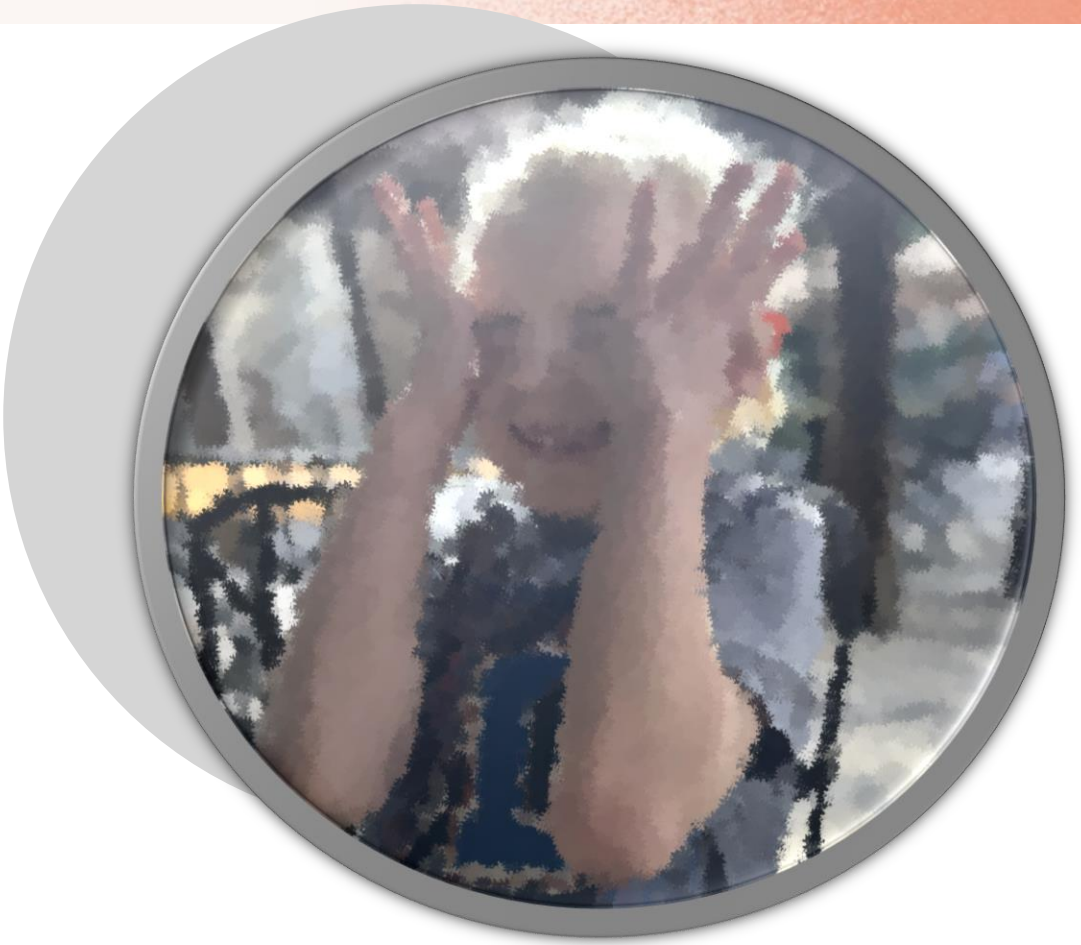
Wednesday, October 31 | 8:00 – 9:45 am ET

From Dream to Reality:

A Scalable Solution for the Treatment of the Nano-rare



PRESENTER

Sarah Glass, PhD

Chief Operating Officer, n-Lorem Foundation

Nano-rare Patient Colloquium 2024

Hosted by: Biogen

n-lorem FOUNDATION

Agenda

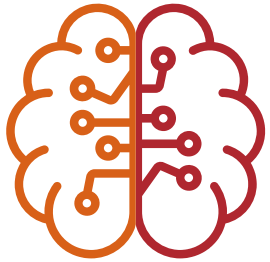
- Creating a Solution for the Nano-rare: Industrialize
- Building the Infrastructure of Integrated Experts and Processes
- Key Achievements and Team Behind the Success
- The Future of n-Lorem

Creating a Solution for the Nano-rare

- Purposeful step-by-step growth towards a scalable individualized ASO treatment solution
  - Recruit internal expertise to lead and build each function
  - Embed external perspectives across the entire process through expert committees
  - Establish a network of partners/ providers.
  - Ensure every step of the process provides direct benefit to the patient.
  - Establish an industrialized approach that *maintains the focus on each individual patient*

in·dus·tri·al·ized

[inˈdəstrēəˌlīz]



