



**2023 Nano-rare Patient
Colloquium**

n-Lorem Clinical Infrastructure Assures Professional Management of our Patients

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Topics Covered Today

- n-Lorem infrastructure supports professional management of patients being treated with experimental ASOs
 - Decades of experience in managing clinical trials
 - Decades of experience with experimental ASOs
 - Customized processes to meet the needs of each unique patient
- Additional evidence of clinical benefit in patients treated with n-Lorem ASOs
 - Given the genetic cause of the disease we treat is known and the ASO is designed to treat the genetic cause, we hope to have a relatively high success rate
 - Over next few years we will accumulate data to know what our success rate is
- Evidence that when optimized ASOs are dosed prudently, is it possible to minimize the risk of adverse events

Bias to Treat Supported by R&D Expertise to Inform Benefit-Risk Assessment

- Not treating a patient with a progressive, debilitating disease has inherent risk with a known endpoint
- Treating a patient with an investigational ASO carries risk that can be mitigated
 - Robust ASO discovery and development based on 30+ years of safety experience
 - Constantly learning from ongoing trials and updating investigators along the way
 - Starting with low doses and escalating in stepwise fashion
 - Objective review of safety database by Data Safety Monitoring Board members who are experienced in the treated organ, the disease, the ASO technology, and clinical trials

Clinical Focus of n-Lorem Is to Treat as Many Patients as Possible Successfully and Professionally

- **'Successfully'** is defined as
 - Treating with an optimized, personalized ASO
 - Tracking valid quantitative and qualitative outcome measures important to patients and physicians
 - Collaborating with an external committee to oversee safety of all our ASOs
- **'Professionally'** is defined as
 - Partnering with capable and invested physicians and institutions
 - Collecting study data in a standardized manner using a validated system
 - Interacting with FDA as needed to move a program forward
- Two key components needed to accomplish this: **Experience** and **Infrastructure**

Success is defined by how robust the experiment was and whether the scientific question was answered; it is not necessarily defined by whether a treatment was proven to be efficacious.

n-Lorem Embeds Years of ASO and Development Experience in Our Collaborations with Investigators

- Objectives of the n-Lorem clinical infrastructure
 - Minimize risk of potential ASO related adverse events
 - Maximize the opportunity for benefit
 - Maximize learnings from each patient and our aggregate experience
- n-Lorem approach to creating a strong clinical infrastructure
 - Maximize experience in clinical trial management
 - Maximize experience with ASO in clinical trials
 - Develop specialized systems for clinical evaluations of ASO treatment effects in individual patients
- Have assembled a versatile group of leaders with deep clinical experience
 - Research/pre-clinical work, manufacturing, FDA interactions, project management, clinical operations, clinical trial oversight
- n-Lorem engages with external subject matter experts
 - Track patients treated with an optimized, personalized ASO with adequate outcomes measures sensitive to measure change
 - Provide oversight from a safety perspective

To meet the demand, we have quadrupled our research capacity and clinical infrastructure

Multiple Checkpoints in Which Independent Peer-Review Assures Optimal Treatment and Maximum Learning



- Access to Treatment Committee (ATTC)** – Committee focuses on ascertaining our ASO approach is amenable to treating a specific genetic mutation
- ~13 members with >200 years of combined experience in research, drug development, ASO technology, ethics, patient advocacy



- Study Treatment and Assessment Review Committee (STAR)** – Committee advises treating physicians on appropriateness of outcome measures to track treatment benefit
- 4 members with >80 years of combined experience in research, clinical trials, outcome measures, ASO technology (plus ad-hoc members when necessary)



Partners of Excellence - Experienced principal investigators, with robust institutional support and staff, who were early adopters of the n-Lorem model

