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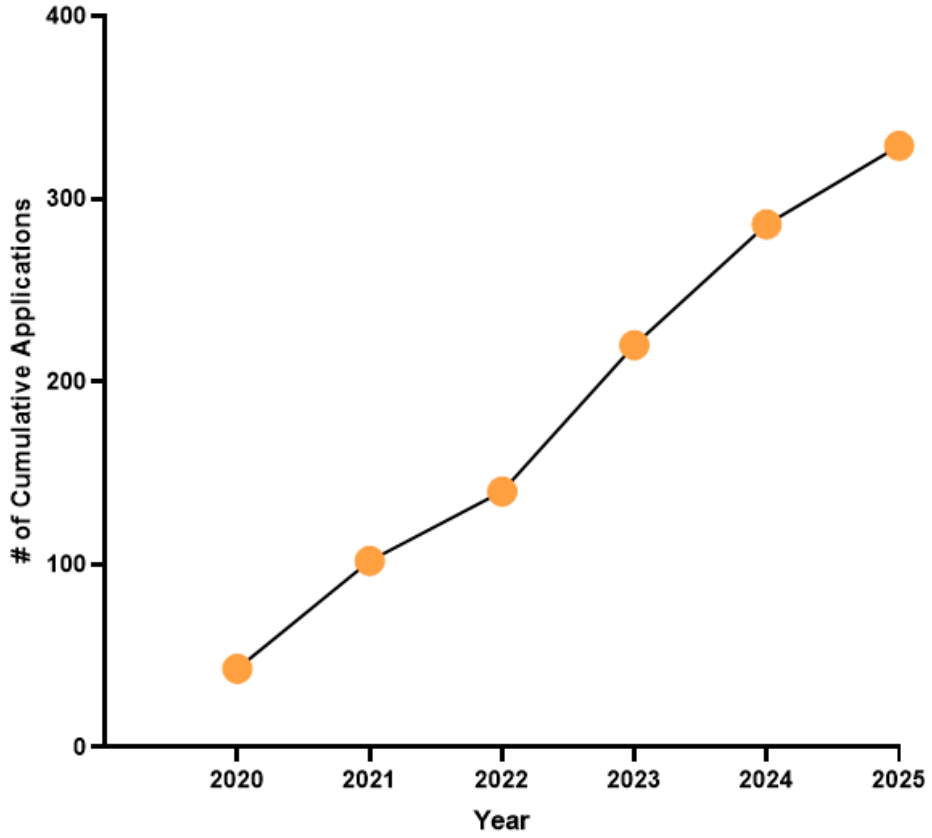
Clinical Benefit: Lessons from the n-Lorem Experience

Laurence Mignon, PhD
Executive Director, Clinical Development

Number of Applications Has Exceeded our Expectations



- Faster growth than anticipated
- Larger fundraising needs
- Faster and enhanced rate at which we are learning about disease and health

Topics to Be Covered Today

Our Clinical Development Approach

- Parallel processes and expert input expedite safe treatment of patients

n-Lorem Clinical Experience

- The modified cross-over design provides the groundwork to assess and track disease progression and treatment response
- Individualized ASOs for nano-rare diseases have moved beyond halting decline to regaining function
- Multi-year follow-up shows consistent, meaningful benefit in severe, progressive disease

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Our Clinical Development Approach

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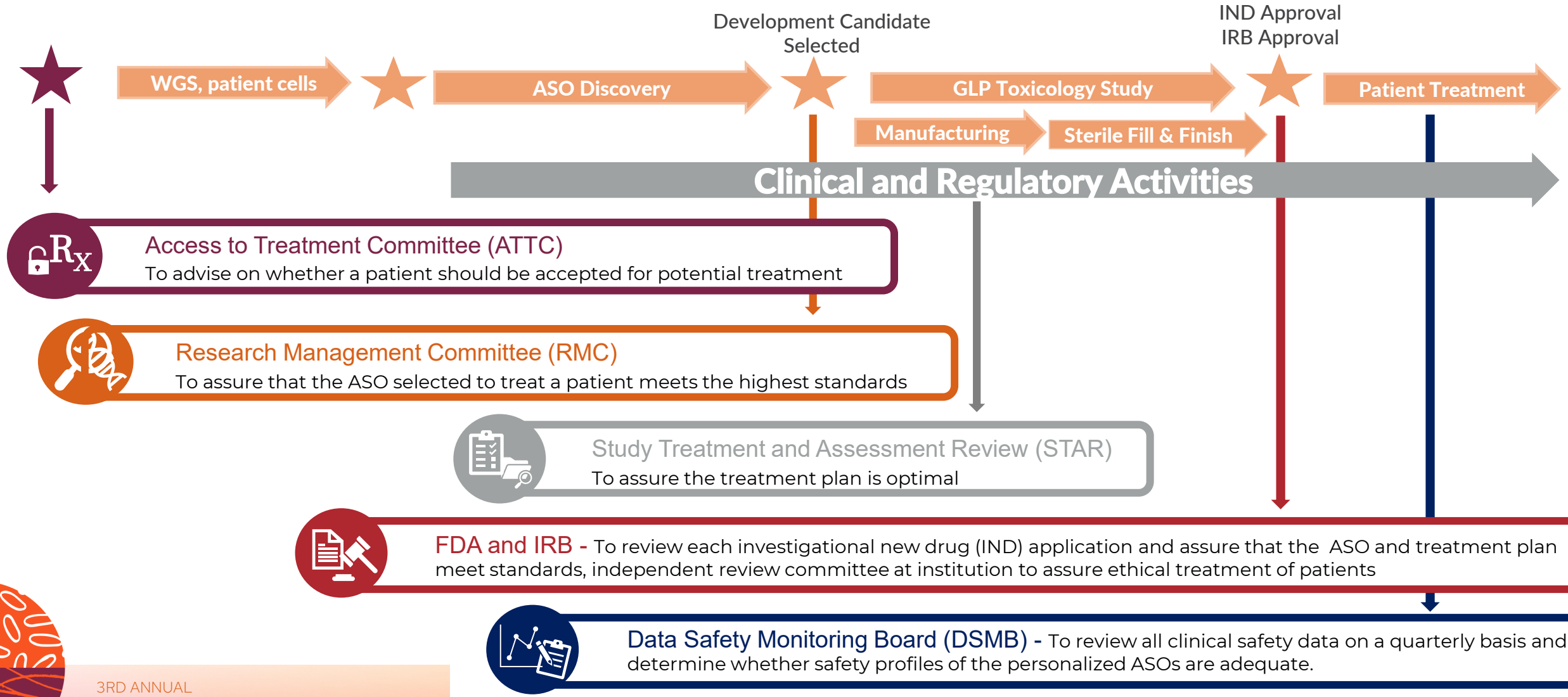
Clinical Expertise and Experience Streamlines the Process from Acceptance to Treatment