One Patient at a Time

- Fundamental, often linear steps in a process one at a time
- Primarily driven by activities performed manually
- Low(er) throughput
- Not scalable (enough)
- Inefficient and costly

Industrialized

- Activities occur in parallel for efficiency
- Leverages robots to ensure comprehensive design
- High-throughput
- Scalable with high-quality
- Efficient and more cost-effective

Building the Infrastructure with Integrated Experts and Processes

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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

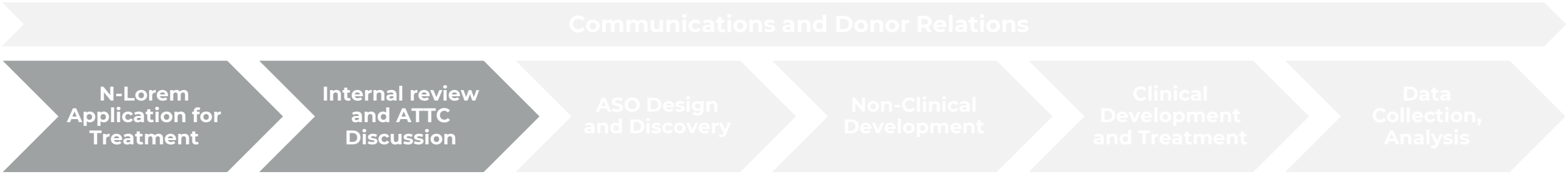
Establishing Systems Processes Creating Unified Cohesive Team | Creating Optimal ASOs ATTC - RMC | Preclinical to Regulatory RMC - IND | Clinical & Safety Patient Mgmt & Treatment STAR - DSMB | Supporting Patient Journey Communication /Education

Key Questions Answered When Establishing an End-to-End Process to Bring Individualized Treatments to Nano-rare

1. How do we evaluate and identify which patients n-Lorem can help?
2. How do we ensure every patient is treated with a quality and optimal ASO?
3. How do we meet regulatory requirements for safety and quality of each ASO?
4. How do we determine whether each patient is benefiting from their ASO?
5. How do we create a nano-rare community, ensure awareness, and share data and progress broadly?

1 How Do We Evaluate and Identify Which Patients n-Lorem Can Help?

- Physician applies to n-Lorem on behalf of their patient
- Requires extensive genotype and phenotype information on each patient
- Internal scientific review by medical genetics and antisense experts
- External Access to Treatment Committee (ATTC) reviews and makes recommendations on amenability to ASO treatment
- n-Lorem Executive Committee decision
- Every (blinded) patient genotype and phenotype information reviewed by >25 experts



Comprehensive Evaluation of Patient's Genotype and Phenotype to Drive Acceptance Decision

n-lorem FOUNDATION

Access to Treatment Committee (ATTC) Case # 255

9-18-20

- **Candidate Gene**: *Kinesin family member 1A* (*KIF1A*)
- **Gene family**: Kinesin family of motor proteins
- **Expression**: Primarily CNS

Genetics

- **Strength of evidence**: Good biochemical evidence that the mutation affects KIF1A binding affinity to microtubules.

Genetic Change and Impact

- **Impact of genetic change on gene function-** The P305L mutation results in a decrease in binding affinity of KIF1A to microtubules. The mutations has an effect on the velocity and force generation of the motor, but the primary defect seems to be a decrement in binding affinity (Lam et al. BioRxiv 09 19 20).

Proposed Antisense Treatment Plan

- **Antisense approach**
  - Allele selective targeting of the P305L allele with RNAseH1 selective ASO
- **Route of delivery**- Intrathecal, intravitreal
- **Potential challenges to discovery of an effective ASO**- Identification of a SNP that is sensitive to A reverses neuronal phenoty

Benefit/Risk Assessment

- **Potential benefit**- Improvement of epilepsy, prevention of further neurodegeneration in CNS and eye. Improvement in peripheral neuropathy
- **Likely residual health issues**: Likely residual neurodevelopmental issues
- **Potential risks of treatment**: Further worsening of condition if not able to get adequate selectivity
- **Risk mitigation approaches:** Work with investigator and patient organization to develop biomarker that can be used to measure axonal transport and release of synaptic vesicles