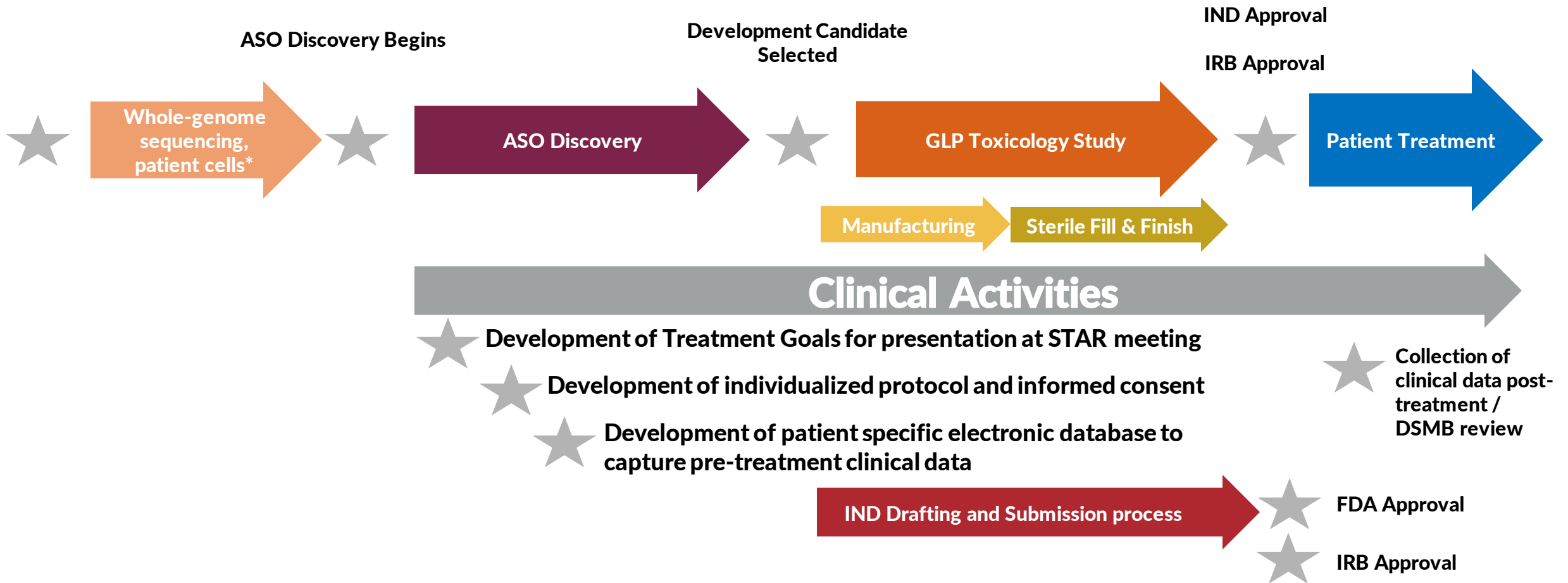


- Data Safety and Monitoring Board (DSMB)** – Committee reviews safety data across all n-Lorem programs to assure appropriate benefit-risk to continue treatment
- 4 members with >80 years of combined experience in research, clinical trials, ASO technology (plus ad-hoc members when necessary)

External Expert Peer-Review Provides Additional Layer of Oversight to Our Programs

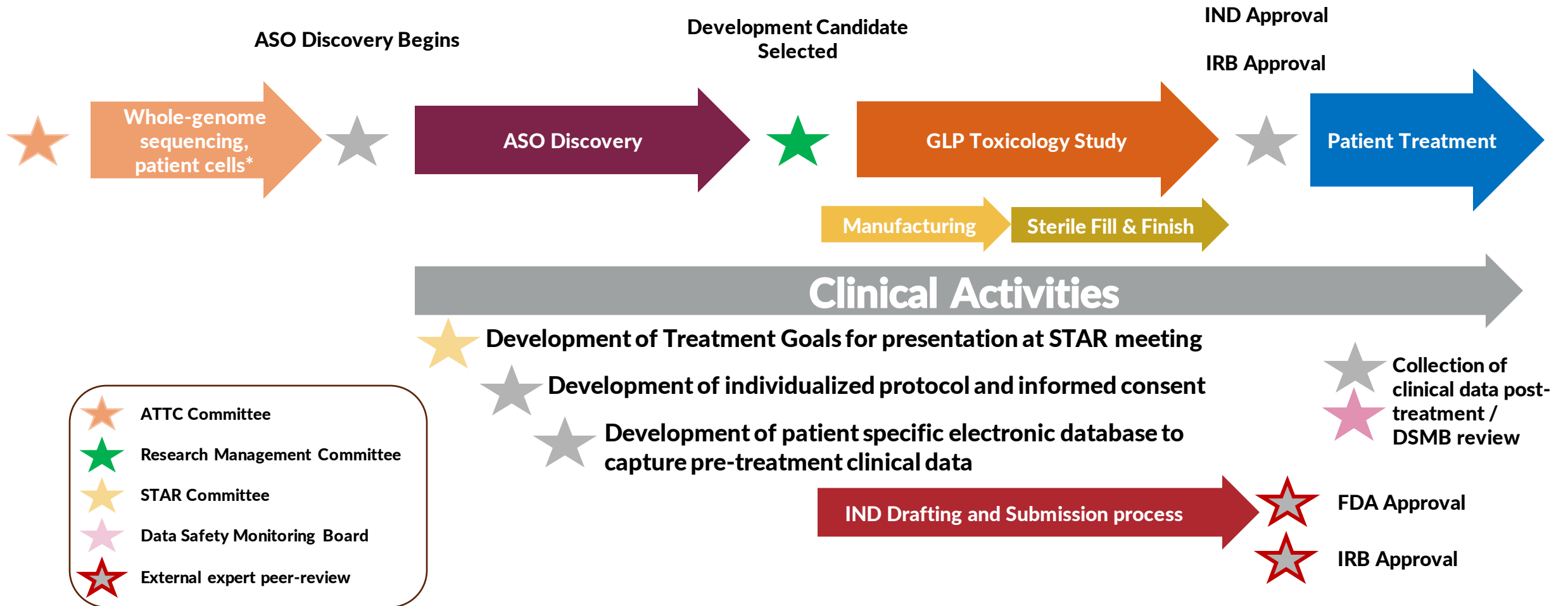
- Food and Drug Administration (FDA)
 - Reviews, comments on, and approves every IND before treatment can be initiated
 - n-Lorem has received approval across 4 divisions of the FDA
 - Neurology 1
 - Neurology 2
 - Cardiology/Nephrology
 - Ophthalmology
 - Positive collaboration with the FDA emphasizes the quality of IND documents put forth by n-Lorem, and the importance of the FDA guidance documents for Individualized ASO drug products
- Institutional Review Boards (IRB)
 - Once FDA approval is received, a hospital or research organization uses their own IRB to do an independent review of the treatment protocol to protect the rights and welfare of the patients