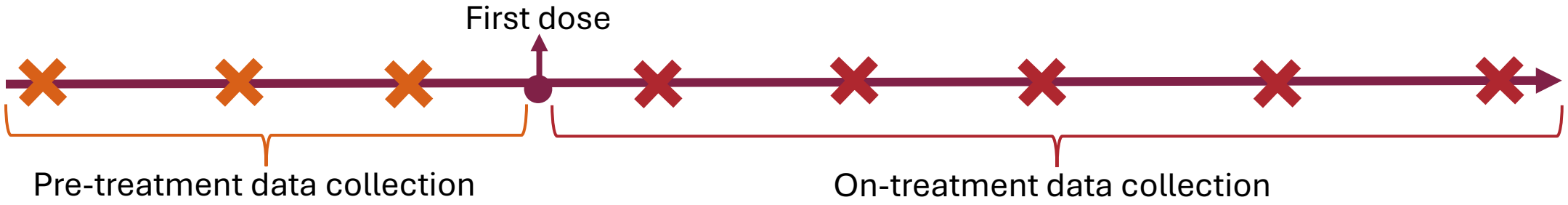


Assessing Clinical Benefit in Nano-rare Patients Can Be Challenging

- Nano-rare patients present with a unique combination of clinical and disease characteristics
  - Severe disease phenotypes
  - Advanced disease
  - Multiple concomitant medications
- Paucity of natural history data
  - It can be difficult to assess clinical benefit when the trajectory of disease progression is unknown

The Modified Cross-over Trial Design Has Proven to Be well Suited for Trials in Nano-rare Patients

- Modified cross-over design compares pre-treatment assessments to on-treatment assessments



- Important aspects include
  - We focus on what is important to the patient
  - Treatment goals and clinical measures important to the patient are pre-defined
  - Pre-treatment assessments are evaluated during time it takes to make ASO, setting baseline and assessing progression rate

We Know How to Interpret the Clinical Data in our Individualized Trials

- Emphasis placed on individualized treatment goals using standardized outcome measures
- Harmonization of measures across programs when possible
- High-quality data that is transferable can be used in aggregate analyses
  - Teaches about one patient relative to other
  - Teaches about mutation and effect on phenotype
  - Teaches about health and disease

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The Clinical Experience

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n-Lorem Is Responding to the Demand

	2023 Colloquium	2024 Colloquium	2025 Colloquium
Total number of patients treated	5	15	**>30**
Organs treated	CNS, Eye	CNS, Eye, Kidney, Liver	CNS, Eye, Kidney, Liver
Routes of administration	IT, IVT	IT, IVT, SC	IT, IVT, SC
Cumulative number of doses	16	68	**>180**

- We are treating more than 90% of all treated nano-rare patients
- Excellent safety and tolerability profile

Clinical Data in Evaluable Patients Shows Greater than 90% Success Rate

- **Evaluable patients** = on treatment for at least 6 months (~ 4 doses) with at least one post baseline visit including quantitative assessment
- **22 evaluable patients**: 9 ALS patients and 13 non-ALS patients
  - **6 of 9 ALS patients** show encouraging clinical results
  - **13 of 13 non-ALS patients** show encouraging clinical benefits
- Benefits observed in **all organs** treated
  - CNS, kidney, liver, and eye
- Benefits observed **early in treatment** and at **low doses**

Patients Currently on Treatment Have Different Genotypes and Phenotypes

Disease types	Gene	# of patients
Neurodegenerative	CHCHD10, TARDBP, LMNB1, ATN1	14
Neurodevelopmental	SCN2A, PACS1, ASXL3, MAPK8IP3, hnRNPH2, H3F3	9
Developmental onset with neurodegenerative features	KIF1A, UBTF, TUBB4A	4
Dysfunction of autonomic nervous system	EPL1	2
Progressive kidney disease	SAA	1
Retinal degeneration	FLVCR1, PRPH2	2

