn't, despite the same exposome? Will people with different exposome histories respond differently to ALS therapies targeting different biological pathways?

You can see from the graphic below that the University of Michigan already has two studies that could be used as templates to design a large-scale, exposome natural history database.

Graphic - Prospective ALS Exposome Natural History Database



Unlike the graphic above, an ALS Exposome database would not be limited to ”enriched Production Occupations” but instead could collect data from all people receiving NurOwn, including:

- Occupational history
- Hobby history
- Sports history
- Social history
- Address History - supported by Census and EPA data to do geospatial mapping

This US ALS Exposome database would allow us to catch up and surpass the data captured in the large, homogenous natural history databases in the EU and other socialized medicine countries. It would enable us to gather data from underrepresented homogenous populations that are highly affected but understudied such as people of MENA or Indian ethnicity, like Petitioners Shahriar Minokadeh and Mayuri Saxena. And because the exposome data would be coupled with a broad biorepository – including GWAS and CSF – it would dwarf both the quantity and the quality of data from the current ALS Registry run by the CDC’s ATSDR or in any other natural history database in the US.

From this open-access dataset, researchers could then use AI to identify at-risk occupations etc and to calculate both a polygenic risk score and an environmental risk score for everyone who submitted samples. It would allow researchers in the future to assess the genome-exposome interaction.

To be clear, Petitioners are not suggesting that Brainstorm be required to analyze this data, nor to fund the collection of this data. Rather, the overwhelming interest in NurOwn would simply give HHS, NIH, and CDC a mechanism by which they can capture biofluids and exposome data from the largest ALS population ever to be sampled in the United States.

The funding for the Exposome database could come from multiple sources: (1) $10 million currently appropriated annually for the CDC Registry; (2) CDMRP appropriations directed towards veterans; (3) NIH/NINDS/NIEH grants; and (4) the Act for ALS funding which runs through 2026.

The ALS community fought vociferously to pass the Act for ALS, making it one of the top most co-sponsored bills in the last half-century. Some fought up until the last days of their lives using eye-gaze to type, and Tobiis to speak as they wanted to leave ALS better than they found it. It would be the most apt tribute to their collective sacrifice if that funding were now used to fund the largest-ever ALS biorepository and natural history database concurrently with a NurOwn Phase 4 post-marketing study.

E. New ALS Biorepositories can Store all Biosamples from a NurOwn Post-Marketing Study

If we are going to use AI to unravel the complexity of rare diseases like ALS as Commissioner Makary has mentioned, we need more data and more biosamples – especially more CSF samples – and we desperately need more samples from Americans.[297] As such Petitioners are asking the FDA to consider how a mandatory Phase 4 NurOwn biorepository could benefit and advance ALS research and enable us to catch up to our European colleagues.

If the FDA does approve NurOwn with a Phase 4 post-marketing biorepository, there is ample existing infrastructure to collect, store, share and utilize data collected from thousands of Americans who would excitedly participate in a NurOwn post-marketing study.

1. The EU & UK have the Largest Biorepositories and Natural History Studies.

Currently, most large ALS natural history studies originate from Europe due to a combination of factors related to healthcare infrastructure, research collaboration, and patient population dynamics. Europe's centralized healthcare systems, particularly in countries like the UK, Germany, and the Netherlands, facilitate comprehensive patient registries and longitudinal data collection through national health services – enabling large-scale, standardized data capture across diverse populations.[298] Americans are lagging behind and our heterogeneous population makes studying our population even more important.

Networks like the European Network for the Cure of ALS (ENCALS) and TRICALS integrate biorepositories with clinical data, facilitating large-scale sample collection across multiple centers. For example, the Project MinE initiative, a European-led effort, has built one of the largest ALS biorepositories, sequencing over 22,000 genomes from patients and controls across 15 countries to identify genetic risk factors.[299] In contrast, the impressive Answer ALS database has 1,000 samples.

But that can easily change as we now have the infrastructure set up as a result of the ACT for ALS that the patient community fought to pass in 2021. Now all we need are thousands of samples. A NurOwn Phase 4 biorepository could significantly advance ALS research.

---

[297] We need ICD-10 codes to match the heterogeneity of the ALS so we can use AI to mine data. But Petitioners also suggest that ALS needs a unique, multi-character code much like the VIN used by DOT and NHTSA. The VIN is a 17-character code that serves as a vehicle's "fingerprint," encoding specific information about its manufacturer and attributes. We need a "disease identifier number" to encode the characteristics of vastly heterogeneous ALS that differ in each person.

