Precision Medicine at Scale: Operationalizing Individualized Trials

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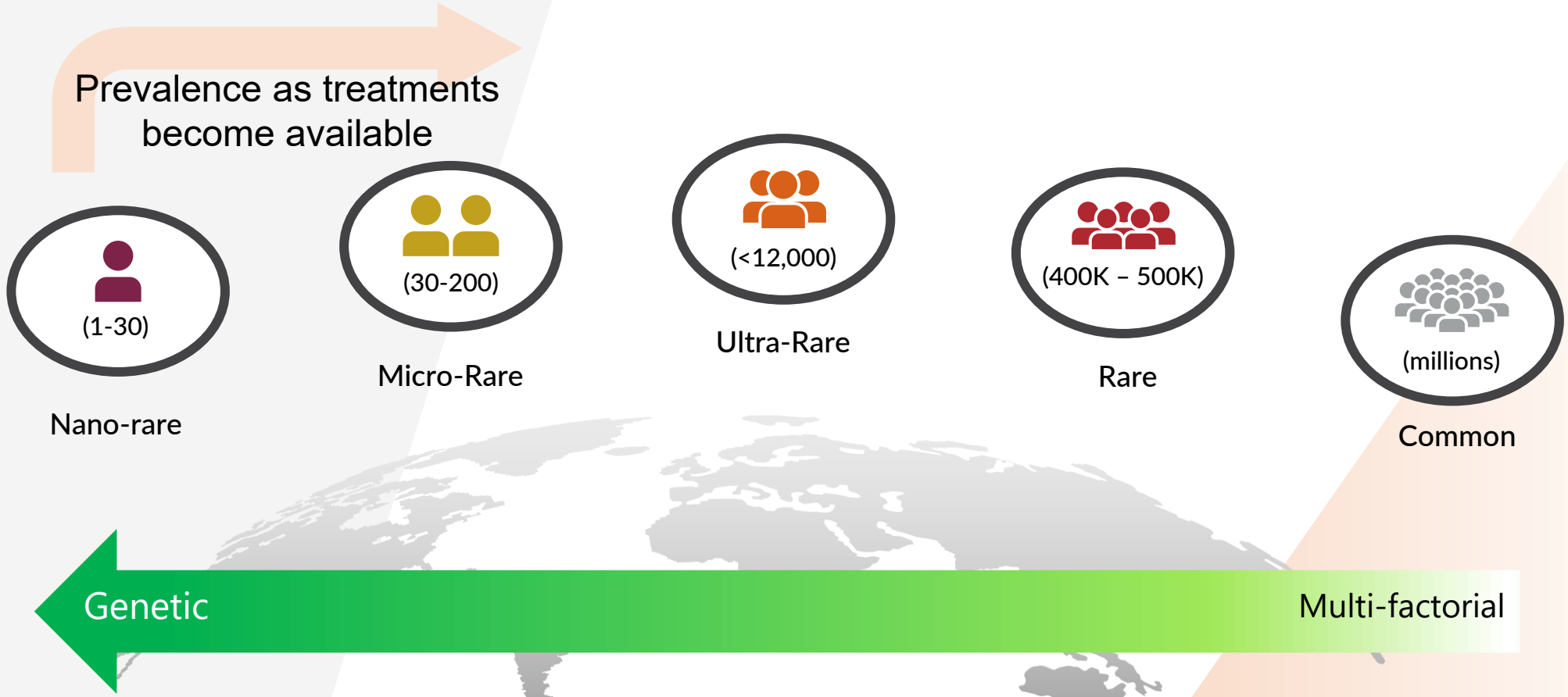
Disclosure:

Sarah Glass is the COO of n-Lorem Foundation, a non-profit

mission

The Foundation’s mission is to apply the efficiency, versatility and specificity of antisense technology to charitably provide experimental antisense oligonucleotide (ASO) medicines to treat patients with nano-rare diseases (<30 patients worldwide).

Nano-rare Patients: Genetic Mutations in 1-30 Individuals Worldwide



ASO Technology and FDA Framework for Individualized ASOs Make a Non-Profit Biotech Organization Feasible

- **Rapid** and **efficient**
- **Versatile**
  - Multiple post-binding mechanisms
  - Multiple routes of administration
  - Multiple organs
- **Validated** and **well understood**
  - Potent
  - Pharmacokinetics
  - Integrated safety databases
- **Cost effective**
  - Sophisticated automation: rapid, inexpensive, optimal ASO discovery
  - Potent and long-lasting ASO effects
  - Low manufacturing cost
- **Scalable**

Supported by regulatory authorities with 4 guidance documents (2021)

- Procedural guidance for Individualized ASOs January 2021
- Pre-clinical guidance for Individualized ASOs April 2021
- CMC guidance for Individualized ASOs December 2021
- Clinical guidance for Individualized ASOs December 2021