Though Caution and Prudence Are important, Time Is of Essence for our Patients: Parallel Workstreams Lead to Faster Treatment



*Dependent on availability of WGS data and patient cell material

Though Caution and Prudence Are important, Time Is of Essence for our Patients: Parallel Workstreams Lead to Faster Treatment



Infrastructure Is Scalable to Support Professional Treatment of Many Patients

- **Standardized** protocol language and template informed consent language
- Streamlined **process** to support IND filing
 - Experience interacting with and responding to FDA queries
- **Standardized** and **validated** REDCap electronic database
 - Harmonizes implementation and training at sites
 - Library of electronic case report forms developed internally using standardized variables will facilitate **data sharing**
 - Outcome measures are **collected uniformly** across multiple individual programs
 - Safety data can be formatted uniformly and exported for review by DSMB

This infrastructure is scalable

Clinical Infrastructure Has Proven to Successfully Support the Treatment of our Patients

- Regulatory Metrics to date:
 - **9 INDs** submitted to **4 FDA divisions** between 17 Aug 2022 – 28 Sept 2023
 - Neurology 1 and 2 (7 INDS), Cardiology/Nephrology (1 IND), Ophthalmology (1 IND)
 - n-Lorem provides 98% of IND content (~10,800 pages for 9 INDs cumulative)
 - **>25 FDA interactions** (meetings and/or responses)
 - 2 more INDs to be submitted before the end of 2023
- Clinical Metrics to date
 - **5 patients** dosed – 4 CNS patients, 1 eye patient
 - Between 1-6 doses given per patient
 - **No treatment-related adverse events**



Each Nano-Rare Patient Requires an Approach Customized to Meet the Needs of That Patient

Nano-Rare Patients are Unique Requiring Individualized Outcomes Measures

- Mutations in the same gene can lead to different phenotypes
- Imperative to find appropriate treatment goals for each patient’s phenotype
 - Individualized treatment goals and appropriate outcome measures discussed at STAR

Assessments	Patient nL00333 - SCN2A	Patient nL00001 - SCN2A
Seizure Diary	X	X
Vineland-3	X	X
Aberrant Behavior Checklist	X	X
Bayley-4	X	X
Observer Rated Communication Ability	X	X

Note: These two patients were treated with different ASOs based on their mutation