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Kidney Disease

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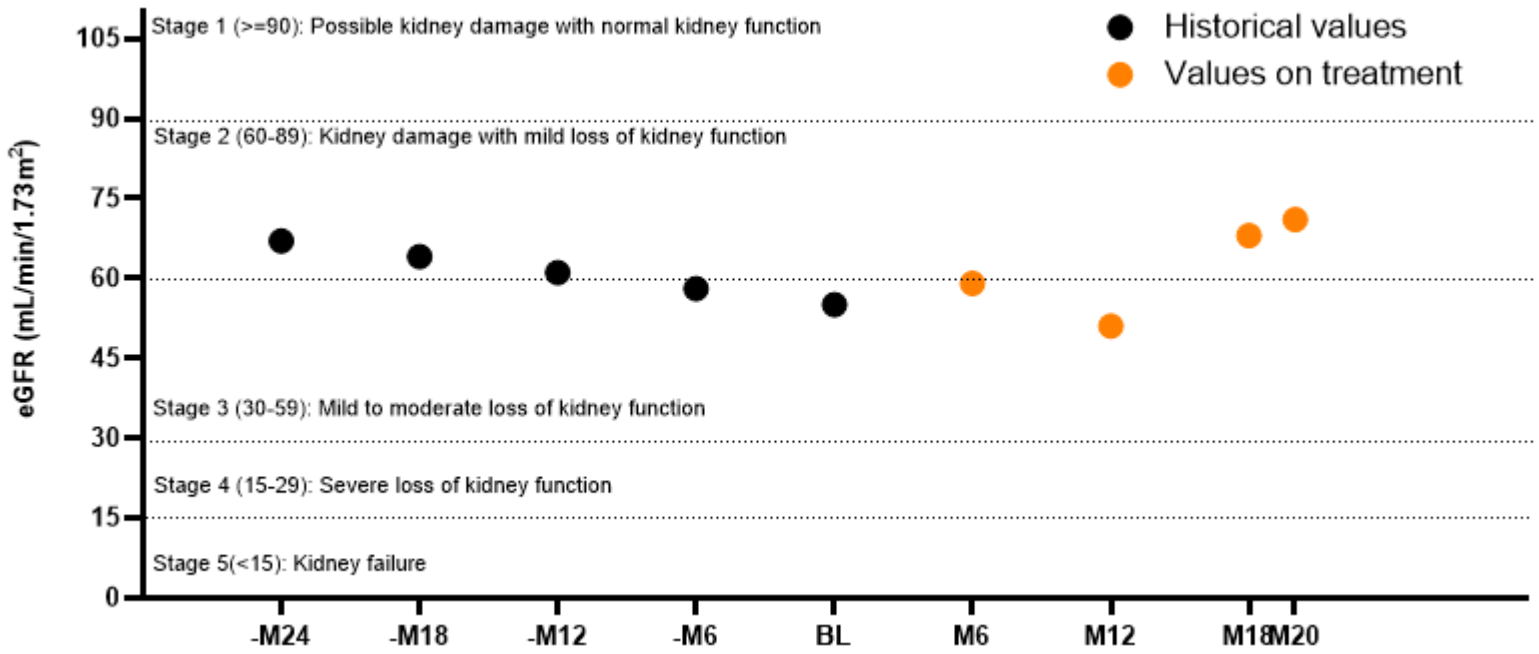
Stabilization of Kidney Function Has Improved Quality of Life of Patient

- 44-year-old male with SAA amyloidosis
  - Two family members passed away from diseas
  - mild to moderate loss of kidney function (loss of 5-ml/min/1.73m2 per year)
- 20 months post-treatment the trajectory of renal dysfunction has been stabilized
- Patient has been able to stop some concomitant medications, be more active and work out



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Amyotrophic Lateral Sclerosis (ALS)

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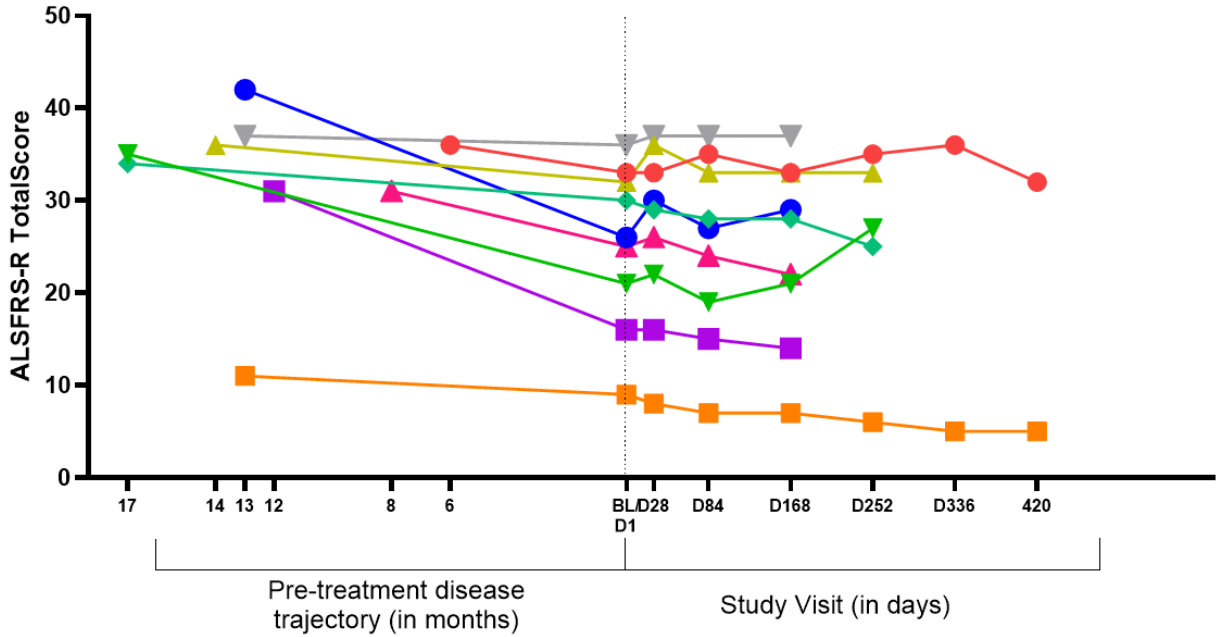
Cautiously Encouraging Experience in ALS Patients Stabilization of Disease

- 9 ALS patients evaluable for benefit
  - All carry the CHCHD10 mutation associated with ALS (R15L)
- 6 / 9 show stabilization of ALS-FRS score
- All showed reduction in neurofilament
- 1 patient passed away
  - Low ALS-FRS score at entry
  - Required overnight ventilatory support at study start
  - Succumbed to a respiratory infection