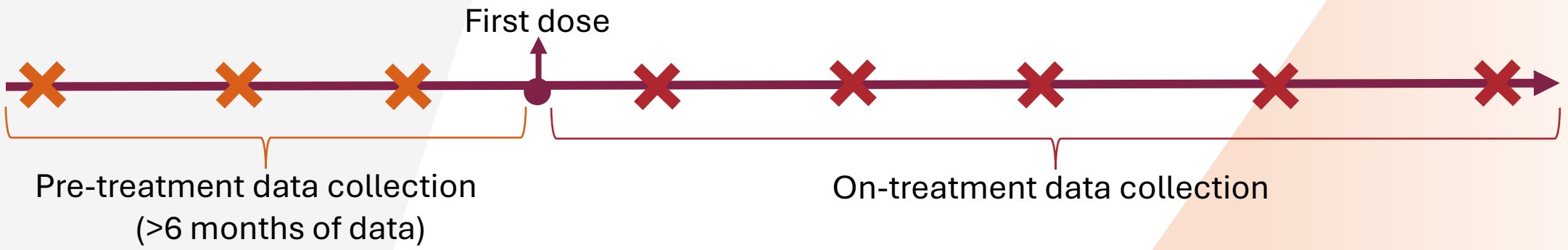
An Industrialized, Integrated and Scalable Process

A Fully-Integrated Operating Model

- An industrialized ASO discovery and development to ensure highest quality at every step
  - **AI-enabled, rapid** ASO discovery and optimization
  - **Automated** high-throughput screening
  - Development, manufacturing and formulation supported by a CRO/CMO network delivering ~40% **cost savings**
  - Several steps done **in parallel** to maximize efficiencies
  - **In-process quality control committees** comprised of external experts advise at key stages throughout

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

- Customized protocol with a focus on what is important to each patient
- Treatment goals and clinical measures are pre-defined
- Pre-treatment assessments are evaluated during time it takes to make ASO, setting baseline and assessing progression rate
- Modified cross-over design compares pre-treatment assessments to on-treatment assessments



Collecting Data from n=1 Trials

- Unique Challenges
  - Individualized protocols → heterogeneous datasets
  - Safety monitoring requires tailored data prioritization & visualization
- The Framework
  - Scalable, end-to-end data lifecycle
  - Use of **validated outcomes measures**, whenever possible
  - Maintains flexibility for individualized patients, but also shared data templates for consistent data capture
  - Custom database for each patient using REDCap (Research Electronic Data Capture)
  - Remote monitoring & data cleaning
  - API-driven data flow into PowerBI dashboards
  - Quarterly Data Safety Monitoring Board (DSMB) review across multiple safety domains
- Goal
  - Enable accurate, timely, and intuitive safety review for decision-making

Customized Protocol Development

- Guided by the Study Treatment and Assessment Review (STAR) Committee
  - Internal and external experts in clinical trial design, outcome measures, and assessments
- Each individualized protocol contains clearly defined clinical efficacy and safety assessments, assessment schedules, and data collection requirements