[298] Tzeplaeff, L., Jürs, A. V., Wohnrade, C., & Demleitner, A. F. (2024). Unraveling the heterogeneity of ALS: A call to redefine patient stratification for better outcomes in clinical trials. Cells, 13(5), 452.

[299] van Rheenen, W., Shatunov, A., Dekker, A. M., McLaughlin, R. L., Diekstra, F. P., Pulit, S. L., … Veldink, J. H. (2016). Genome-wide association analyses identify new risk variants and the genetic architecture of amyotrophic lateral sclerosis. Nature Genetics, 48(9), 1043–1048.

2. New ALL-ALS Biorepository has the Infrastructure to Store Phase 4 Biosamples

In 2021, Congress passed the Accelerating Access to Critical Therapies for ALS Act ("AACT for ALS"). The bill was the result of the Herculean efforts by people in the ALS community who made calls, sent emails, participated in zooms, attended town halls, and rolled through the halls of Congress. With over 400 bipartisan co-sponsors, it was one of the most co-sponsored bills in the last half century.

In addition to funding intermediate-sized Expanded Access Programs for small pharma's drugs in Phase 3 trials, it also created a nationwide biorepository and natural history study with two interconnected initiatives under the supervision of Dr. Bhattacharya at NIH and Dr. Koroshetz at NINDS.

(1) **ALL-ALS**: Access for All in ALS Research Consortium – collection of data
(2) **AMP-ALS**: Accelerating Medicines Partnership for ALS – research, storage and sharing of data

ALL-ALS is a clinical research consortium established to operationalize a natural history study for ALS, collecting critical clinical data and biospecimens from people with ALS and those at genetic risk for developing ALS. It is a key component of the AMP-ALS initiative. Its focus is:

- Collecting longitudinal biosamples to support the AMP-ALS biorepository and for future research.
- Collecting longitudinal clinical data (e.g., motor, speech & respiratory function; symptoms)
- Providing RWD to inform biomarker discovery, clinical trial design & therapeutic development
- Integrating new clinical and digital outcome measures to current trial measures
- Integrating patient-reported outcomes (PROS) with established trial measures

ALL-ALS is led by the country's top ALS biomarker experts: (1) James Berry MD at MGH's Healey Center for ALS; and (2) Bob Bowser PhD and Jeremy Shefner MD of the Barrow Neurological Center. You'll recall that Dr. Bowser is the biomarker expert in the NurOwn trials and Dr. Shefner is one of our country's top experts in ALS clinical trial design.

AMP-ALS is a public-private partnership designed to create the largest, centralized, open platform for data sharing and analysis through a cloud-based AI infrastructure. AMP-ALS integrates data and biospecimens from ALL-ALS with multiple other sources, including TargetALS, ACT for ALS expanded access studies, and existing clinical, molecular, and genetic datasets.

AMP-ALS is managed by the Foundation for the National Institutes of Health (FNIH) and the Critical Path Institute (C-Path). It involves the NIH, NINDS, FDA, pharma, non-profits, and patient-focused groups.

Thus, Petitioners ask the FDA to weigh the possible "benefit" of a Phase 4 post-marketing study, which could collect biomarker data on a much larger population than is enrolled in post-approval trials or natural history studies. In underfunded, heterogeneous rare diseases with small trial populations, biomarker studies can advance both scientific understanding and drug development, transforming the future for Americans who today have no hope.

V. This Citizens' Petition is our Only Recourse as the FDA Has Failed to Act Despite our Myriad of Efforts Over the Last Decade.

In the advocacy arsenal fighting for their lives, people in the ALS community have mobilized unlike any other community since the HIV-AIDS fight in the 80s. ALS advocates have repeatedly met with the FDA in PFDD meetings and have sent an onslaught of emails. They fought for an ALS Guidance Document, have stressed their different risk-tolerance, and have implored the FDA to exercise the utmost of promised regulatory flexibility. They have turned their pain into purpose.