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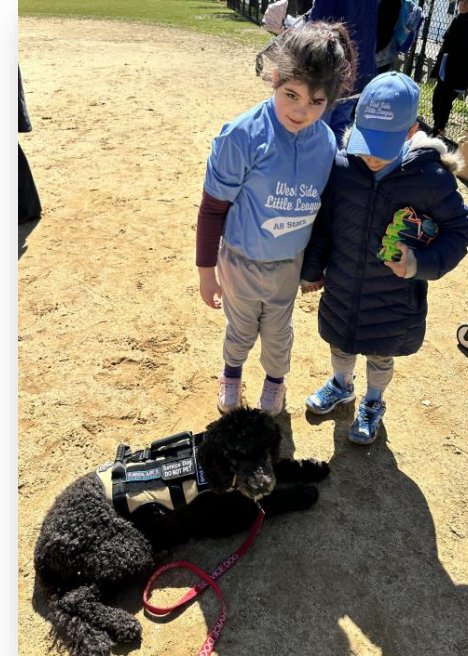
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Aberrant Behavior Checklist	X	X
Bayley-4	X	X
Observer Rated Communication Ability	X	X
Repetitive Behavior Scale	X	
Short Sensory Profile	X	
Weighted Intentional Communication Scale	X	
Dyskinetic Cerebral Palsy Functional Impact Scale		X
Bristol Stool Scale		X
Quality of Life questionnaire		X

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Anna and Susannah Provided Early Evidence That Optimized, Individualized ASOs Can Lead to Clinical Benefit



Anna
(FUS-ALS)



Susannah
(KIF1A)

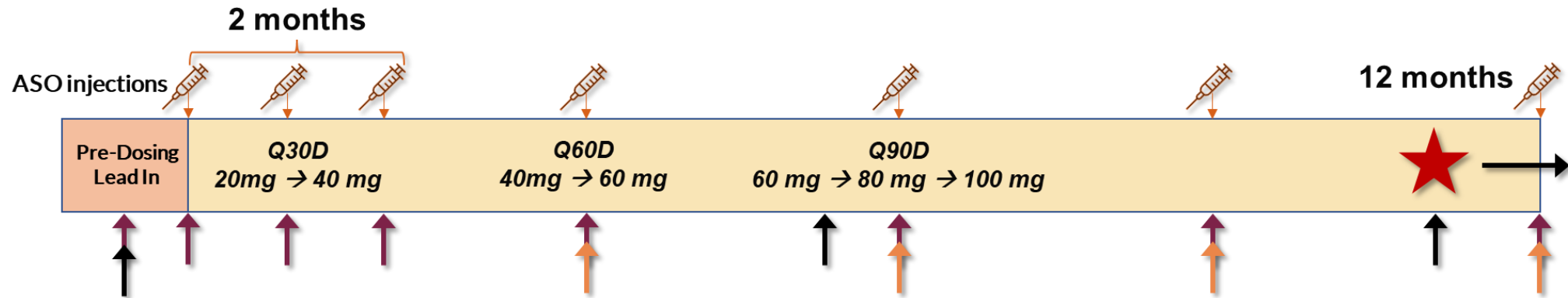
Baseline Presentation of nL00255-KIF1A Patient Prior to Treatment Start

Mutation in *KIF1A* gene that encodes a microtubule motor protein responsible for transport along axons

- 8 years old
- Severe epilepsy
- Intellectual disability
- Peripheral neuropathy
- Spasticity
- Optic nerve atrophy
- Cerebellar atrophy

Prior to treatment start, this patient needed to use a wheelchair to move around, and had debilitating neuropathy

Patient nL00255 Has Been Treated for Almost 12 Months to Date, and Has Received 6 Doses Successfully