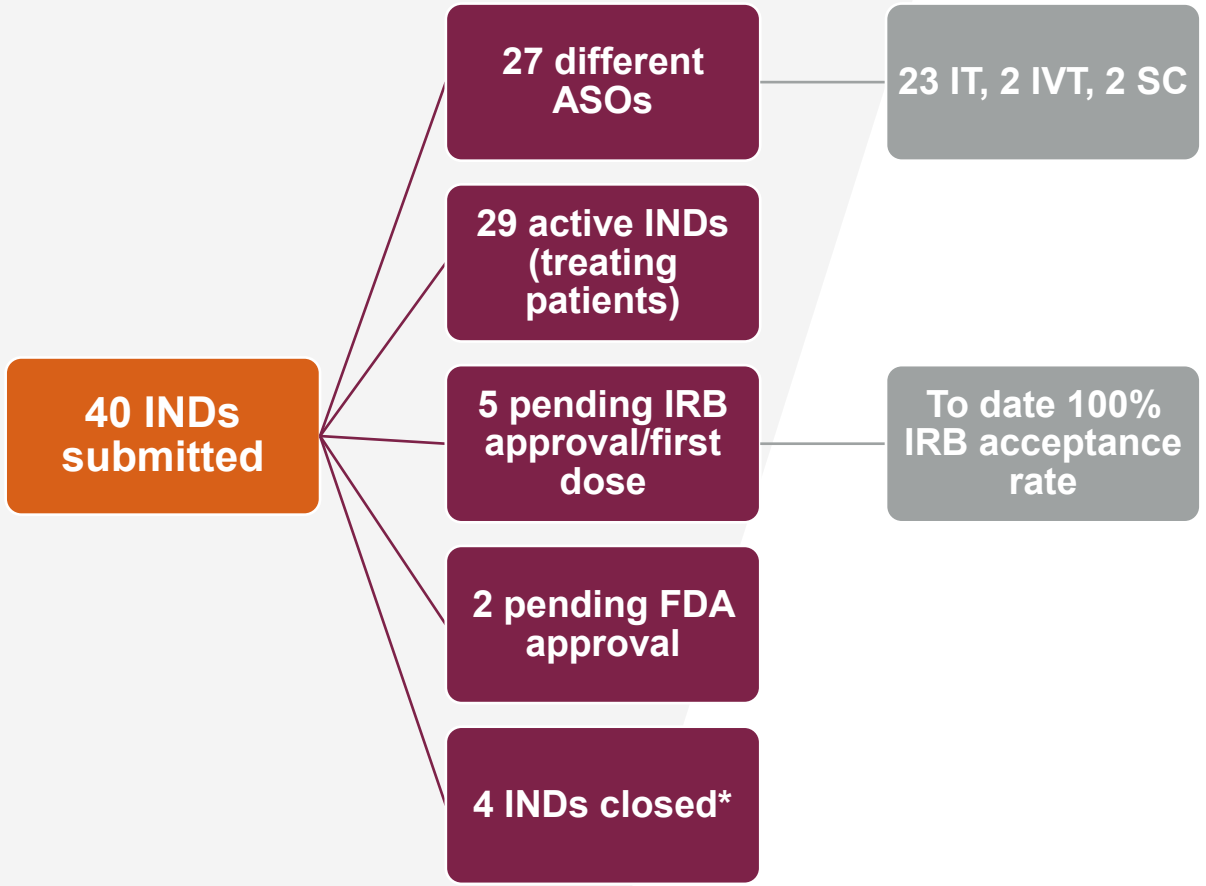
Study Visits (Days)	Baseline	Initial dose D1		Follow-up visit 1 D8	Second dose D28		Follow-up visit 2 D35	Third dose D84		Follow-up visit 3 D91	Fourth dose D168		Follow-up visit 4 D175	Maintenance Phase		
Study Window	45 Days	-		(+/- 3days)	(+/- 7 days)		(+/- 3days)	(+/- 7 days)		(+/- 3days)	(+/- 7 days)		(+/- 3days)	Doses every 84 days (+/- 7 days)		Follow-up 1-week post-dose (+/- 3days)
Location	Onsite	Onsite		Phone	Onsite		Phone	Onsite		Phone	Onsite		Phone	Onsite		Phone
		Pre-Dose[a]	Post-Dose[i]		Pre-Dose[a]	Post-Dose[i]		Pre-Dose[a]	Post-Dose[i]		Pre-Dose[a]	Post-Dose[i]		Pre-Dose[a]	Post-Dose[i]	
Informed consent	X															
Review eligibility	X															
Medical history[b]	X															
Ancillary Procedures	X															
Physical examination	X	X	X		X	X		X	X		X	X		X	X	
Neurological exam	X	X	X		X	X		X	X		X	X		X	X	
Clinical lab testing[c]	X	X			X			X			X			X		
Syde w ankle accelerometer[d]	X															
Gait analysis	X															
WCS	X										X			X[e]		
Vineland-3	X													X[f]		
BSID-4	X													X[f]		
ORCA	X										X			X[e]		
QI-Disability	X										X			X[e]		
ABC-C	X										X			X[e]		
RBS-R	X										X			X[e]		
Brain MRI[g]	X															
12-lead ECG	X	X			X			X			X			X		
Vital signs	X	X	X		X	X		X	X		X	X		X	X	
CSF Sampling[h]		X			X			X			X			X		
Study drug injection		X			X			X			X			X		
Adverse events		X														
Concomitant medications	X															

Collecting Data from n=1 Trials

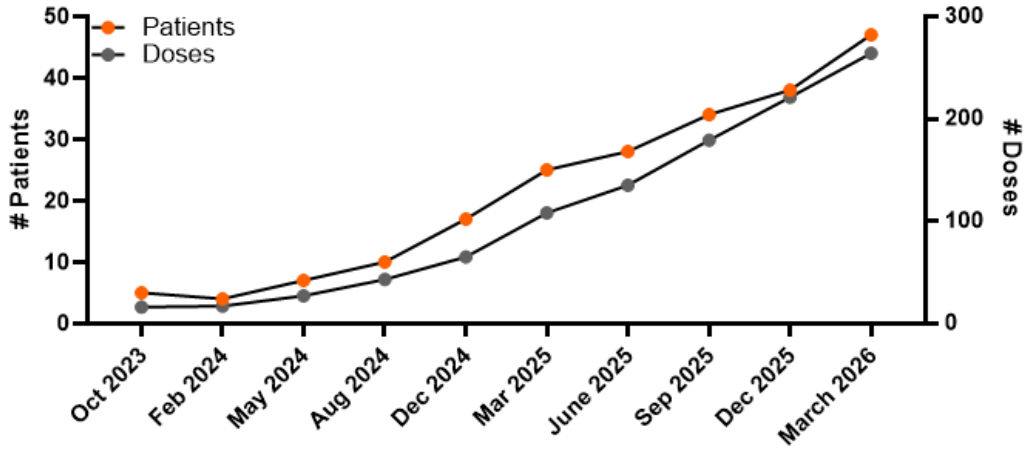
- Build a customized and consistent data collection database
  - Collaborate with investigators and study teams to provide input on site-specific assessments
- Train and activate the site
- Timely data entry at site and query resolution
- Data storage, management, export and analysis