ALS advocates have written OpEds. Some of the many include Dr. Robert Woods' Stat News OpEd entitled: *"As a pediatric cancer researcher, I admired the FDA. Then I got ALS."*[300] The wife of a NurOwn trial recipient had her OpEd published in the WSJ: *"A Slow FDA is Denying ALS Patients their Only Hope."*[301] And NurOwn trial participant, Elizabeth McCormick's OpEd was entitled: *"FDA's Inflexible Approval Process doesn't Work for Rare Diseases like ALS."*[302]

ALS advocates made documentaries. One of the most compelling films about access to therapies is the HBO Vice documentary *"Die Trying: the Battle for ALS Treatments,"* which was produced by Angelina Fanous, who had recently been diagnosed with ALS at just 29 years old. Three people with ALS shared their stories in a PBS documentary "*Matter of Mind: My ALS*" that gives insight into late-stage ALS as well as the decision to use MAiD. The documentary *"Three Sisters"* tells the story of Jenifer Estess who started Project ALS to fund cooperative ALS research and then testified twice before Congress about the importance of ALS stem cell research.

Veterans with ALS like Brigadier General Tom Mikolajcik testified before the House VA committee to ensure that ALS would be recognized as a service-related disease. Chris Mulholland authored an OpEd published in the Military Times entitled: *"ALS is Killing Veterans."*[303] And of course, Matt Bellina passed the Right to Try law named after him.

ALS advocates had protests, signed petitions, and joined patient advisory committees. They've attended town halls, walked and rolled through the halls of Congress, made thousands of zoom calls, sent tens of thousands of emails, and testified at Congressional hearings imploring Congress to help. They've passed historic legislation like the $500 million Act for ALS, which has funded research and created the country's largest ALS biorepository and natural history study called AMP-ALS and ALL-ALS.

People have shared their unfathomable stories of losing multiple people in their families to genetic forms of ALS. Rebecca Andrews buried both her sons at just 29 & 30. One North Carolina family has lost 39 people in their extended family; Jean Swidler started the non-profit End the Legacy, a patient-led organization dedicated to the research and advocacy interests of the Genetic ALS & FTD

[300] Woods, W. G. (2022, August 16). As a pediatric cancer researcher, I admired the FDA. Then I got ALS. STAT.
[301] Cimbura, N. (2021, May 2). A slow FDA is denying ALS patients their only hope. The Wall Street Journal.
[302] McCormick, E. (2021, October 10). FDA inflexible approval process doesn't work for those with rare diseases like ALS. Tulsa World.
[303] Mulholland, C. (2021, October 28). ALS is killing veterans. Military Times.

community. And in the film *"Coping With ALS: My Last Days,"* Anthony Carbajal shared his story of familial ALS, first taking care of his mother with ALS and then diagnosed with ALS himself at just 26 years old. National reporters like Matthew Perrone have written stories like Cassandra Weber Haddad's fight to get Tofersen after SOD1-ALS took the lives of her mother and 32 others in her extended family: "*A Deadly Legacy Raises the Stakes in the War Over Faster Drug Approvals*."

Other ALS advocates have started non-profits. Executives with ALS, Dan Doctoroff and Ed Rapp, started non-profits Target ALS and Answer ALS to focus on biomarker and OMICs research. Jenifer Estess and her sisters started Project ALS to expedite and fund research, and encourage a collaborative research structure. Team Gleason has raised tens of millions to help people with assistive technology. Matt's Place has built ALS accessible smart homes. Her ALS Story helps raise awareness about how ALS impacts young women. Jodi O'Donnell Ames founded Hope Loves Company to help children whose families are dealing with the unbearable burden of ALS.[304]

ALS advocates have done endless stories with the media to raise money, raise awareness and talk about the inequities in regulatory policy. They've been on national TV shows like Ellen, CBS Sunday Morning and The Today Show. They've told their stories to MLB Network, ESPN and Outside The Lines. News anchor Sheree Paolello of WLWT in Cincinnati broadcast multiple stories about Petitioner Patty Manhardt and interviewed NurOwn participants and their families.

To raise awareness, the ALS community fought to establish an annual Lou Gehrig Day in MLB. They've taken to social media to share their stories. Men with ALS, Pat Quinn and Pete Frates innovated the Ice Bucket Challenge raising over $100 million dollars for research. Sadly, Pete Frates died at 34 and Pat Quinn died at 37.

