Wednesday, October 31 | 8:00 – 9:45 am ET

n-Lorem's Clinical Experience Paves the Way for Precision Medicine using Antisense Oligonucleotides

PRESENTER

Laurence Mignon, PhD

Executive Director, Clinical Development

Nano-rare Patient Colloquium 2024

Hosted by: Biogen

n-lorem FOUNDATION

Integrated Processes & Building a Cohesive Team

Providing an optimal ASOs to nano-rare patients is the product of high-quality processes and years of expertise and experience

Sarah Glass

Molecular Geneticist
Clinical trial expertise
Operational Management

Konstantina (Nadina) Skourti-Stathaki

RNA Expert
ASO discovery and design

Julie Douville

Toxicologist
ASO expertise
Non-clinical development

Laurence (Laury) Mignon

Neuroscientist
ASO expertise
Clinical development

Amy Williford

Communications
Educator
Fundraising expertise

Establishing Systems Processes Creating Unified Cohesive Team | Creating Optimal ASOs ATTC - RMC | Preclinical to Regulatory RMC - IND | Clinical & Safety Patient Mgmt & Treatment STAR - DSMB | Supporting Patient Journey Communication /Education

Topics Covered Today

- Introduction to the clinical team and their expertise and focus
- Accumulation of knowledge through the breadth of submitted applications
- Clinical processes supporting the industrialization of individualized ASOs development
- Clinical data providing important insight of the impact of ASO treatment

But First … High-level Clinical Summary

- All patients evaluable for benefit (7/7) show clinical benefits
- Benefits seen in all organs treated
  - In CNS, benefits seen at surprisingly low doses, and early in treatment
    - Improvements in multiple domains
  - Sustainable benefits seen in kidney function with liver-targeting ASO
  - Eye treatments safe upon multiple injections
- Pristine safety and tolerability profile
- Continued benefit with long-term treatment

Clinical Expertise Supporting n-of-1 Treatments

Nano-rare Patient Colloquium 2024

Hosted by: Biogen

n-lorem FOUNDATION

Clinical Team: >50 Years of Experience in ASO Development, Clinical Trials, and ASO Safety