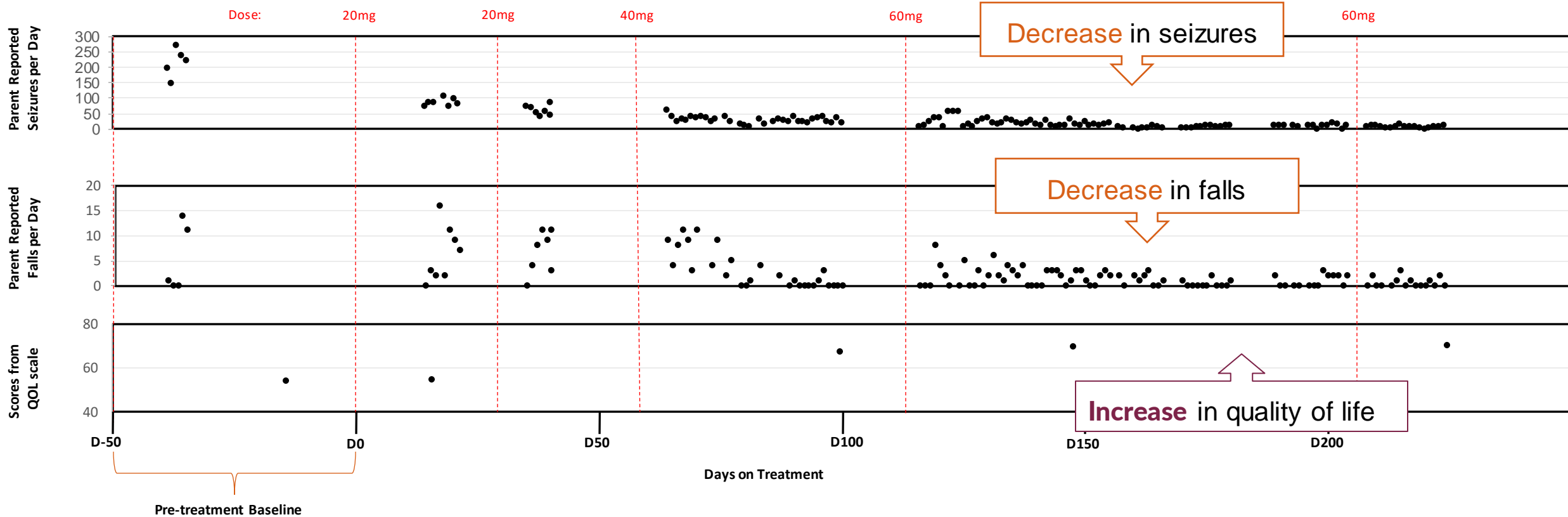
↑ **Baseline and with each dose**
 History/Exams
 Vitals
 EKG
 Overnight EEG
 6-Minute Walk
 QOL (QI-Disability)
 Labs (inc. CSF sampling & PKs)
 Seizure & Fall tracker review
 Video recording review
 Safety Tracking (AEs, CMs, Procs)

★ ↑ **With each dose (starting at 4th dose)**
 GMFM-66
 9-hole peg

↑ **Baseline and 6 monthly**
 DAS

↑ **PRN**
 MRI (safety to monitor for ventricular enlargement)

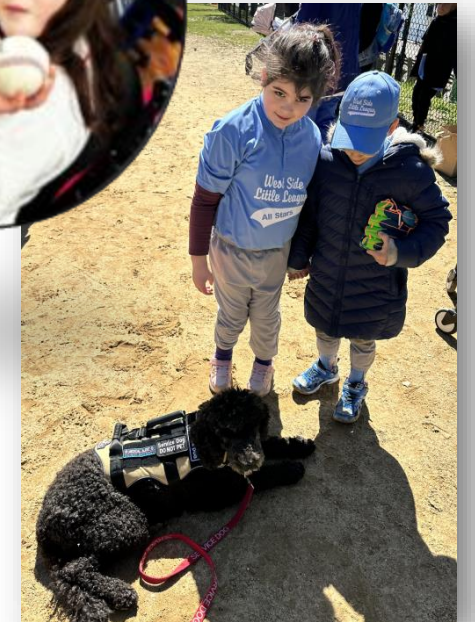
Clinical Improvements in Multiple Domains, Including Seizures, Falls, and Quality of Life



No ASO-related Adverse Events

Additional Improvements Reported by Family: Domains Outside of Clinical Measures

- Additional comments from parents:
 - *Her tremor is almost gone, meaning she can now hold a baseball.*
 - *She no longer falls because of her disease, now she may fall because she is so excited to do something.*
 - *She sings.*
 - *The pain in her hands and feet resolve with treatment but comes back close to the next dose; hopefully we can fine-tune the dose, so she does not have pain.*
 - *She is able to make it through the day without a nap.*