People like Brooke Eby (@limpbroozkit) have given the world a front-row seat to watch as ALS takes a little bit more of her function every day. After losing his Dad to ALS, Vikram Bhaskaran, created the Roon App to make information from patients, caregivers and top ALS experts easily accessible to the community. Mayuri Saxena's family created an App called HelpMayuri that helped advocates easily contact their Congressional members. Pat Dolan, a geospatial engineer, used his talents to create the ALS Geospatial Hub which includes maps to help pass legislation, find VA resources, rate ALS clinics, and track exposomes – and he did it all using eye gaze.

ALS advocates like Sandy Morris have discussed the incidence of MAiD[305] and posed the common sense question to Congress: why does the law make it easier to end one's own life than to access a drug that could extend your life?

We have done all we can. Now we need the FDA to do all it can. Help us get promising therapies like NurOwn approved with Phase 4 post-marketing studies.

---

[304] Dozens of smaller non-profits are doing amazing work to help people deal with the financial burdens and caregiving needs of people with ALS.

[305] Vollers, A. (2021, December 17). Death with dignity: Right-to-die laws leave patients with impossible choice. Bloomberg News.

A. The 2021 Emails after FDA told Brainstorm the Data was Insufficient for a BLA

On February 21, 2021, Brainstorm announced it had received "FDA feedback on a high-level data summary" from the Phase 3 trial. From their initial review, the FDA concluded that the clinical data does not meet the "substantial evidence" threshold required to support a BLA.

In response, still-blinded principal investigators expressed their opinions about efficacy in that same Press Release. Dr. Robert Brown of UMass and Dr. Anthony Windebank of Mayo each have over 40 years of experience conducting clinical trials and treating people with ALS. Dr. Brown pronounced:

> *"**Many of us with longstanding experience in ALS therapy development agree that there was evidence of benefit from NurOwn** cell therapy and hope that there will be an **opportunity for further assessment** of this modality in ALS."*

Dr. Windebank added context and clarity about the efficacy signals in a disease like ALS with critical unmet needs:

> *"ALS is a devastating disease with worse outcomes than most forms of cancer. The **clear signal in this trial -- that some patients with ALS respond to treatment with NurOwn** -- is a light at the end of the tunnel."*

Kathy Thompson pointed out the weaknesses in the ALSFRS-R long before Brainstorm published its data about floor effect.

> *"What were the end points? They are usually set way too high in ALS trials and they continue to use the **ALSFRS, which is a questionable measurement standard - especially in more advanced PALs. They also don't consider & study the 'subset'** of PALS that most of these trials have had success in. They must allow the PALS it works for to continue receiving treatments. **In cancer - they allow 'cut, burn, poison' for treatments that work 'sometimes' and can have brutal side effects - and yet they approve it."***

B. The Improper FDA Statement commenting on the NurOwn Data

But before Brainstorm and the world-renowned PIs had an opportunity to "fully explore the findings" as Dr. Cudkowicz suggested, or to "further assess" the modality as Dr. Brown suggested -- the FDA issued an unprecedented statement:[306]

> ***"Although FDA generally cannot provide confidential information about unapproved products**, given the tremendous public interest in this product, we have concluded that it is important to provide high-level information about the status of the NurOwn development program. With the recent completion of a randomized phase 3 controlled clinical trial comparing NurOwn to placebo, it has become clear that data do not support the proposed clinical benefit of this therapy. Data indicated that none of the primary or secondary endpoints were met in the group of patients who were randomized.*
> *For the main (primary) endpoint, 27.7% of people given the placebo were scored as responding compared to 32.6% of people given NurOwn. The 4.9% absolute difference in responders was not at all statistically significant, and the small difference between the two groups was most likely due to chance. In addition, there was a **modest** excess in deaths in those treated with NurOwn, the significance of which is unclear at this time.*

In June 2021, Dr. Woodcock responded to an email from Dayna Sullivan:

> *"We released some data on NurOwn's product. In the clinical trial, there was a **slight** excess of death in the people treated with NurOwn. This does not mean NurOwn caused the excess, but that it is not compatible with the product having a big effect on extending life."*

The FDA's statements and emails violated long-standing regulatory policy. Not only was it wrong in its commission, it was also wrong because of its omissions. Here is the context of what it did not say:

First, the public statement said **"modest"** to the media and the private email to an ALS caregiver said **"slight."** And neither mentioned that the actual number was too small to draw any statistical conclusions as evidenced by the FDA's own Kaplan Meier Curve at the AdComm.