Laurence Mignon, PhD
Exec. Dir. of Clinical Development

ATTC Co-Chair
STAR Committee
DSMB Lead

Neuroscientist, ASO expertise, clinical development, clinical outcome measures

Joe Gleeson, MD
Chief Medical Officer

ATTC Co-Chair
STAR Committee
DSMB Member

Neurogeneticist, clinical development, clinical outcome measures

Cedrik Ngongang, MD
Medical Geneticist

ATTC Lead
STAR Committee
DSMB Medical monitor

Medical geneticist, medical monitor, safety and clinical data analysis

Helen Pu, PhD
Sr. Clinical Data Scientist

STAR Lead
DSMB Data Scientist
Clinical Data Scientist

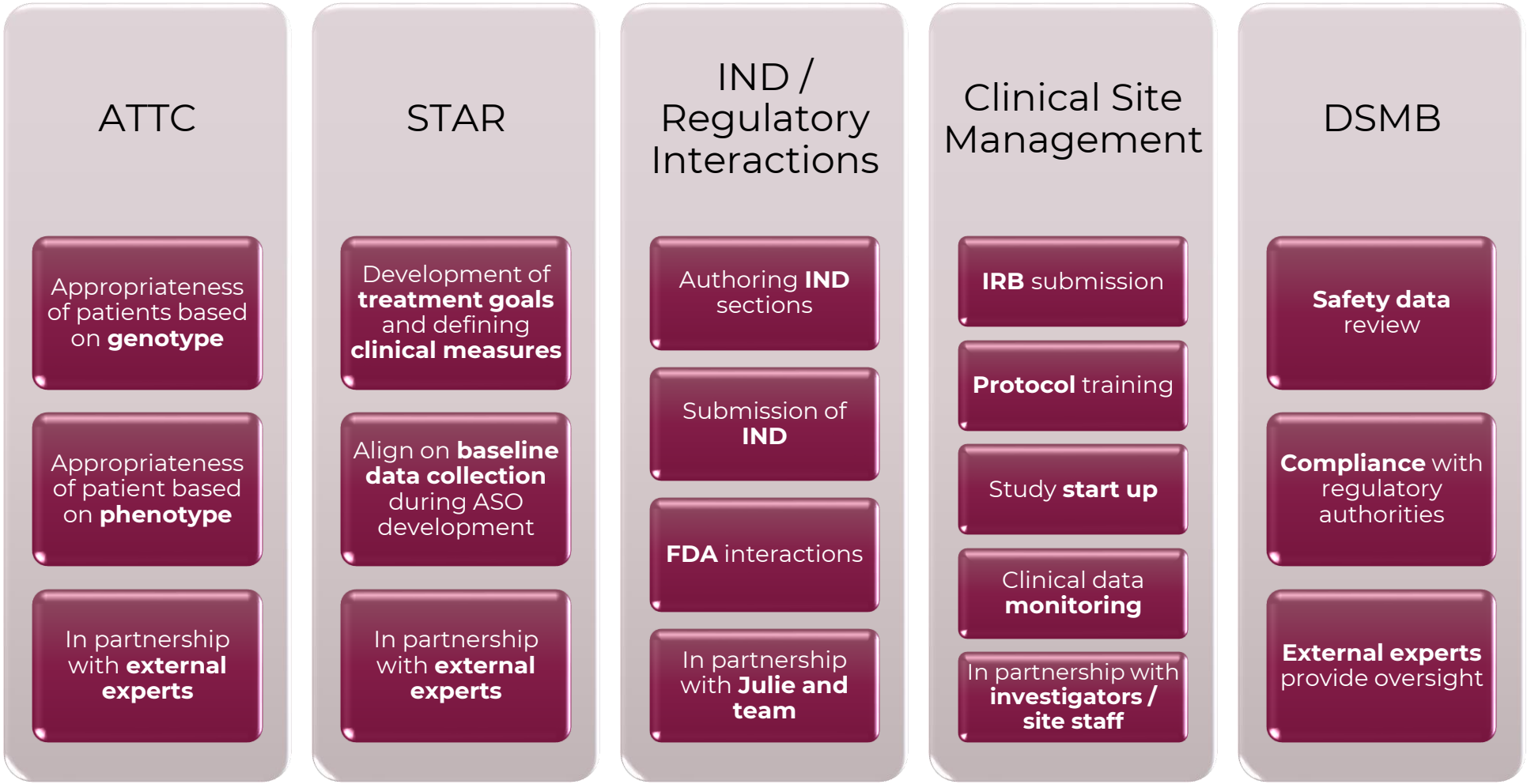
Clinical development, electronic data capture builds, safety and clinical data analysis

Stan Crooke, MD, PhD
CEO

R&D Oversight
Clinical Development

ASO technology founder, drug development expertise from biotech to large pharma

Expertise and Judgment of Clinical Team Important from Case Application to Treatment



ATTC – Access to Treatment Committee; STAR – Study Treatment and Assessment Review Committee; DSMB – Data Safety Monitoring Board

n-lorem FOUNDATION

What Patients Should be Treated with ASOs

Systematic Personalized Process

Genotype

- Is the pathogenic mutation understood?
  - Yes
- Are other pathogenic mutations excluded?
  - Yes
- Is the type of mutation fully understood?
  - Yes
- Is the mutation amenable to ASOs?
  - Yes

Phenotype

- Is the phenotype well characterized?
  - Yes
- Are potentially important treatment goals apparent?
  - Yes
- Are there validated clinical assessments for treatment goals available?
  - Yes
- Is the patient severely affected or likely to be so?
  - Yes
- What is the progression rate?
  - Yes
- Is the cellular phenotype sufficiently understood?
  - Yes

Administrative

- Is the prevalence of treatable patients with the mutation <30?
  - Yes
- Is the patient located where n-Lorem can treat?
  - Yes
- Are the treating physicians and institution willing and able to treat?
  - Yes
- Are patient cells available?
  - Yes

Thorough Review of Genotype/Phenotype by the Access to Treatment Committee (ATTC)

Why are we looking at genotype?

Responsibility to confirm ability to target a specific gene

- Is the mutation causal?
- Is the mutation amenable to an ASO treatment?

Why are we looking at phenotype?