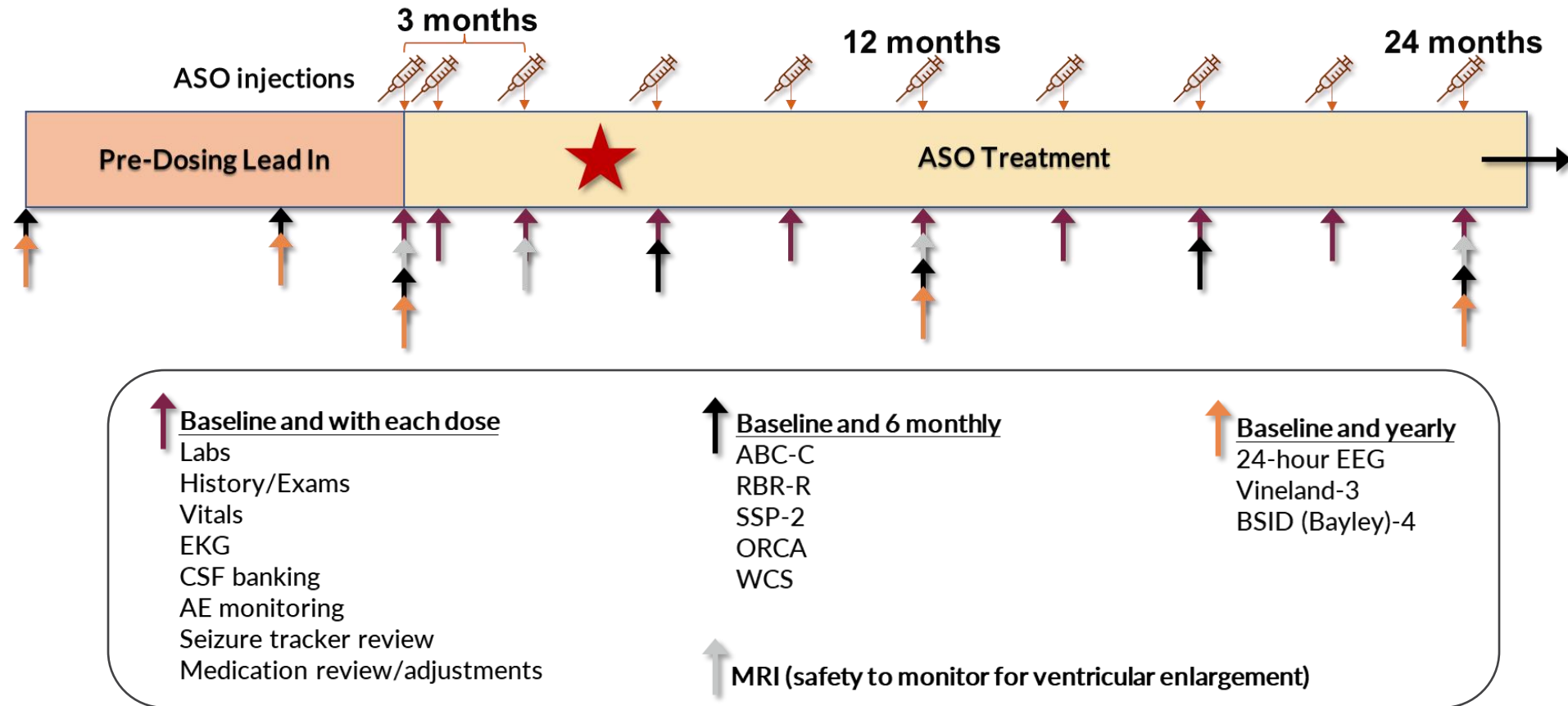


Baseline Presentation of nL00333-SCN2A Patient

Mutation in SCN2A gene, a voltage gated sodium channel, leading to hyperexcitability of neurons due to increased sodium currents

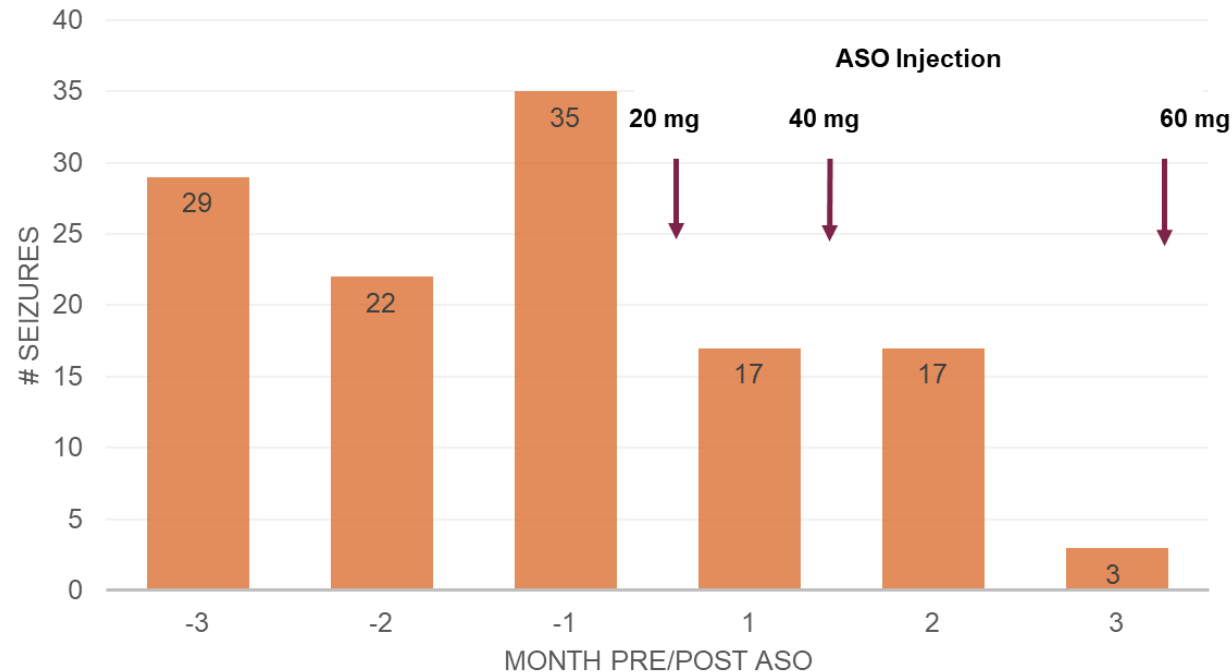
- 9 years old
- Severe intractable epilepsy uncontrolled by any known anticonvulsants
 - Tried 10 drugs unsuccessfully, needs to be on high phenytoin levels
- Cognitive, language and adaptive impairments
- Non-verbal
- Ranks around 1–2-year age equivalency on most outcome measures