Second, the statement didn't mention that the trial did meet statistical significance on the subgroups of people earlier in ALS progression. Just as people with stage 1/2 cancer respond better to chemotherapy than those with stage 4 cancer, people with ALS whose baseline scores were ≥ 27/48 responded better to NurOwn; and that population met unadjusted statistical significance.

[306] Brainstorm's stock price plummeted. On February 19, 2021, it closed at $7.20. It closed at 3.77 the day after the FDA's public statement and has never rebounded since.

Third, the statement didn't mention that the world-class neurologists with "longstanding experience" in ALS treatment and trials believed there was a "clear signal" that NurOwn worked on "some" people with this 100% fatal and paralyzing, heterogeneous disease with a critical unmet need.

Fourth, the statement didn't mention that biomarker data showed *"clear intended biological effects"* with important changes in pre-specified biomarkers.

Fifth, the statement didn't mention the substantial and unprecedented evidence it had repeatedly received from people with ALS who regained function on NurOwn. Even worse, it made no attempt to understand or reconcile that ALSFRS-R data with the pre-specified biomarkers and unprecedented response from people who had received NurOwn since 2015.

Sixth, the statement didn't mention that NurOwn passed every single DSMB review in both Phase 2 and Phase 3 trials. Yes, there was an excess in deaths in the NurOwn arm but many had starting baseline ALSFRS-R scores below 20. Anyone with ALS experience will tell you that once your ALSFRS-R scores drop into the teens, your risk of aspirating, choking or asphyxiating increases as does your risk of death or needing a tracheostomy. Sicker people die quicker.

Finally, many people with ALS choose suicide or Medical Assistance in Dying (MAiD)[307] because they want to end the cruel brutality of ALS.

C. The Unintended Consequence of the FDA's Improper Statement

Not unexpectedly, the FDA's statement turned out the light for tens of thousands of Americans who had hoped to get NurOwn but instead have died waiting. The impact was especially cruel for those people like Petitioner Lesley Krummel and Elizabeth (Betsy) McCormick who had RWE **proving** NurOwn had worked on them, were scheduled to get EAP doses, then had that promised dosing withdrawn.

Betsy shared:

> *"I participated in phase 3 of this same trial. **My progression stopped**. I was invited to participate in an EAP that would give me access to NurOwn pending FDA approval. Then the FDA issued a statement ignoring the proof of effectiveness and suggesting, despite evidence to the contrary, that Nurown was not safe. My opportunity to get this potentially lifesaving treatment disappeared. If NurOwn doesn't help me, and only has a 1% chance of helping me, how exactly is it more of a risk than ALS?"*

[307] ALS/MND has one of the highest rates of suicide and MAiD. One in four people with ALS in Toronto choose MAiD. In the US people travel to states where MAiD is allowed.

<u>Graphic</u> - Prospective ALS Exposome Natural History Database

<u>CLOSING</u>

Recently at the Gene and Cell therapy roundtable, Broad Institute endocrinologist Michelle Rengarajan, MD, PhD, shared her perspective both as a clinician-scientist as well as the mom of two preschoolers with Duchenne Muscular Dystrophy. Her wisdom applies not just to boys battling Duchenne but equally to other rare, heterogeneous neuromuscular and neurodegenerative diseases like ALS:

> *"We need to accelerate the pace of development so that people alive today can access the exciting science and clinical development that we are talking about.* ***We cannot let quests for cures be barriers to incremental advances*** *that not only provide meaningful quality of life, but they also set up patients to be healthy enough to provide access to future, better therapies. A 20-year-old man in a wheelchair who can lift his arms, type on a computer and put on a headset has a fundamentally different ability to interact independent of society than someone who can't. A therapeutic product that preserves that ability for a few more years would be a massive win….*
>
> ***I'm grateful that the Commissioner and Dr. Prasad recognize the scientific and clinical challenges of running trials in rare diseases, where small populations with super-imposed heterogeneity can make it very easy to miss efficacy within the timescale of a clinical trial, and where terminal diseases raise real ethical concerns about long placebo arms.***

I appreciate the recognition of the importance of accelerated approvals with strong post-marketing commitments for drugs with biologically plausible mechanisms and strong genetic basis in rare disease. However, the qualification process for surrogate biomarkers can itself be quite challenging and inefficient.