Responsibility to confirm patient is appropriate for treatment

- Prevalence of the disease
- Manifestation of the disease
- Rate of progression of the disease in the current patient
- Affected organ to treat

Patient-specific Treatment Goals Guide the Choice of Clinical Assessments: STAR

STAR – **S**tudy **T**reatment and **A**ssessment **R**eview – meeting: collaboration between treating physicians and panel of experts to refine individualized treatment goals

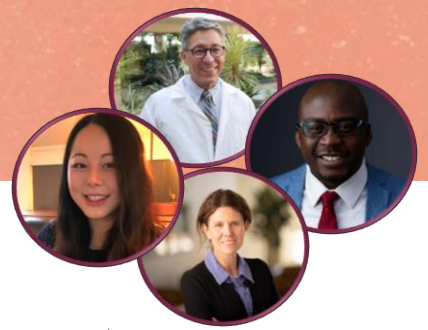
Importance of setting treatment goals

- Select treatment goals that matter to the patient and are quantifiable
- Treatment goals define the measures to use as endpoints

Importance of baseline data collection

- Important to understand the patient's status
- Key to assess changes on treatment
- Standardization of assessments across patients if possible

Continuous Review of Safety Data with External Experts: Data Safety Monitoring Board (DSMB)



Assess safety and tolerability of portfolio

- Continuous monitoring of safety data throughout the study
- Quarterly review of safety data from all actively treated n-Lorem patients
- Review of both individual and aggregate safety data

Assure compliance of n-Lorem with regulators

- Independent review of our ASOs
- Independent review of our processes

Learn Maximally from Each Patient: The Aggregate Experience, Part 2

Nano-rare Patient Colloquium 2024

Hosted by: Biogen

n-lorem FOUNDATION

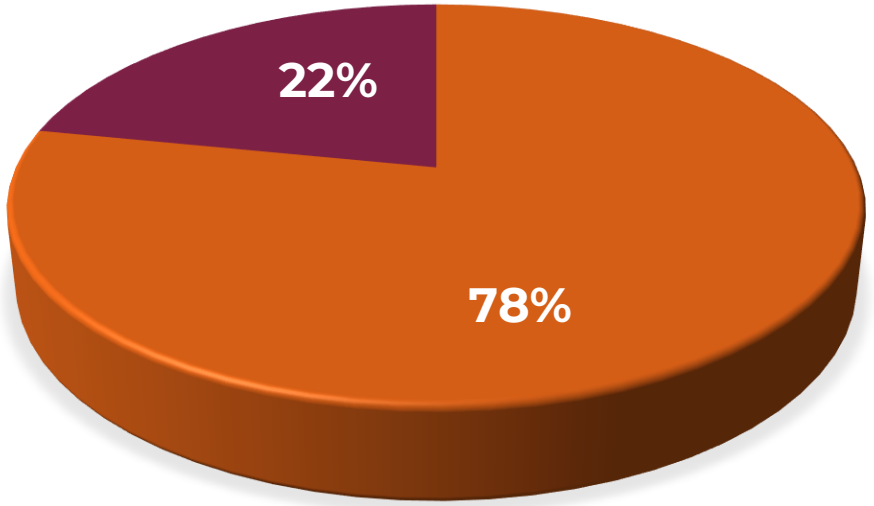
Applications For Treatment Continue to Increase

January 2020 to January 2023:

173 Applications: 4.8 apps/month

78% unique genes

22% repeat genes

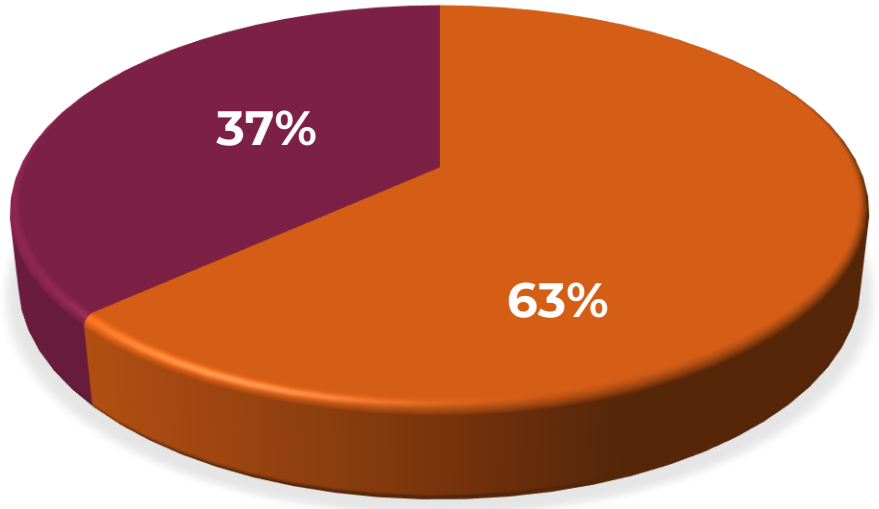


January 2023 to June 2024:

123 Applications: 7.2 apps/month

63% unique genes

37% repeat genes



- More applications for repeat genes
- Unique genes – more complicated applications

Total applications processed to date: 296

Inheritance Status of Mutations in All Applications: Submitted and Accepted

Applications Submitted

	De novo	Inherited	Unknown	Total
Number of **submitted** applications	162	103	16	281
% of **submitted** applications	57.6%	36.6%	5.6%	

Patients Accepted

	De novo	Inherited	Unknown	Total
Number of **accepted** applications	82	49	11	142
% of **accepted** applications	57.7%	34.5%	7.8%	

Familial Mutations: Phenotypic Diversity

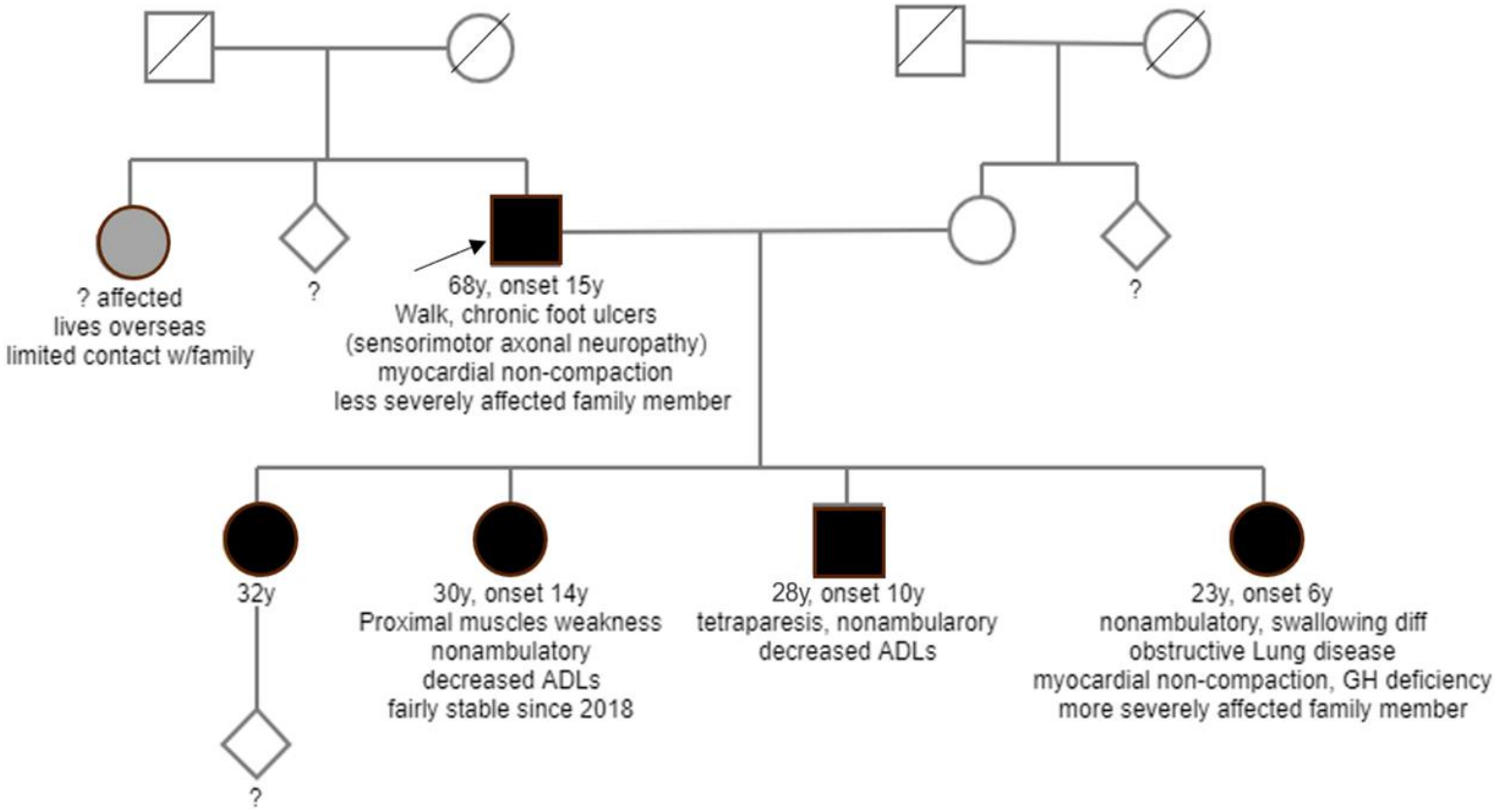
Nano-rare Patient Colloquium 2024

Hosted by: Biogen

n-lorem FOUNDATION

Case of Family with SPTLC1 Mutation

SPTLC1 is associated with both juvenile ALS and hereditary sensory neuropathy



Familial Mutation Showing Variable Expressivity: *SPTLC1*

Patient #	Gene	Gene function	Mutation	Functional Consequence	Patient age at application	Sex	Shared Phenotype	Difference/unique phenotype	
nL00790	**SPTLC1**	Sphingolipid metabolism	c.115_117delCTT, p.Leu39del	GOF	32yrs.	F	Lower motor neuron disease with progressive lower limb spasticity and prominent proximal muscle weakness; Myocardial non-compaction, Growth hormone deficiency, lactose intolerance, eczema, behavioral issues	polycystic ovary syndrome	Juvenile ALS
nL88845					23 yrs.	F		Progressive dysphagia, obstructive lung disease	
nL35793					28yrs.	M		nil	
nL71997					30yrs.	F		Restrictive lung disease	
nL30059					68yrs.	M	Myocardial non-compaction, Lactose intolerance, dysphagia, behavioral issues	Sensorimotor axonal polyneuropathy – No lower motor neuron disease. Less severely affected family member	Hereditary Sensory Neuropathy

Shadings show different patients of the same family