Regulatory and Clinical Experience

Number of INDs Submitted and Patients Treated Continues to Grow Rapidly



Increasing # of patient and doses



- 47 patients treated; **43 on active treatment**
  - 264 doses received
  - 43.9 patient years
- 19 clinical sites / PIs

Data as of Jan 16, 2025

* 2 INDs closed due to patient travel limitations;
1 IND closed due to GLP tox failure (patient never dosed)
1 IND closed due to patient passing away (patient never dosed)

ASOs with Authorized INDs to Treat Multiple Patients

ASO	Gene	ASO strategy	Patients Treated	Additional Accepted Patients in the US
nL-KIF1-001	KIF1A	Allele-selective	4	4
nL-TARD-001	TARDBP	Allele-selective	2	0
nL-UBTF-001*	UBTF	Allele-selective	1	0
nL-TUBB4-001	TUBB4A	Non-allele-selective	5	3
nL-ATN1-002	ATN1	Non-allele-selective	3	1
nL-CHCHD-001	CHCHD10	Non-allele-selective	11	2
nL-RNPH2-001	HNRNPH2	Non-allele-selective	3	7
nL-PACS1-001	PACS1	Non-allele-selective	3	2
nL-IKBK-001	ELP1	Splicing	2	1
nL-PRPH2-001**	PRPH2	Allele-selective	1	0

*Originally 1 additional patient who could have used this ASO, but program was discontinued due to patient progression.
** ASO is designed to the pathogenic mutations, thus can be used by additional patients already identified by the PI, but not yet accepted at n-Lorem.

Analytical Approaches Support Learning Across the Population of Individual Patients

- Nano-rare patients present with a unique combination of clinical and disease characteristics
  - Severe disease phenotypes, advanced disease, multiple concomitant medications
- Limited or intermittent natural history data
- Emphasis placed on individualized treatment goals using **standardized outcome measures**
- High-quality data on **harmonized measures** across programs (when possible) that is transferable and can be used in **aggregate analyses**
  - Teaches about one patient relative to another
  - Teaches about mutation and effect on phenotype
  - Teaches about health and disease

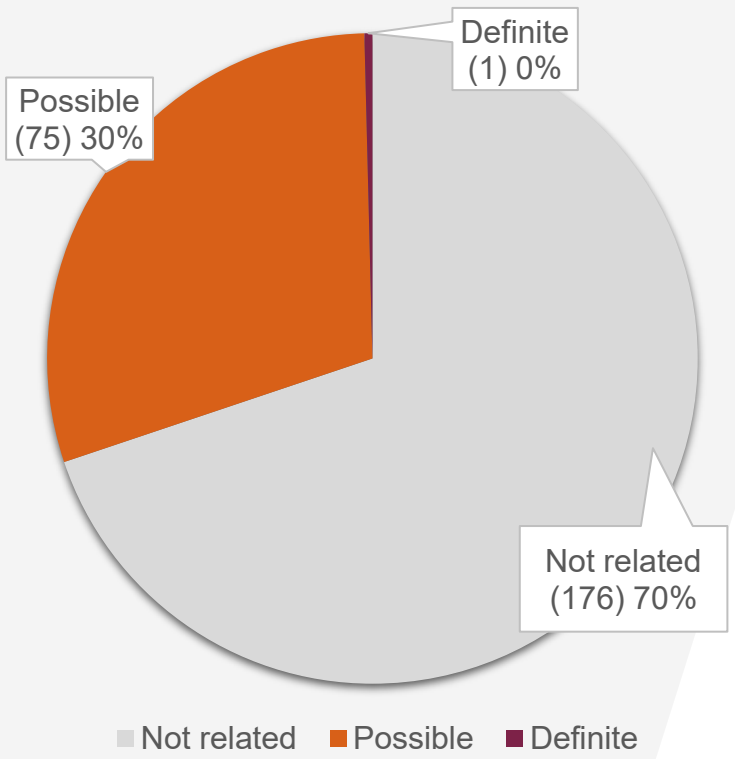
Robust Safety Oversight and Clinical Management: Excellent Safety and Tolerability Profile