I certainly would appreciate greater clarity on how such markers combined with real-world evidence can be better optimized, particularly for ***rare diseases where the risks of not treating are very clear and remarkably high….***

For patients and families, ***the single most important commodity is time.*** *As you think about improving efficiency and advancing therapeutic products I hope you remember: for many patients* ***time is muscle, time is brain and time is life."***

Petitioners request that the FDA keep Dr. Rengarajan's wisdom in mind when it considers the propriety of approving NurOwn with a Phase 4 post-marketing study, coupled with a broad mandatory biorepository and exposome database. There is both new unprecedented evidence and existing "substantial evidence" to support the approval of NurOwn, a first-in-class autologous, mesenchymal stem cell therapy, uniquely enhanced with neurotrophic factors.

That "substantial evidence" supporting accelerated or conditional approval includes the "totality of the evidence" collected over the last 8 years, which buttresses and far exceeds the efficacy data from the previously considered 28-week randomized control trial:

1. New EAP data demonstrating a 5.5 month Improvement in OS as of 2022
2. New EAP data demonstrating a 100% five-year survival rate far in excess of the 20% median ALS natural history
3. New and unprecedented data demonstrating years of improvement over median trach-free survival, as of June 2025
4. New, long-term respiratory function data that demonstrates a significant preservation of breathing function as evidenced by improvements in Forced Vital Capacity and significant extensions in Time-to-Event data for non-invasive ventilation
5. New long-term functional data that demonstrates a significant slowing in ALS progression (as much as 85%), outperforming any ALS therapy currently on the market
6. New survival data that far exceeds the survival data used to support accelerated approval of many cancer therapies
7. New, long-term progression free survival data that significantly outperforms any ALS therapy currently on the market

8. New, long-term functional data that demonstrates an ORR that meets or exceeds the ORR used to support accelerated approval of many cancer therapies
9. New EAP Neurofilament light data that demonstrates a significant decrease in neurodegeneration, and demonstrates a dose-dependent response in both the magnitude of change as well as the durability of those changes
10. Biomarker data that demonstrates target engagement and a plausible mechanism of action supporting accelerated or conditional approval
11. Biomarker data that demonstrates target engagement across ALS disease progression – regardless of ALSFRS-R score – but only in the NurOwn-treated arm, with no similar biological changes evidenced in the placebo arm
12. "Totality of the evidence" demonstrating that NurOwn had a dose-dependent response, with those who received the most doses of NurOwn the earliest in their ALS progression demonstrating the largest magnitude and longest durability of functional response
13. Expert opinions from world-renowned neurologists who opined that NurOwn caused unprecedented stabilization (and some improvements) in ways they had never seen in their 40-plus years as physician-scientists conducting ALS clinical trials
14. Expert opinions from treating neurologists, pulmonologists, respiratory and physical therapists who had never seen similar slowing, stabilization or improvements in function as they observed in clinic with their ALS patients who participated in the NurOwn trial
15. Real-world evidence, real-world data and newly unblinded lived patient experiences and PROs documenting that NurOwn interrupted, slowed and halted their lethal ALS progression and in some ways, improved how they felt and functioned
16. "Totality of the evidence" including dozens of "n of 1" case studies that demonstrate that NurOwn had a "clinically meaningful" impact on how people felt, functioned and survived

We further request that the FDA consider the risks and benefits of approving NurOwn with a Phase 4 post-marketing study, and a mandatory biorepository with a natural history and exposome database that could significantly advance ALS research, drug discovery and future drug approvals.

In contrast, if the FDA requires yet another Phase 3 randomized, placebo-controlled trial, that Type II error will cause irreparable harm as 6,000 Americans with ALS will die each year.

NurOwn has shown efficacy in some people over the past decade: since 2011 in Israel, in the Phase 2 trial in 2015, again in 1 person via Right to Try in 2019-2020, next in the Phase 3 trial that ended in 2020, and finally in the 10 people who received NurOwn via EAP. Since NurOwn first worked in the US, 60,000 Americans with ALS have died waiting for the regulatory system to act with the same urgency as ALS is killing their motor neurons.

Please exercise your regulatory flexibility and approve NurOwn with a phase 4 post-marketing study. Please do not let another generation of ALS patients die when we know there is a stem cell therapy that could help them live.