Additional Patient with *SPTLC1* Mutation: Different Mutation but Similar Phenotype to Children

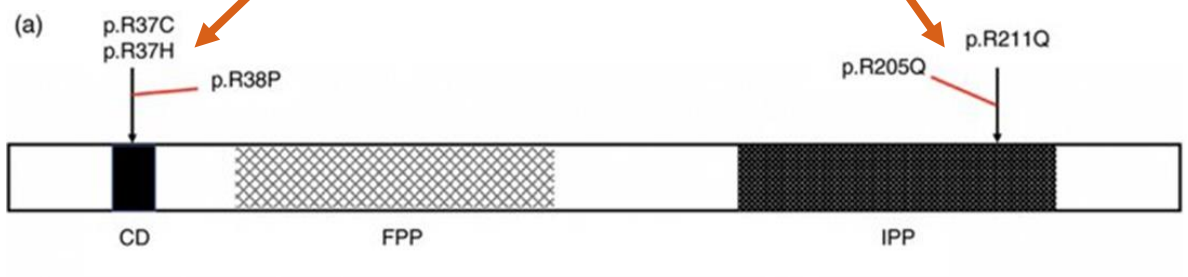
Patient #	Gene	Gene function	Mutation	Functional Consequence	Patient age at application	Sex	Shared Phenotype	Difference/unique phenotype	
nL00790	**SPTLC1**	Sphingolipid metabolism	c.115_117delCTT, p.Leu39del	GOF	32yrs.	F	Lower motor neuron disease with progressive lower limb spasticity and prominent proximal muscle weakness; Myocardial non-compaction, Growth hormone deficiency, lactose intolerance, eczema, behavioral issues	polycystic ovary syndrome	Juvenile ALS
nL88845					23 yrs.	F		Progressive dysphagia, obstructive lung disease	
nL35793					28yrs.	M		nil	
nL71997					30yrs.	F		Restrictive lung disease	
nL30059					68yrs.	M	Myocardial non-compaction, Lactose intolerance, dysphagia, behavioral issues	Sensorimotor axonal polyneuropathy – No lower motor neuron disease. Less severely affected family member	Hereditary Sensory Neuropathy
nL00156			c.58G>T, p.Ala20Ser	GOF	19 yrs.	F	Lower motor neuron disease with progressive muscle weakness and atrophy; behavioral issues	Possible autonomic dysfunction (frequent dizziness upon sitting and standing quickly), cataract	Juvenile ALS

Pink shading represented patient not part of family

Location of Mutations Dictates the Severity of the Phenotypes: *DHDDS*

Patient #	Gene	Gene function	Mutation	Functional Consequence	Patient age at application	Sex	Shared Phenotype	Difference/unique phenotype
nL64799	**DHDDS**	Dolichol synthesis	c.110G>A, p.Arg37His	Dominant negative/GOF	8 yrs.	F	Global developmental delay/mild intellectual disability; movement disorders, behavioral issues	No current seizures
nL70324					14 yrs.	M		No history seizures
nL00901			c.614G>A, p.Arg205Gln	Dominant negative/GOF	11 yrs.	F		Intractable seizures