- Aim to treat every patient, even if severely progressed at baseline
- Safety is tracked diligently in every trial
  - Close collaboration between the physicians and ASO discovery and development organization
- Adverse events are defined as any unfavorable events that occur during the study
  - These events may or may not be due to the ASO; are often due to the underlying disease
- Thorough scientific and clinical evaluation occurs for every AE
- Foundation maintains commitment to reporting to the FDA and community through specific defined mechanisms as swiftly as possible

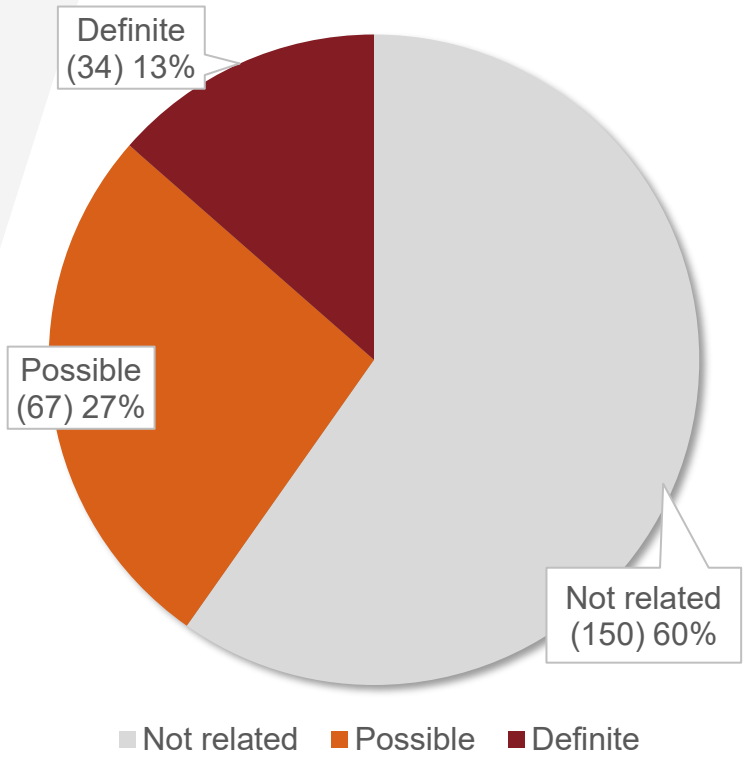
Across all patients, we have seen no ASO-related Serious Adverse Events

Our ASO Discovery and Development Process Leads to Safe and Well-Tolerated ASOs

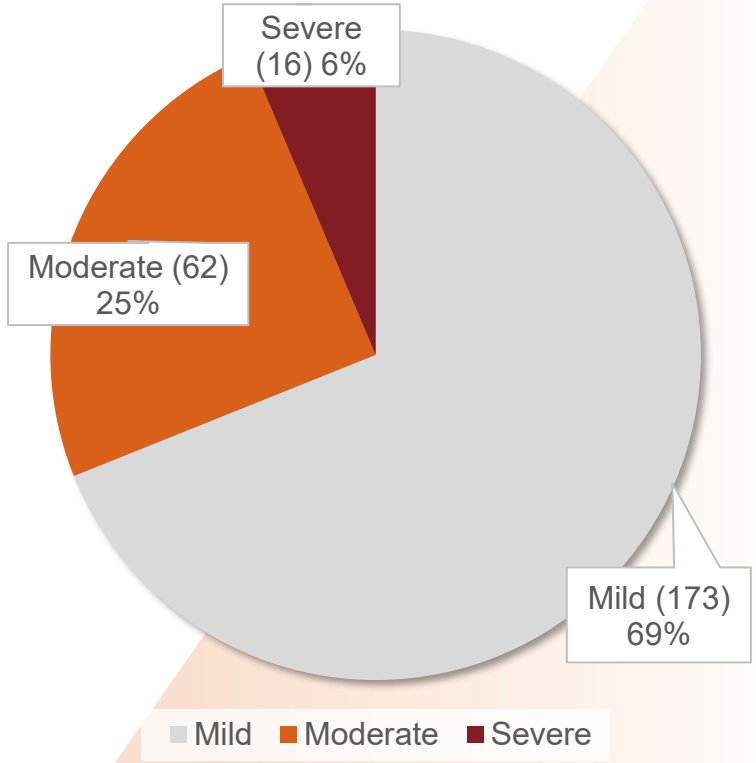
Relatedness to Study Drug



Relatedness to Drug Administration



Severity



***To date across all patients, we have seen 1 ASO-related AE that data suggests is a novel ASO-disease interaction**

Clinical Data in Evaluable Patients Shows that Greater than 90% Experience Clinical Benefit