"For us, the future is hopeful, and not a lot of people with ALS can say [that]" – wife of ALS patient

Treating physicians:
Dr. Shneider, Columbia University
Dr. Oskarsson, Mayo Clinic

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Neurological Diseases - Seizures

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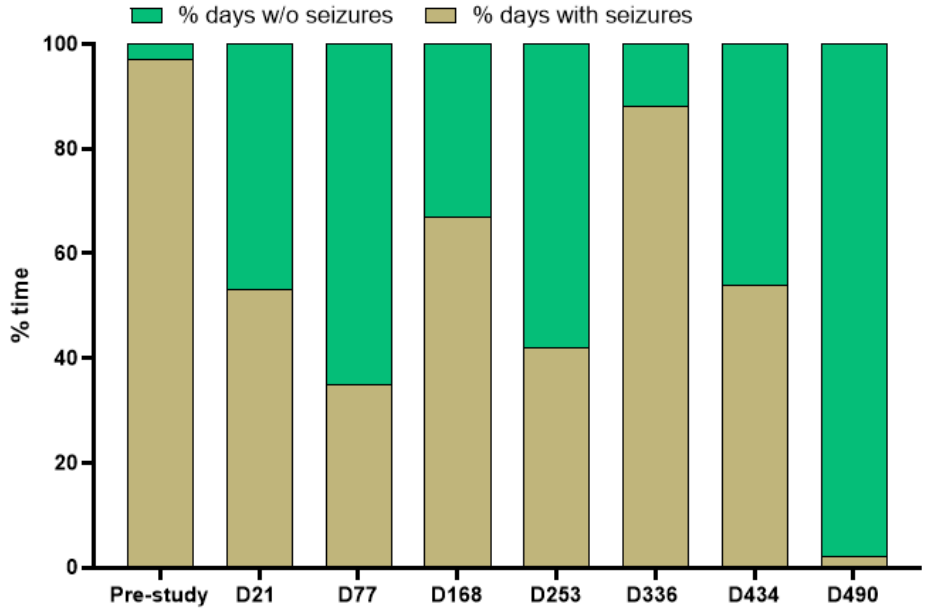
Improvement in Seizures in Multiple Patients

Ziegler et al., NEJM 2024

Patient with KIF1A mutation

- Significant reduction in seizures / epileptic episodes
- First period of seizure free days for a patient with SCN2A mutation
- Ability to stop other antiseizure medication
  - one patient stopped **high doses of phenytoin** completely, and has not required ER visit for rescue medications since study start



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Neurological Diseases - Communication

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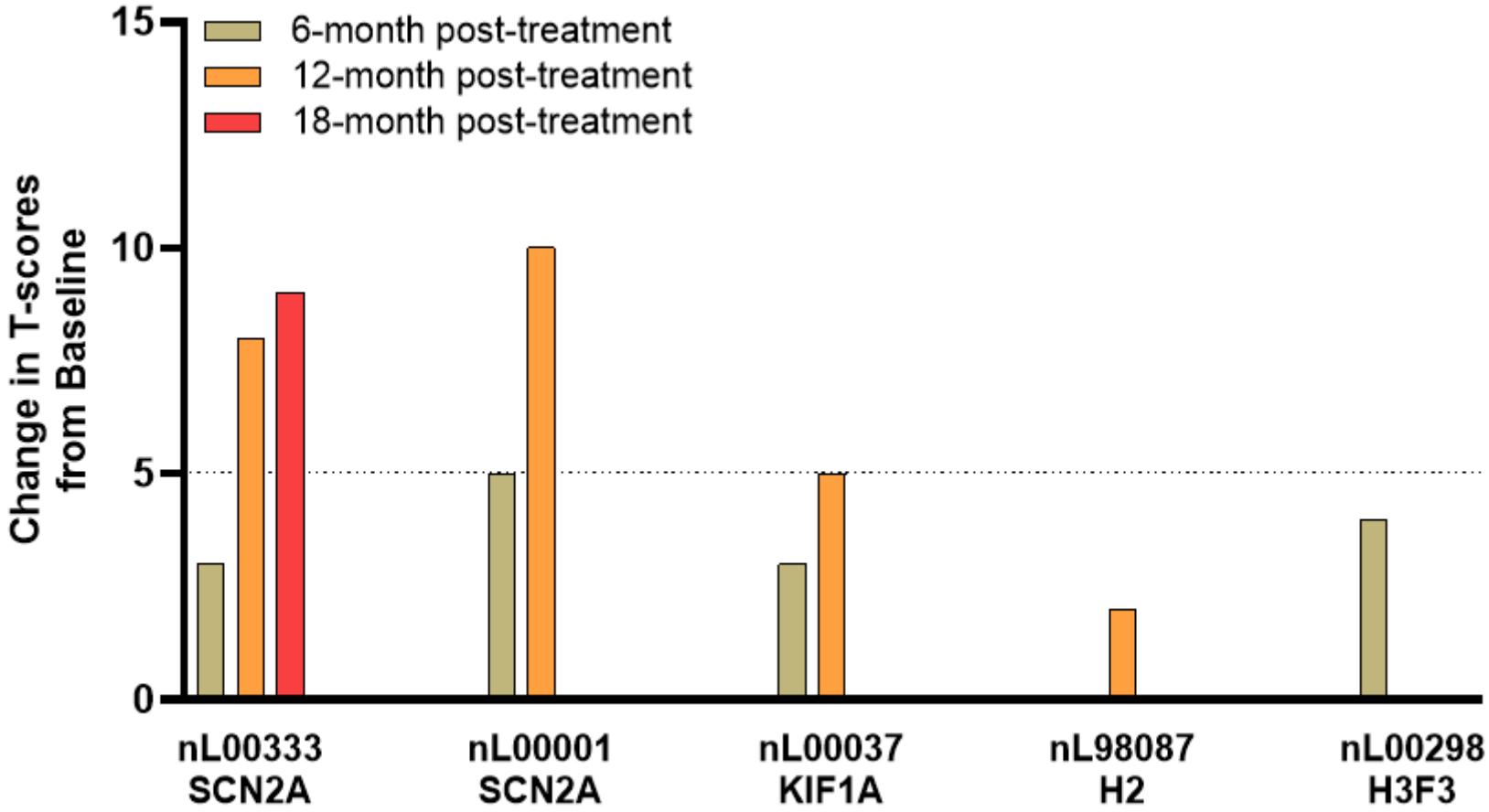
Improved Communication Observed Across Multiple Mutations and Diseases