Patient nL00333 Has Received 3 Doses to Date and Will be Followed for 24 Months to Assess Cognitive / Developmental Symptoms



Promising Trends Observed in Seizure Frequency in nL00333-SCN2A - 3 Month Data

- Too early to discuss other outcomes measures



Optimized ASOs Are Safe When Dose-Escalated Prudently

- Treatment well tolerated for all patients
 - **No ASO related** adverse events
 - **No ASO related** serious adverse events
- 2 patients (*) who were quite advanced at study start further progressed making it impossible to travel to site for subsequent treatment

Patient	Dosing details	Route of Administration
nL00380-SERPINI*	3 doses in 4 months (up to 60 mg)	Intrathecal
nL00947-TARDBP*	3 doses in 2 months (up to 100 mg)	Intrathecal
nL00255-KIF1A	6 doses in 10 months (up to 80 mg)	Intrathecal
nL00333-SCN2A	3 doses in 2 months (up to 60 mg)	Intrathecal
nL00180-FLVCR1	First dose (60ug)	Intravitreal

Integrated Safety Databases Provide the Foundation for Experienced Clinical Decision-Making

From NHP Toxicity Studies Through All Controlled Clinical Trials

NUCLEIC ACID THERAPEUTICS
Volume 27, Number 3, 2017
Mary Ann Liebert, Inc.
DOI: 10.1089/nat.2016.0650

Original Articles

The Effects of 2'-O-Methoxyethyl Containing Antisense Oligonucleotides on Platelets in Human Clinical Trials

Stanley T. Croke,¹ Brenda F. Baker,¹ Joseph L. Witztum,² T. Jesse Kwoh,¹ Nguyen C. Pham,¹ Nelson Salgado,¹ Bradley W. McEvoy,¹ Wei Cheng,¹ Steven G. Hughes,¹ Sanjay Bhanot,¹ and Richard S. Geary¹

NUCLEIC ACID THERAPEUTICS
Volume 28, Number 1, 2018
Mary Ann Liebert, Inc.
DOI: 10.1089/nat.2017.0693

Original Articles

The Effects of 2'-O-Methoxyethyl Oligonucleotides on Renal Function in Humans

Stanley T. Croke, Brenda F. Baker, Nguyen C. Pham, Steven G. Hughes, T. Jesse Kwoh, Danlin Cai, Sotirios Tsimikas, Richard S. Geary, and Sanjay Bhanot

Official journal of the American Society of Gene & Cell Therapy

MTOpen

original article

Integrated Safety Assessment of 2'-O-Methoxyethyl Chimeric Antisense Oligonucleotides in NonHuman Primates and Healthy Human Volunteers

Stanley T Croke¹, Brenda F Baker¹, T Jesse Kwoh¹, Wei Cheng¹, Dan J Schulz¹, Shuting Xia¹, Nelson Salgado¹, Huynh-Hoa Bui¹, Christopher E Hart¹, Sebastien A Burel¹, Husam S Younis^{1,2}, Richard S Geary¹, Scott P Henry¹ and Sanjay Bhanot¹

NUCLEIC ACID THERAPEUTICS
Volume 29, Number 1, 2019
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DOI: 10.1089/nat.2018.0753