- **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**

* As of October 2025

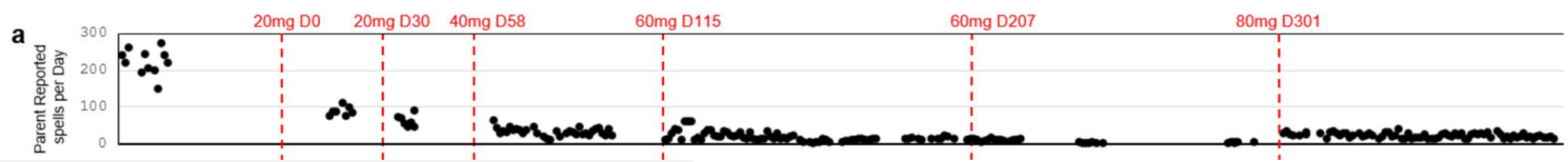
The Impact on Patients Has Been Extraordinary

Patient with SCN2A Mutation Walking Independently (nL-00001)

- SCN2A - Sodium voltage-gated channel
- Phenotype at Treatment Start
  - 14 years of age
  - Significant seizure activity
  - Severe movement disorder
  - Developmental delays
  - GI issues
  - Autistic behaviors
- Treatment Response:
  - No side effects
  - Sustained benefit in multiple domains
  - Recovered functions he never had

Neurological Diseases - Mobility

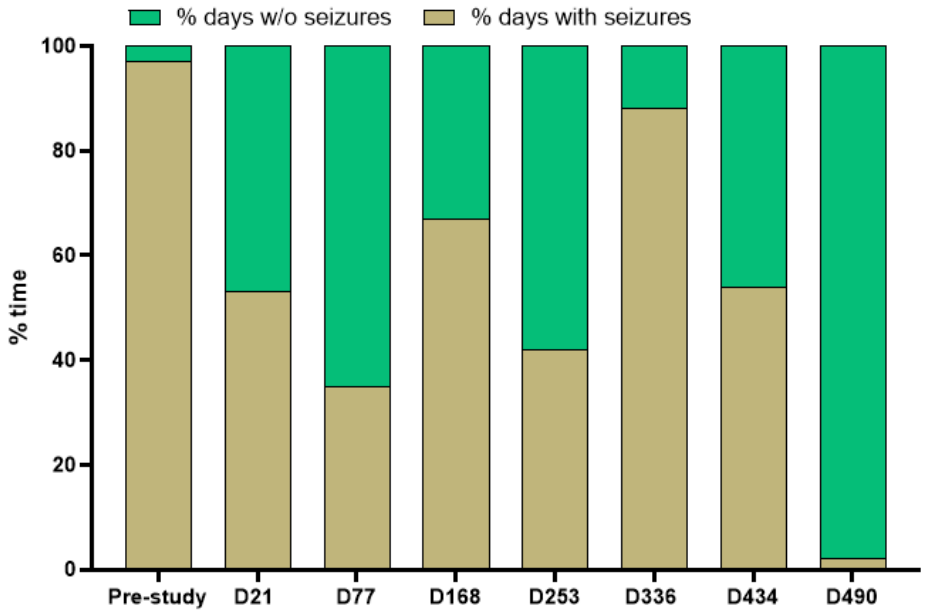
Improvement in Seizures in Multiple Patients