Orange shadings show patients from same family



IPP mutation seems to be associated with a more severe phenotype

CD: catalytic domain
FPP: farnesyl diphosphate binding site
IPP: isopentenyl diphosphate binding site

Industrialization of n-of-1 ASO Treatments

Nano-rare Patient Colloquium 2024

Hosted by: Biogen

n-lorem FOUNDATION

N-of-1 Trials Are Unique and Require Flexibility in Paradigm

- Modified cross-over design
  - Robust pre-treatment data collected instead of lead-in placebo treatment
  - Data analysis of individual pre-treatment and post-treatment data based on prespecified goals, even when multiple patients are treated with the same ASO
- The patients we are treating are very ill and severely debilitated
  - Use of multiple concomitant medications
  - Comorbidities
  - Various stages of disease
- Limited natural history data for the diseases/ patients we are treating
  - We know less about our patients and their disease progression than during regular trials
  - Opportunity to learn and share learnings

Systematic Industrialization of the Clinical Data Collection Platform Accelerates Treatment for all Patients

- Secure, validated online web platform
- Familiar to academic and clinical sites
- Versatile and flexible system

REDCap®

Standardization of phenotypic data collection

Streamlined collection of clinical and safety assessments via
> 100 unique case report forms

Fast deployment for new patients

Patient 1 – Phenotype X

Patient 2 – Phenotype Y

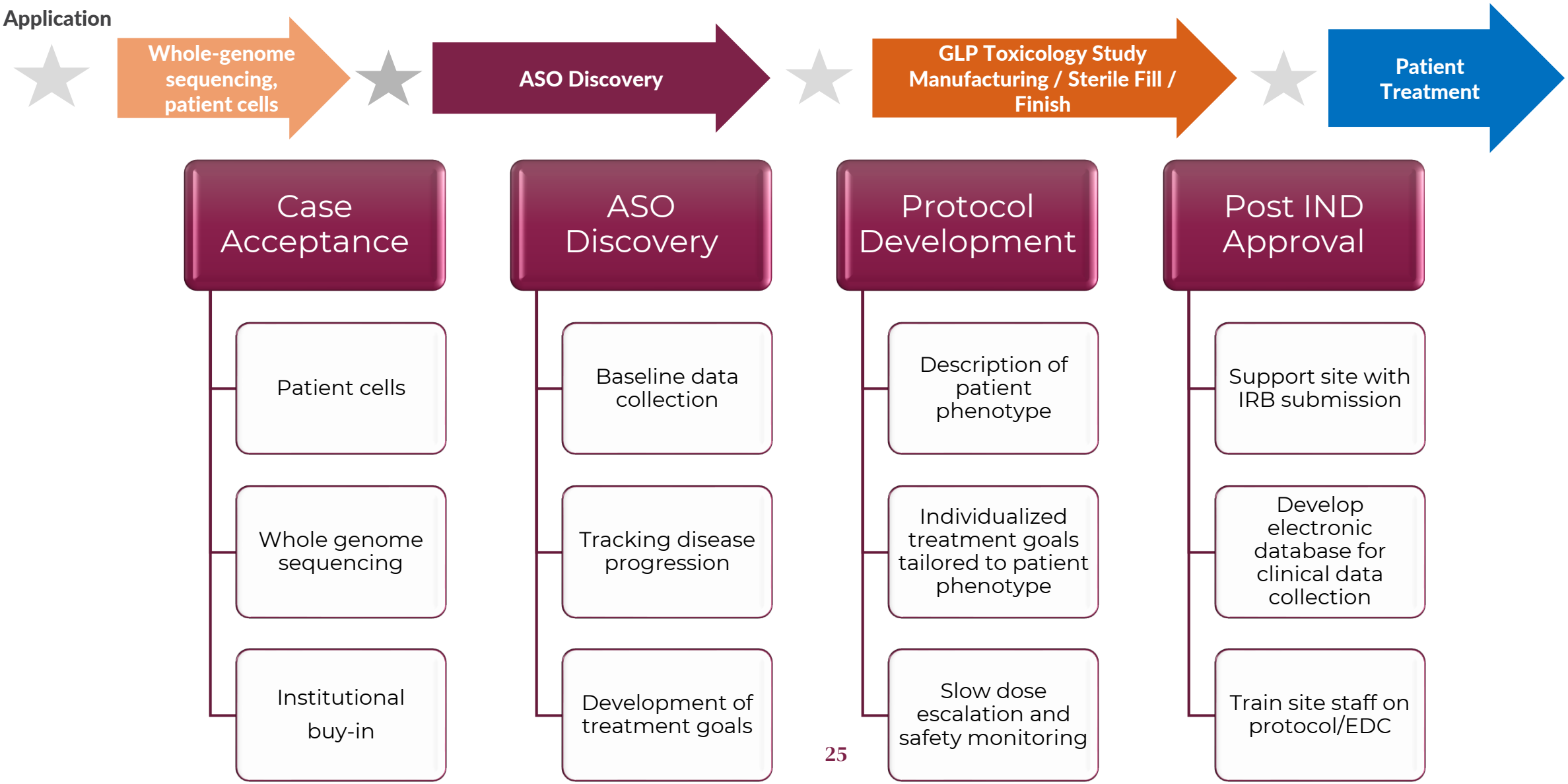
Pediatric Neurology Programs Utilize Similar Assessments: Leads to Faster Inter-program Deployment and Data Interpretation