Original Articles

Integrated Assessment of the Clinical Performance of GalNAc₃-Conjugated 2'-O-Methoxyethyl Chimeric Antisense Oligonucleotides: I. Human Volunteer Experience

Stanley T. Croke, Brenda F. Baker, Shuting Xia, Rosie Z. Yu, Nicholas J. Viney, Yanfeng Wang, Sotirios Tsimikas, and Richard S. Geary

Extensive Clinical Experience With ASOs of the Same Chemical Classes Provides Support for Individualized ASO Treatments

- Finkel, Richard S et al. "Treatment of infantile-onset spinal muscular atrophy with nusinersen: final report of a phase 2, open-label, multicentre, dose-escalation study." *The Lancet. Child & adolescent health* vol. 5,7 (2021):491-500.
- Darras, Basil T et al. "An Integrated Safety Analysis of Infants and Children with Symptomatic Spinal Muscular Atrophy (SMA) Treated with Nusinersen in Seven Clinical Trials." *CNS drugs* vol. 33,9 (2019):919-932
- De Vivo, Darryl C et al. "Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study." *Neuromuscular disorders : NMD* vol. 29,11 (2019):842-856.
- Mummery, Catherine J et al. "Tau-targeting antisense oligonucleotide MAPTRx in mild Alzheimer's disease: a phase 1b, randomized, placebo-controlled trial." *Nature medicine* vol. 29,6 (2023): 1437-1447. doi:10.1038/s41591-023-02326-3
- Tabrizi, Sarah J et al. "Targeting Huntingtin Expression in Patients with Huntington's Disease." *The New England journal of medicine* vol. 380,24 (2019): 2307-2316.
- Finkel, Richard S et al. "Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy." *The New England journal of medicine* vol. 377,18 (2017): 1723-1732. doi:10.1056/NEJMoa1702752
- Mercuri, Eugenio et al. "Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy." *The New England journal of medicine* vol. 378,7 (2018):625-635.
- Miller, Timothy et al. "Phase 1-2 Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS." *The New England journal of medicine* vol. 383,2 (2020): 109-119.



Disseminating Clinical Learnings From our Programs Will Help Advance the Knowledge for All

Data Sharing

- Providing information to the patient and medical community through different venues
 - Presentations
 - Publications in peer reviewed journals
 - Case studies on patient treatment

Data Pooling

- Collection of clinical data through our REDCap electronic database facilitates data pooling and data analysis across our programs
- Integration of clinical data sets from different sources
 - Requires equivalent quality and rigorous processes
 - Requires adequate systems to protect patient information and use of data

Industrialization of the n-Lorem Process Is Working: Our Successful Start Provides Promise for the Future

- n-Lorem has successfully industrialized the development of optimized ASOs, and our clinical infrastructure is solid and delivering high value for our current patients
 - Our clinical processes are scalable to meet the needs of tomorrow's patients
- We appreciate the FDA's collaboration
 - We have successfully navigated the regulatory landscape across 4 FDA divisions
- In collaboration with our physicians, n-Lorem is sharing clinical data via publications and presentations
- We are treating patients! We are honored by all the families who have put their trust in our hands.

Thank You to All Participating Institutions and Collaborators and to All Who Aim to Advance the Treatment of Nano-rare Patients

- Columbia University- Irving Medical Center
- Advent Health Research Institute
- Baylor College of Medicine
- Boston Children's Hospital
- Children's Hospital Colorado
- Children's Hospital of Philadelphia
- Cook Children's Medical Center
- University College London
- Icahn School of Medicine
- Los Angeles Children's Hospital
- Lurie Children's Hospital of Chicago
- Massachusetts General Hospital
- Mayo Clinic Minnesota
- Mayo Clinic Florida
- National Institute of Health
- Northwestern University Feinberg School of Medicine
- NYU Langone Health
- Rady Children's Hospital- San Diego
- Rutgers Health
- St. Jude Children's Research Hospital
- Stanford Medicine
- University of Texas Health Science Center
- UCI Health
- UC San Diego Medical Center
- UCSF Benioff Children's Hospital
- University of Miami Health System
- St. Louis Children's Hospital-Washington University
- Genomics England
- Seattle Children's
- Jefferson Health
- Children's Healthcare of Atlanta
- Medical College of Wisconsin
- Children's Healthcare of Atlanta
- SickKids Toronto
- Hackensack Meridian Health
- Oregon Health & Science University Hospital
- Rush University Medical Center
- N = 1 Collaborative
- Genomics England
- 1M1M



THANK YOU

More importantly, our **patients** and **families** thank you!



n-lorem
FOUNDATION