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

Ziegler et al., NEJM 2024

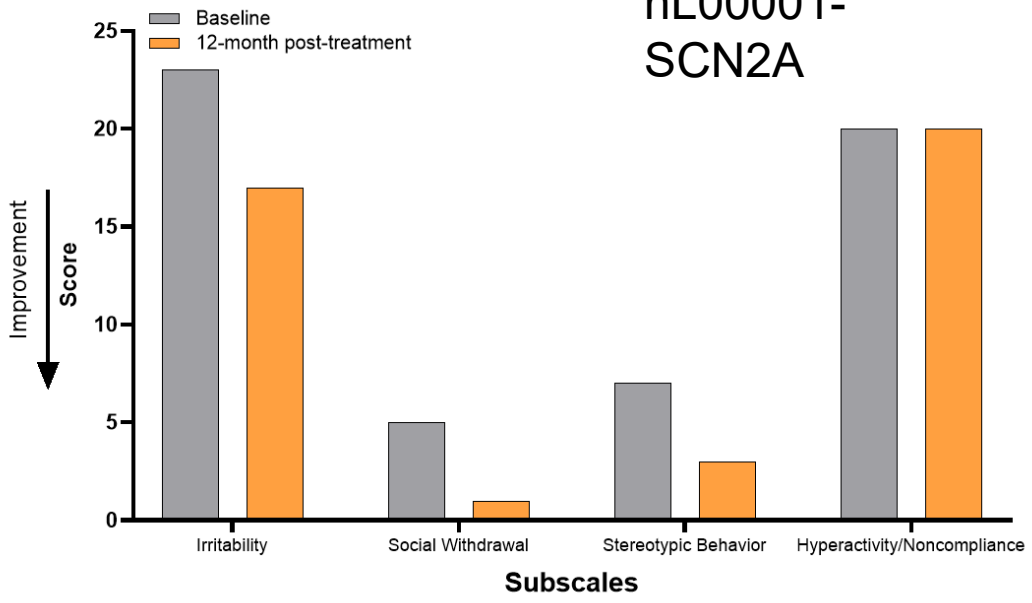


Neurological Diseases - Seizures

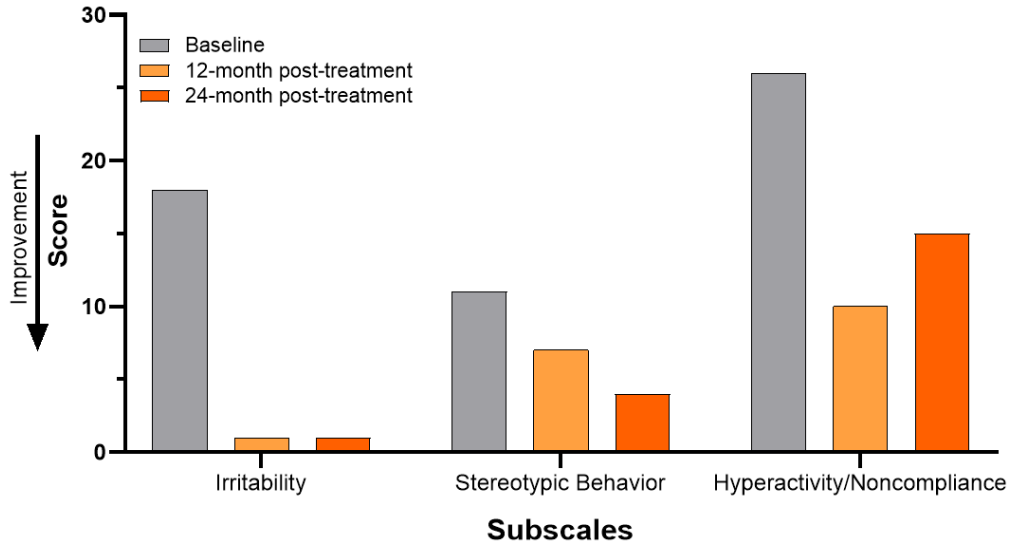
Treating physicians:
Dr. Bain, Columbia University
Dr. Kim McManus, UCSD/Rady

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

nL00001-SCN2A



nL00333-SCN2A



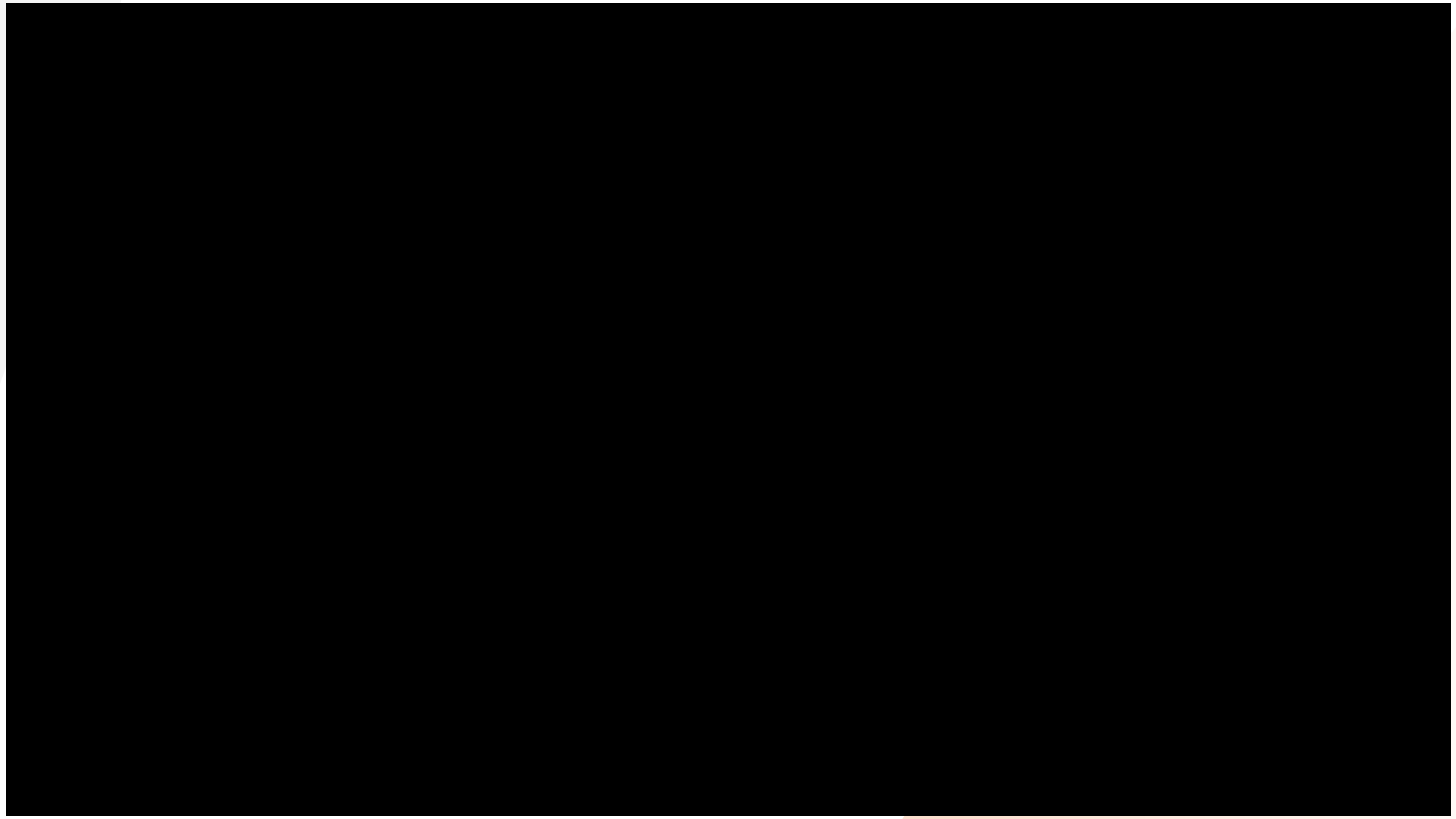
- The two patients with different SCN2A mutations had behavioral varying phenotypes at baseline
- Both showed improvements in irritability and stereotyped behavior