Assessment	Phenotype	SCN2A	KIF1A	KIF1A	SCN2A	ATN1	hnRNPH2	ATN1	hnRNPH2
Seizure Diary	Seizures	X	X	X	X	X	X		X
EEG	Seizures	X	X	X	X		X	X	X
6-Minute Walk Test (6 MWT)	Mobility			X					
Gross Motor Function Measurement – 66 (GMFM-66)	Gross Motor		X	X					
Gross Motor Function Measurement – 88 (GMFM-88)	Gross Motor		X						
Modified Gross Motor Function Measurement (GMFM)	Gross Motor						X		X
Gross Motor Function Classification Scale (GMFCS)	Gross Motor		X				X		X
9-hole Peg Test (9 HPT)	Fine Motor			X					
Gait analysis	Mobility			X		X			
Mobility Tracker (Wearable)	Mobility		X			X	X		X
Sleep Tracker	Sleep		X						
Fall Diary	Mobility			X					
Differential Ability Scales II	Cognition			X					
Quality of Life Inventory in Disability (QI-Disability)	Quality of Life	X		X			X		X
Bayley Scales of Infant Development (BSID-4)	Development	X	X		X		X		X
Vineland Adaptive Behavioral Scales (Vineland-3)	Behavior	X	X		X				
Observer Reported Communication Ability (ORCA)	Communication	X	X		X	X	X		X
Modified Friedreich Ataxia Scale (mFARS)	Ataxia		X				X		X
Scale for the Assessment and Rating of Ataxia (SARA)	Ataxia					X			
Brief Ataxia Rating Scale (BARS)	Ataxia								
Dyskinetic Functional Impact Scale (DFIS)	Motor	X							
Bristol Stool Form Scale	GI	X							
Aberrant Behavior Checklist (ABC)	Behavior	X			X				
Repetitive Behavior Score – Revised (RBS-R)	Behavior				X				
Short Sensory Profile-Version 2 (SSP-2)	Sensory Issues				X				
Weighted Communication Scale (WCS)	Communication				X				
Activities of Daily Living (ADL)	Activities of Daily Life					X			
Caregiver Global Impression of Change (CGI-C)	Quality of Life					X			
NIH Toolbox Cognition Battery for Intellectual and Developmental Disabilities (NIHTB-CB IDD)	Cognition					x	X		X

US Institutional Footprint Needs to Expand to Provide Access to All Communities

- Established relationships with institutions across the US
  - These institutions have been early adopters of the n-Lorem work
- There is still work to be done to onboard new institutions to ascertain patient access to treatment

Close Collaboration with Clinical Sites Starts at Case Acceptance: Goal is to Ensure Quality Data Collection to Enable Treatment Decisions



Clinical Update

Nano-rare Patient Colloquium 2024

Hosted by: Biogen

n-lorem FOUNDATION

Safety & Tolerability Are Essential

First, Do No Harm

- Most nano-rare patients suffer from advanced severe diseases
- Most are treated with other medicines with potential side-effects
- This has never been done before
  - Extremely limited preclinical data
  - Limited knowledge about the diseases
  - No human normal volunteer data
- Until we have **more experience**, we must be **cautious**
  - As we gain experience, we can be more assertive