2 How Do We Ensure Every Patient is Treated with a Quality and Optimal ASO?

- Leverages deep understanding of antisense technology and 30 years of experience
- Commercial-level automation
- Comprehensive design ensures the optimal ASO (>500 ASOs in initial screen for non-allele selective)
  - Quality and scientific rigor
- Individual program decisions that leverage cross-portfolio knowledge and experience
- Partnerships for small-scale synthesis, equipment providers, non-GLP tolerability studies

ASO Design and Discovery Data Anchors Each Research IND

Table 1 n-Lorem Research and Development Process

Step	Purpose	Minimum criteria
ASO design including in silico off-target assessment	Exclude motifs associated with ASO structure, repeat sequences, cytotoxicity, pro-inflammatory effects and off targets, and to include attractive motifs	All important attractive motifs included, unattractive excluded
Primary ASO screen	To identify optimal sites in target RNA for ASO and H-1 binding	>80% target reduction
5-point dose response evaluation of multiple ASOs	To select at least 20 ASOs for in vivo tolerability screening	IC50 1 µmol (free uptake)
In vitro off-target analysis	To confirm selectivity of ASO for target RNA vs. any worrisome off-target	~10-fold difference in IC50s for target RNA vs. off target
BJAB Assay	To exclude activators of innate immunity	Less than 2-fold increase in TNF-alpha at high ASO concentrations
Single dose tolerability screen in mouse and rat	To identify any ASO with high potential for transient paresis, and to identify optimally tolerated lead ASOs	Predicted safety margin in rodents in GLP studies of 25-40
Repeat-dose GLP 3-month rodent toxicity	To identify NOAEL and cell types at risk	An attractive therapeutic index with an acceptable NOAEL
GMP Manufacturing	Quality ASO drug substance	Pure, stable drug product
Sterile Fill and Finish	Quality, stable and sterile ASO drug	Sterile vials for administration

2.4.2 Pharmacology

2.4.2.1 Primary Pharmacodynamics

2.4.2.1.1 *In Vitro* Studies

ASO Design – Close to 500 antisense oligonucleotides (ASO) of mixed backbone design (PO/PS) were designed to target the pre-mRNA of the pathogenic allele of *KIF1A*. Oligonucleotides were designed to promote selective degradation of the mutant *KIF1A* RNA through recruitment of RNase H1 to the RNA-oligonucleotide heteroduplex (Crooke ST, et

2.4.4 Toxicology

The toxicity of nL-CHCHD-001 was assessed in an 8-week single intracerebroventricular dose study in mice (Study No. CHCHD10-230221), an 8-week single intrathecal dose study in rats (Study No. CHCHD10-230301), and a GLP compliant 13-week once monthly intrathecal dose study in Sprague Dawley rats (Study No. nL00010-tox-r/CRL Study No. 5550047).

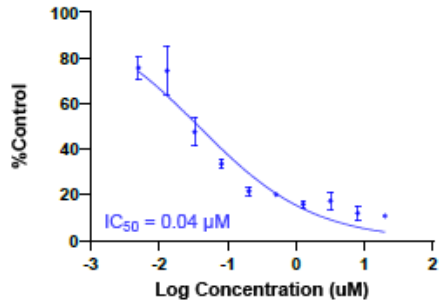
Genotoxicity, carcinogenicity, reproductive and developmental toxicity studies were not conducted as they are not required based on the Draft FDA guidance on, "Nonclinical Testing of Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases" (FDA 2021).

A summary of completed and ongoing toxicity studies is provided in Table 4 below.

Table 5 Summary of nL-CHCHD-001 (ION-1757626) Toxicology Studies

Study No.	Study Title	Dosing Route	Doses and Regimen	GLP	Start Date	End Date
Completed Studies						
CHCHD10-230221	8-Week Single ICV Dose Tolerability Study with nL-CHCHD-001 (ION-1757626) in Mice	ICV	0.7 mg on Day 0	No	21 Feb 2023	18 Apr 2023
CHCHD10-230301	8-Week Single Intrathecal Dose Tolerability Study with nL-CHCHD-001 (ION-1757626) in Rats	IT	3 mg on Day 0	No	01 Mar 2023	26 Apr 2023
Ongoing Study						

Figure 1: Dose-response Analysis of nL-CHCHD-001 Targeting Human *CHCHD10* pre-mRNA.