- A 5 point-change is considered clinically meaningful on the Observer-rated Communication Ability scale (ORCA)
- Across different diseases, we see communication improve over time



Treating physicians:
Dr. Bain, Columbia University, Dr. Berry-Kravis, Rush University,
Dr. Kim McManus, UCSD/Rady

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Neurological Diseases - Mobility and Motor Control

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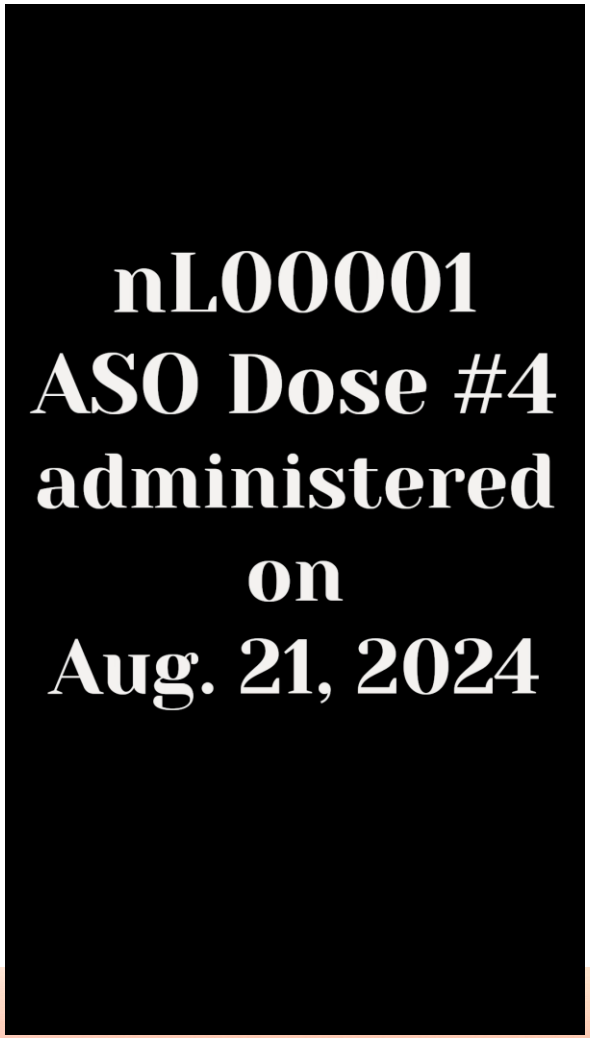
Independent Walking was Achieved for the First Time in Patient with SCN2A Encephalopathy

- Patient had never been able to walk independently
- After ~ 6 months on treatment (4 doses), patient felt comfortable to take independent steps
- Milestone was achieved at low ASO dose



Treating physician:
Dr. Kim McManus, UCSD/Rady

Another Patient Was Able to Take First Steps Independently After ASO Treatment

- Patient with neurodevelopmental disorder due to mutation in the *hnRNPH2* gene
- Patient started treatment at 8 years of age
- Patient received 5 doses (~ 9 months on treatment) at time of video

Treating physician:
Dr. Bain, Columbia University

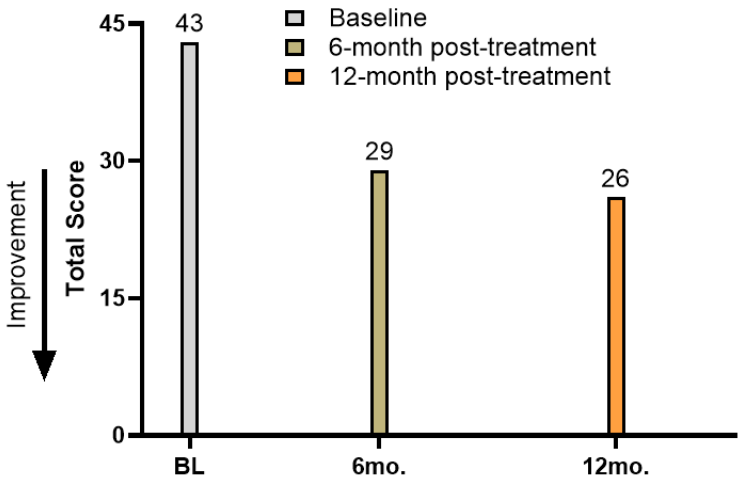
Motor Improvements Enhance Patients' Ability to Engage in Daily Activities

"We are noticing slightly lower tension in her legs and a stronger core. Not nearly as many collapses when she's crawling around and better balance overall and improved fine motor control. Also her hand tremors have not come back. We are so excited with the change we are seeing."
from a **KIF1A** patient mother

Treating physicians:
Dr. Bain, Columbia University, Dr. Eichler and Dr. Nagy, MGH
Dr. Kim McManus, UCSD/Rady