Excellent Safety Profile Across all ASO Programs: Multiple Patients Treated for 1-2 years

- 4 patients have been treated for 12+ months
- Pristine safety and tolerability profile
- Evidence of clinically important benefit in 7/7 evaluable patients
  - Improvement in multiple domains in CNS
  - Evidence of CNS benefit at low doses
  - Continued benefit with continued treatment
  - Target reduction and stabilization of renal function

Patient	First dose	# of doses given	Safety
nL00255 – KIF1A	Oct 2022	11	√
nL00068 – SAA1	Nov 2023	10	√
nL00333 – SCN2A	Jun 2023	8	√
nL00180 – FLVCR1	Aug 2023	6	√
nL00001 – SCN2A	Mar 2024	4	√
nL01183 – ATN1	Feby 2024	4	√
nL00010 – CHCHD10	Apr 2024	4	√
nL00037 – KIF1A	May 2024	4	√
nL00808 – ELP1	Jun 2024	3	√
nL00152 – CHCHD10	Jun 2024	3	√
nL00214 – TUBB4A	Sep 2024	2	√
nL98087 – hnRNPH2	Sep 2024	2	√
nL00250 – CHCHD10	Oct 2024	1	√

as of Oct 25, 2024

Clinical Scorecard Since the Last Colloquium

- More than doubled the number of patients currently on treatment
  - Expecting an additional 8-9 patients to receive their 1st dose before the end of the year
- We are treating multiple organs amenable to our ASO strategies, using several routes of administration

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

ASOs with Submitted INDs to Treat Multiple Patients: Shortens Time to Treatment and Maximizes Benefit per Dollar/ Time Invested

ASO	Gene	ASO strategy	Patients Treated	Additional Accepted Patients	Available to New Patients
nL-KIFA-001	KIF1A	Allele-selective	2	5	Dependent on SNP
nL-UBTF-001	UBTF	Allele-selective	0	2	Dependent on SNP
nL-TARD-001	TARDBP	Allele-selective	1	1	Dependent on SNP
nL-SCN2-001	SCN2A	Allele-selective	1	0	Dependent on SNP
nL-SCN2-002	SCN2A	Allele-selective	1	0	Dependent on SNP
nL-TUBB4-001	TUBB4A	Non-allele-selective	1	4	Yes
nL-ATN1-002	ATN1	Non-allele-selective	1	2	Yes
nL-CHCHD-001	CHCHD10	Non-allele-selective	3	6	Yes
nL-RNPH2-001	HNRNPH2	Non-allele-selective	1	5	Yes
nL-H3F3A-001	H3F3A	Non-allele-selective	0	1	Yes
nL-LMNB1-001	LMNB1	Non-allele-selective	0	1	Yes
nL-SAA1-001	SAA1	Non-allele-selective	1	0	Yes
nL-SERP-001	SERPINI1	Non-allele-selective	1	0	Yes
nL-FLVD-001	FLVCR1	Splicing	1	0	Dependent on mutation
nL-IKBK-001	ELP1	Splicing	1	0	Dependent on mutation

as of Oct 25, 2024

Types of Benefits Observed Across Evaluable Patients

- Improvements in
  - Seizure frequency
  - Motor function/ mobility
  - Behavior (attention, stereotypies, repetitive behavior, irritability)
  - Communication
  - Quality of life
- Other benefits in specific patients
  - Improvement in pain
  - Improvement in drooling
  - Increased stamina
  - Improved GI symptoms

What We Are Learning from Our Patients Is Optimistic for the Other Programs in the Pipeline

- Eye treatments safe upon multiple injections
  - Actively working on additional eye targets
- Sustainable benefits seen in kidney function with liver-targeting ASO
  - Actively working on additional liver and kidney targets
- In CNS, benefits seen at surprisingly low doses and early in treatment
  - Timing of treatment – the earlier the better!
    - Stop neurodegeneration as early as possible
    - Impact neurodevelopment as early as possible

Concluding Remarks

- Clinical experience is outstanding
  - ASOs given via multiple routes of administration are safe
  - Clinical benefits are seen across all organs and at low doses and early in treatment in CNS
- Process can be further expanded to address the need of tomorrow
- Nimble experienced drug development team in partnership with FDA, and following the Individualized ASO guidance, has treated the most patients under this model
- This could not have been accomplished without our Pioneer Patients and the trust they put in us – THANK YOU!


Thank you!