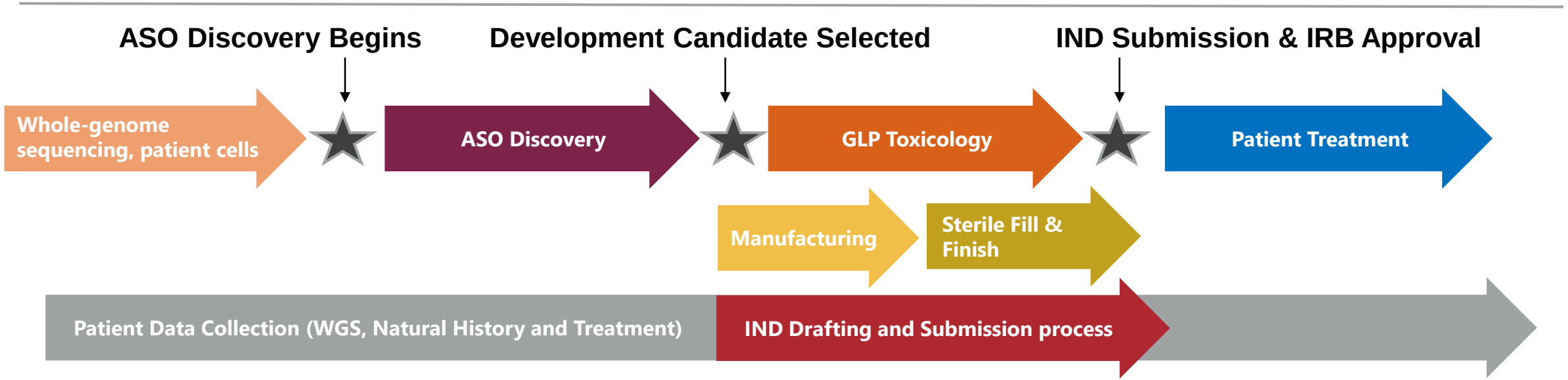


3 How Do We Meet Regulatory Requirements for Safety and Quality of Each ASO?

- Establish streamlined system for coordination of CRO/ CMO activities with associated regulatory-caliber data review, analysis and reporting
- Toxicologists apply experience leading individualized ASO GLP-toxicity studies to ensure safety of clinical compound
- ASO CMC experts apply experience with commercial grade drug product/ substance and relevant commercial processes and learnings leading to quality drug product for the patient
- Partner with leading CRO and CMO organizations who enable high-volume efficiencies
- Highest priorities: Safety of an ASO and quality of drug product

n-Lorem's ASO Discovery & Development Process

- Individualized and infinitely scalable
- n-Lorem uses the efficiency of ASO technology and the FDA guidance for nano-rare patients to provide rapid, effective and affordable treatments



Meeting All Requirements for IND Submission and Approval

Initial Investigational New Drug (IND) Application

Drug Name: nL-KIF1-001

Indication: Treat an individual patient with a Kinesin family member 1A (*KIF1A*) c914C>T gene mutation

n-Lorem Foundation | Initial Investigational New Drug Application

nL-CHCHD-001 | IND No. 171604, Serial No. 0000

3.2.P.5 CONTROL OF DRUG PRODUCT

3.2.P.5.1 Specifications

The specification for nL-CHCHD-001 for Injection, 15 mg/mL is shown in Table 8. Unless noted otherwise, all methods are defined by Argonaut or ChemGenes method SOP numbers.

Table 8. Specification for nL-CHCHD-001 for Injection, 15 mg/mL

Test	Method	Acceptance Criteria
Identity by mass spectrometry	ESI-MS	Mass of major product within 5% of expected mass
Appearance (visual inspection)	SOP-0129	Clear colorless to slightly yellow solution essentially free from visible particles
Purity	IP-RP HPLC IE0-80-100-30min	Purity ≥ 90.0% area No single impurity > 4%
pH	SOP-0087	7.0 – 7.4
Osmolality	SOP-0136	Report mOsm/kg
Endotoxin Kinetic chromogenic method	USP <85>	≤ 1.5 EU/mL
Concentration based on free acid of parent oligonucleotide	SOP-0093	14.0 – 16.0 mg/mL
Sterility	USP <71>	No growth
Particulate Matter	USP <788>	≤ 6000 particles ≥ 10 um ≤ 600 particles ≥ 25 um

FDA U.S. FOOD & DRUG ADMINISTRATION

IND [redacted]

STUDY MAY PROCEED

n-Lorem Foundation
Attention: Julie Douville
Executive Director ASO Discovery and Development
2888 Loker Street
Carlsbad, CA 92020

Dear Julie Douville:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA) for nL-[redacted]-001.