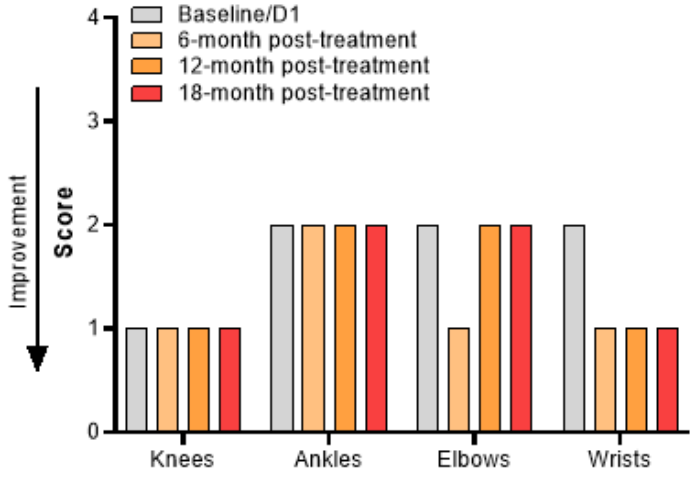
Motor Improvements Enhance Patients' Ability to Engage in Daily Activities

Reduction in abnormal involuntary movements



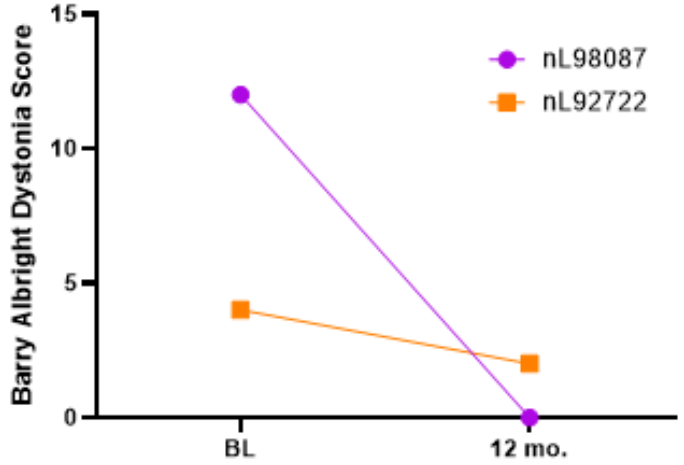
SCN2A patient shows early and sustained improvement on Dyskinesia Functional Impact Score

Reduction in spasticity



TUBB4A patient has seen early and sustained improvement in spasticity in the both wrist

Reduction in abnormal sustained contractions



2 patients with hnRNPH2, with varying dystonia at study start, show improvement after 12 month of treatment

Treating physicians:
Dr. Bain, Columbia University, Dr. Eichler and Dr. Nagy, MGH
Dr. Kim McManus, UCSD/Rady

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Neurological Diseases - Improvement in Autonomic Function

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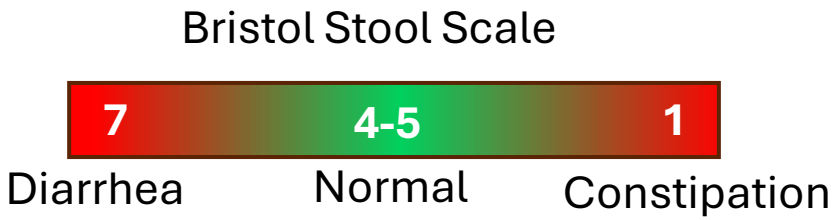
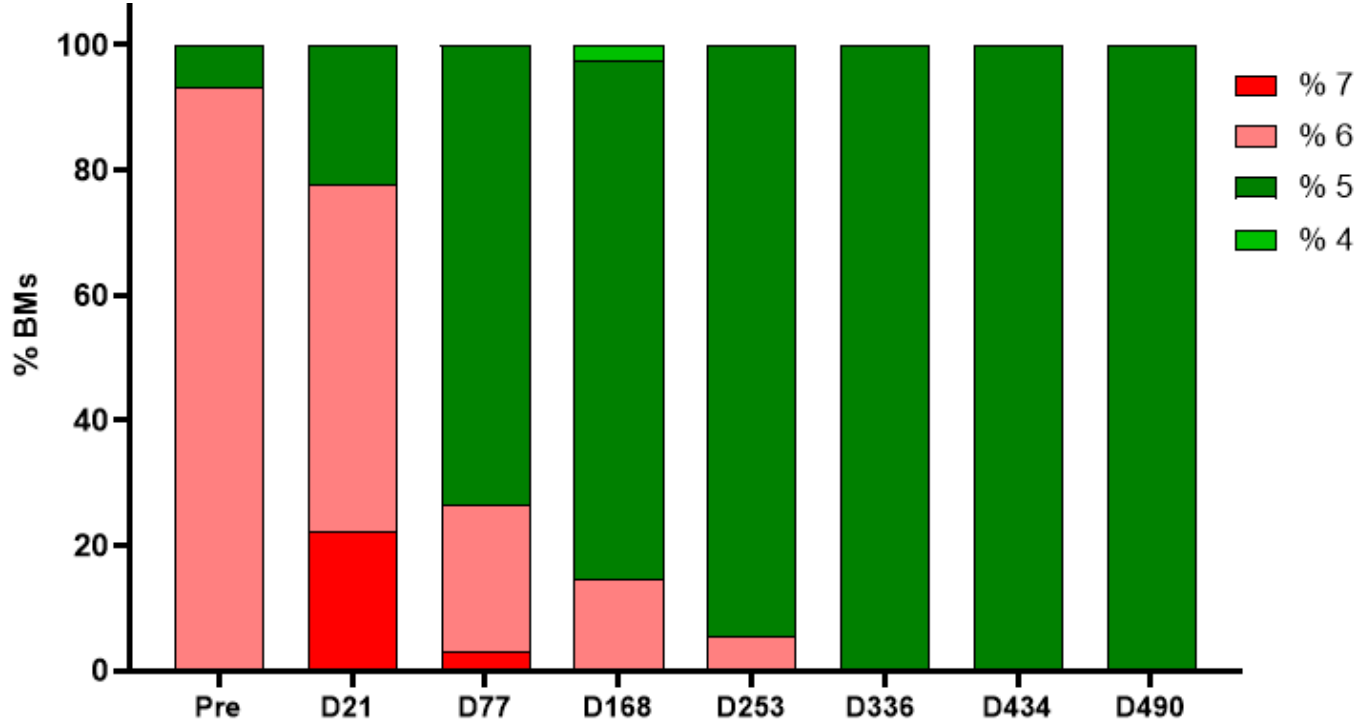
Improved Autonomic Function in Patient with SCN2A Encephalopathy



Patient showing improved and sustained normalization of bowel movement starting at 3 months post-treatment.



Treating physician:
Dr. Kim McManus, UCSD/Rady

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Neurological Diseases - Sensory Processing

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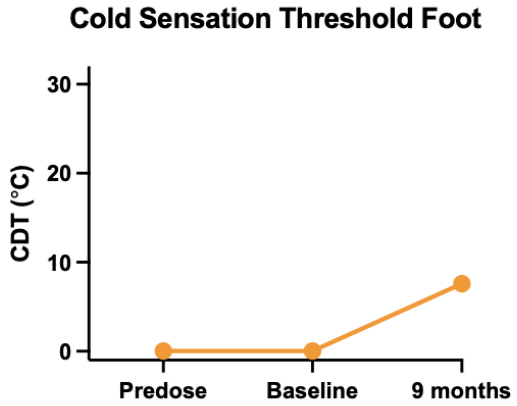
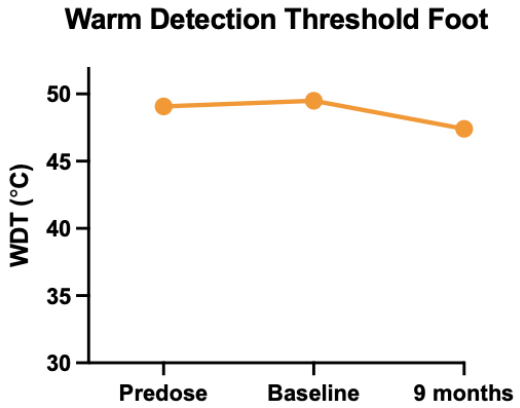
Improvement in Sensory Processing Allows Patient to Better Detect Temperature Changes

Patient with mutation in ELP1 gene (dysfunction of autonomic nervous system)



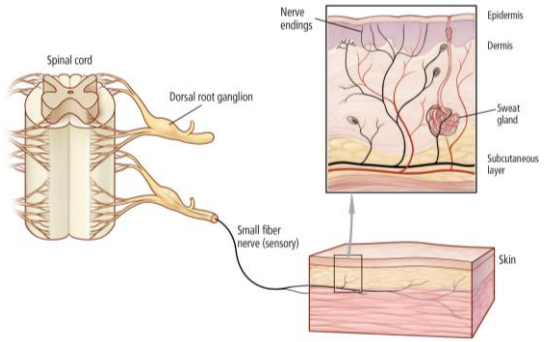


"Sometimes I can feel heat in my mouth when I'm eating."

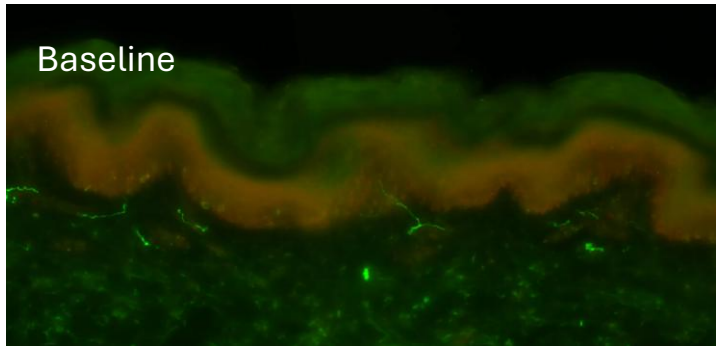
Temperature sensation metrics over time – is showing increased cold and hot sensitivity, suggesting enhances small fiber function.

Compelling Evidence of Nerve Fiber Regeneration

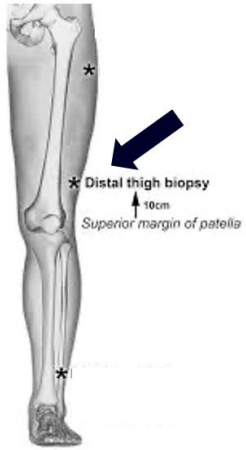
From ELP1 patient father: *"It has been the best year for my son!"*

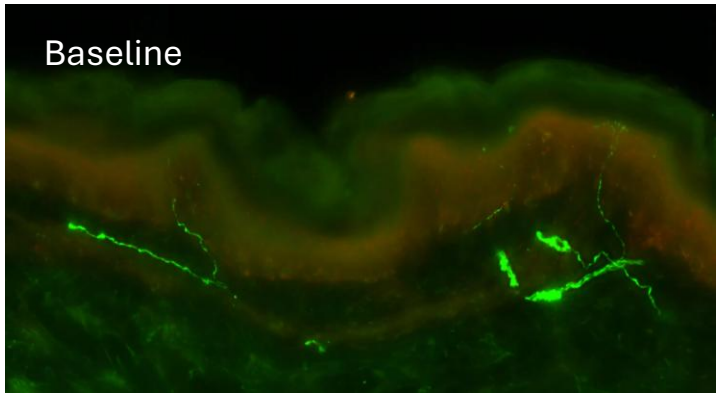


Patient with mutation in ELP1 gene (dysfunction of autonomic nervous system)



0.2 fibers/mm² (normal ≥9.1)