This IND includes your protocol entitled, "An open-label, single-center, single-participant study of an experimental antisense oligonucleotide treatment for a patient with *LMNB1* mutation associated [redacted]

We have completed our safety review of your protocol and, as discussed with you by electronic mail with [redacted] RPM, of this Division on September 4, 2024, have concluded that you may proceed with your proposed clinical investigation.

Sponsor Reference No. nLorem-00255

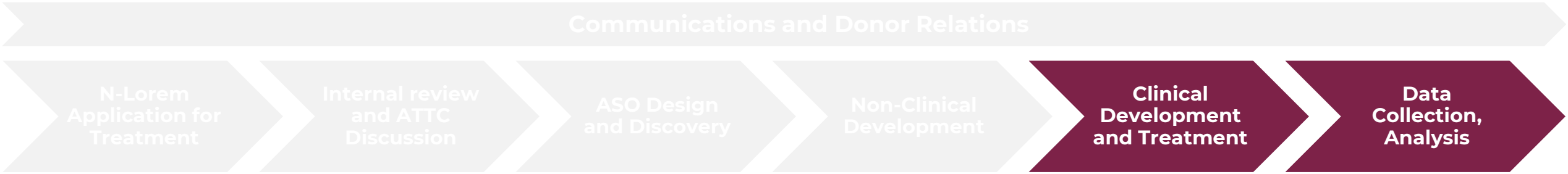
A 13-Week Repeat Dose Toxicity Study of ION-1615907 by Intrathecal Injection in Rats

GLP

SPONSOR:
n-Lorem Foundation
2888 Loker Avenue East, Suite 113
Carlsbad, CA 92010
USA

4 How Do We Determine Whether Each Patient is Benefiting from Their ASO?

- Study Treatment and Assessment Review (STAR) committee to support decision regarding treatment goals and assessments
- Data Safety Monitoring Board (DSMB) to provide independent quarterly review of data to ensure patient safety
- n-Lorem hosted REDCap platform allows physicians to directly enter data into patient-specific case report forms
- Partner with leading institutions to enable patient treatment
- Data supports physicians' continual treatment decision



The Path to Treatment

An open-label single center, single-patient study of an experimental antisense oligonucleotide treatment for Kinesin family member 1A (*KIF1A*) gene mutation

Regulatory Sponsor: n-Lorem Foundation
2888 Loker Avenue East, Ste. 110
Carlsbad, CA 92010
760-552-7113

Study Product: Experimental Antisense Oligonucleotide nL-KIF1-001

IND Number: **161670**

Protocol Version Number: 4.0

Protocol Version Date: 21JUN 2024

REDCap

Record ID 2

Demographics

Record ID 2

Case Number ____ Document Version v1

Demographics

Date of Birth (year)	Age	Race	Ethnicity
4 digit year 4 characters remaining	years old 3 characters remaining	☐ American Indian or Alaska Native ☐ Asian ☐ Black or African American ☐ Native Hawaiian or Other Pacific Islander ☐ White ☐ Unknown ☐ Not reported	○ Hispanic or Latino ○ Not Hispanic or Latino ○ Unknown ○ Not reported
Sex (Assigned at Birth)			
○ Male ○ Female			

Form Status

Complete? Incomplete

Consent Form to Participate in a Research Study and HIPAA Authorization

Title of research study and general information

Study title:	*An open-label single center, single patient study of an experimental antisense oligonucleotide treatment for Kinesin family member 1A (KIF1A) gene mutation*

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KIF1A Treatment Protocol IRB # AAAU1165
nL-KIF1-001 Study Drug Manual

An Open-Label Single Center, Single Patient Study of an Experimental Antisense Oligonucleotide Treatment for Kinesin family member 1A (*KIF1A*) Gene Mutation

nL-KIF1-001 Study Drug Manual

(Version 1.6 – JULY 2024)

5 How Do We Create a Nano-rare Community, Ensure Awareness, Share Data and Progress Broadly?

- n-Lorem Podcast provides a platform for partners and stakeholder to discuss their perspectives with n-Lorem
- Foster open dialogue with the nano-rare community through our annual nano-rare patient colloquium
- Constant and timely social media coverage is critical to driving awareness of successes and challenges
- Patient stories inspire and motivate
- Collective public posture drives fundraising
- Publish early and often ensure accurate information reaches the community
- Create a groundswell of excitement of hope realized for nano-rare

Public Posture and Publications

Brief Communication | Published: 09 August 2024

Antisense oligonucleotide therapy in an individual with KIF1A-associated neurological disorder

Alban Ziegler, Joanne Carroll, Jennifer M. Bain, Tristan T. Sands, Robert J. Fee, David Uher, Cara H. Kanner, Jacqueline Montes, Sarah Glass, Julie Douville, Laurence Mignon, Joseph G. Gleeson, Stanley T. Crooke & Wendy K. Chung

Nature Medicine (2024) | Cite this article

935 Accesses | 2 Citations | 99 Altmetric | Metrics

nature medicine

ENDPOINTS NEWS

A teenager faced constant seizures. Could a drug developed just for him stop them?