3.1 fibers/mm² (normal ≥12.7)

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Neurological Diseases - Autistic Behaviors

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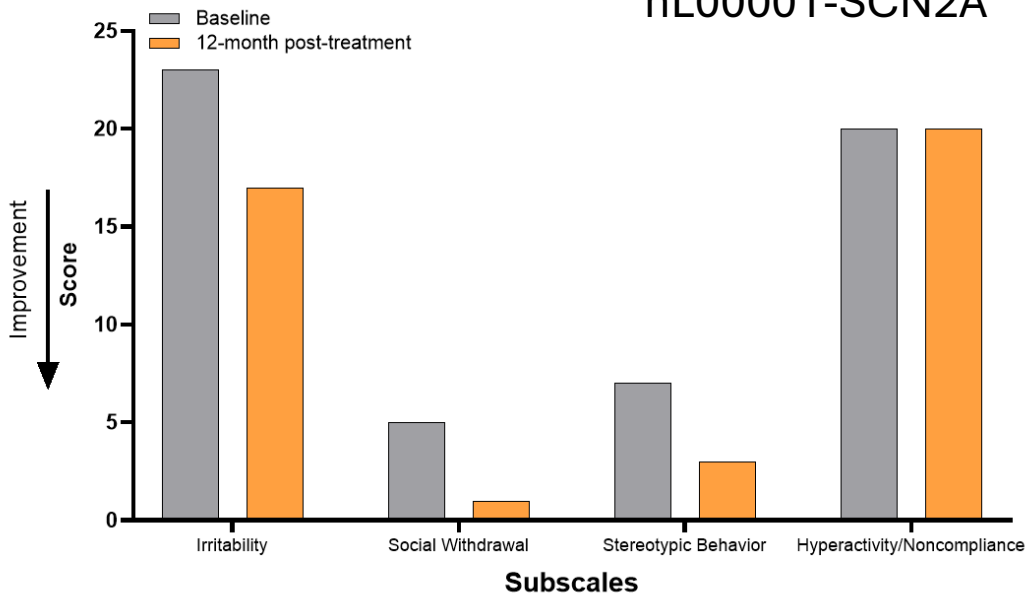
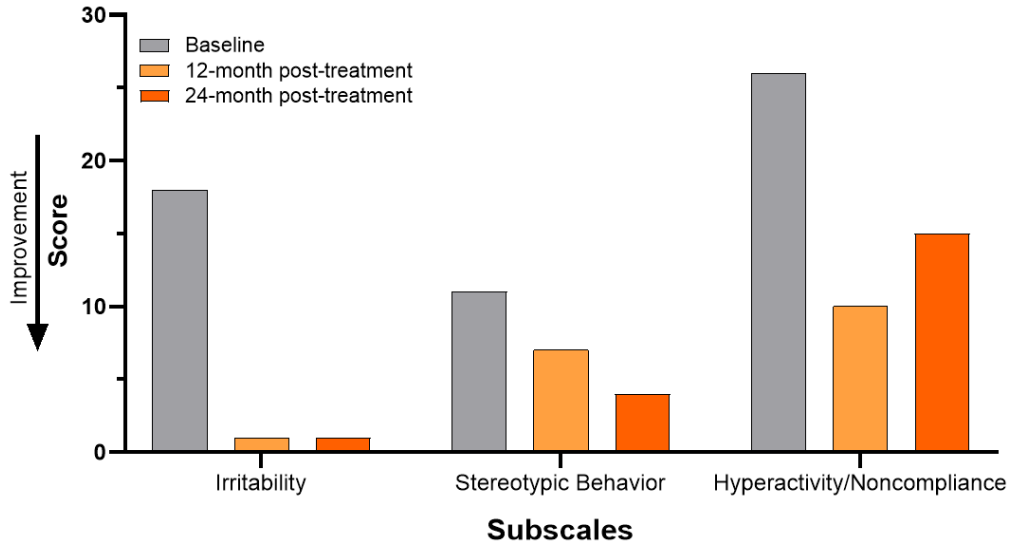
Improvement in Autistic Symptoms Leads to Better Interactions with Family and Friends

nL00001-SCN2A



nL00333-SCN2A



- The two patients with different SCN2A mutations had behavioral varying phenotypes at baseline
- Both showed improvements in irritability and stereotyped behavior

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Neurological Diseases - Gained Independence

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Increased Independence

- KIF1A patient putting on her shoes for the first time

From ATN1 patient mother:
"Our son took his t-shirt off yesterday without being asked. He hasn't done that in years."

- hnRNPH2 patient able to focus and feed herself

From mother of hnRNPH2 patient
"Since receiving the ASO treatment, she has improved in various areas. Her general awareness has improved, her eye contact has improved, her ability to follow directions has also improved, and we're seeing better motor skills."

Treating physician:
Dr. Bain, Columbia University

Recap: The Clinical Benefits Seen to Date Are Varied, Sustained and Meaningful

- Stabilization in kidney function
- Stabilization of vision
- Slowing / halting of ALS disease progression
- Reduction in seizures and rescue medications
- Reduction in neuropathic pain
- Improvement in motor function
- Improvement in gait
- Evidence of ASO effect on autonomic function
- Recovery of functions lost
- New functions gained

Conclusion

- What we are learning from our patients provides optimism for future patients
- Disease-modifying ASOs lead to clinical benefit in patients with different genotypes and phenotypes
- Multi-year data confirm long-term safety, sustained function and broad benefit
- We see clinical benefits
  - In every organ
  - Early in treatment
  - At low doses

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thank you

Thank you to all our investigators and all site staff – we could not do this without your dedication!!

Thank you, committee members
ATTC Committee, RMC Committee, STAR Committee, DSMB Committee

Thank you to our patients and families!!

Thank you to everyone at n-Lorem!!

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Thank you!