This lifesaving treatment was designed for one. Could it be the future of medical care?

Karen Weintraub
USA TODAY

Published 5:07 a.m. ET Nov. 26, 2023 | Updated 9:27 a.m. ET Nov. 28, 2023

USA TODAY

The New York Times

They Created a Drug for Susannah. What About Millions of Other Patients?

Rare Disease ADVISOR

ASOs Drive Foundation's Work to Develop Treatments for the World's Rarest Diseases

Read the full story at arediseaseadvisor.com

n-lorem FOUNDATION

The San Diego Union-Tribune.

A devastating rare disease. A medicine created just for her son. Will it work?

San Diego nonprofit n-Lorem plans to treat patients with rare genetic diseases for free, and for life. It's an approach some say could revolutionize medicine — if it can be scaled.

Jonathan Wosen September 16, 2021 at 8:30 a.m.

NUCLEIC ACID THERAPEUTICS
Volume 00, Number 00, 2024
© Mary Ann Liebert, Inc.
DOI: 10.1089/nat.2024.0060

Open camera or QR reader and scan code to access this article and other resources online.

Addressing the Challenges of Treating Patients with Heterozygous Gain of Function Mutations

Stanley T. Crooke

A bespoke genetic therapy is helping Susannah. Can similar drugs be made at scale for other rare diseases?

By Jonathan Wosen[2 3] Aug. 9, 2024

STAT

Key Achievements

- Created an independent world-class team of 31 experts in antisense and drug development
- Industrialized scalable quality systems and processes to efficiently discover and develop quality ASOs for as many patients as we can
- Every ASO program involves >75 leading experts with decades of experience
- Sufficient growth to meet the demand
- Minimize cost per patient by establishing a network of CROs and partners
- Build a network of leading clinical sites and physicians who are committed to the care of nano-rare patients
- Ensure optimal benefit and safety
- Establish platforms and systems to learn maximally from each patient and in aggregate
- Rapid creation of assets that we hope will assure n-Lorem's sustainability

2024: A New Era of Opportunity for Nano-rare Patients

21 approved INDs for 29 patients in <2 years

Pristine safety and tolerability

7/7 showing clinical benefit

The Team Behind Our Success

‘The whole is greater than the sum of the parts’


Alexia Cordova


Amy Williford


Ana Foroughishafiei


Andrew Sanginario


Andrew Serrano


Anthony Vu


Billy Lilley


Catherine Parisien


Cedrik Ngongang


Craig McIntosh


Elena Gonzalez


Emily Miyoshi


Helen Pu


Julia Pytte


Julie Douville


Katherine Smith


Kim Butler


Laury Mignon


Lesley Saldana


Megan Knutsen


Mike Taylor


Nadina Skourti-Stathaki


Nafiso Hussein


Natalie Abu Hamdan


Ria Thomas


Sarah Glass


Stan Crooke


Swappi Mittal


Thuy Nguyen


Travis Radford


Virginia Sankey


Wei Zhang

Looking to the Future: Sky's the Limit

- Maintain focus on each patient throughout the process and the quality of the ASO
- Individual patient-centered decisions at every step become more efficient and concise through iteration
- Continue to optimize the ASO discovery and development process and grow the partner network
- Continually increase and improve upon capacity and scalability through partnerships and internal growth
- Innovating molecular mechanisms through research will broaden the type and number of patients' mutations we can target
- Focus on challenges with access to the medicines
  - Treatment institutions, funding

Thank you

Nano-rare Patient Colloquium 2024

Hosted by: Biogen

n-lorem FOUNDATION

Session Ahead: n-Lorem Leaders Introducing Their Functional Areas

Nadina Skourti-Stathaki, PhD

Lived in 5 Countries
Loves to Paint

Director,
ASO Design and Discovery

Julie Douville, PhD

French-speaking world traveler

Executive Director,
ASO Discovery and Development

Laury Mignon, PhD

Luxembourgish Surfer

Executive Director,
Clinical Development

Amy Williford, PhD

Tennessee-born World-class Paddler

Senior Director,
Communications and Donor Relations