Neurological Diseases- Autistic Behaviors

Treating physicians:
Dr. Berry Kravis, Rush University;
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



Neurological Diseases- Mobility and Motor Control

Treating physician:
Dr. Bain, Columbia University

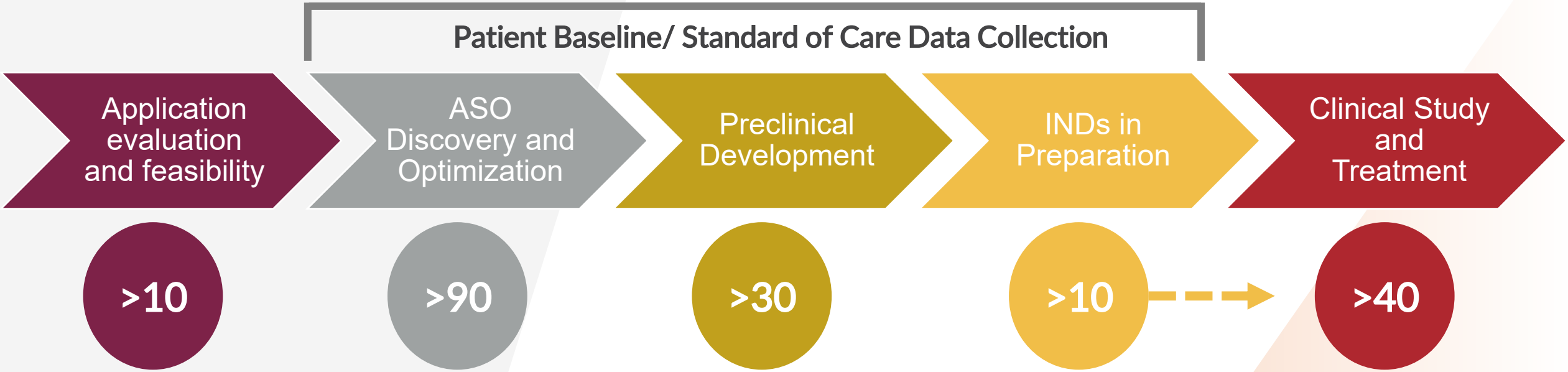
~90% of Evaluable Patients Experiencing Clinical Benefit

- Favorable safety and tolerability profile
- 19/22* evaluable patients show evidence of clinically important benefit
  - Benefits observed in all organs treated: CNS, Liver, Kidney, Eye
  - Improvement in multiple domains in CNS
  - Continued benefit with continued treatment
  - Evidence of CNS benefit at low doses
  - Target reduction and stabilization of renal function
  - Recovery of functions lost demonstrating plasticity of CNS
  - Reduction in Neurofilament light in ALS
  - Reduction in neuropathic pain
  - Ability to feel pain
  - Improvement in motor function, gait, spasticity
  - Evidence of ASO effect on autonomic functions

*three severely ill patients with advanced ALS show reduced neurofilament and perhaps stabilization on of ALS

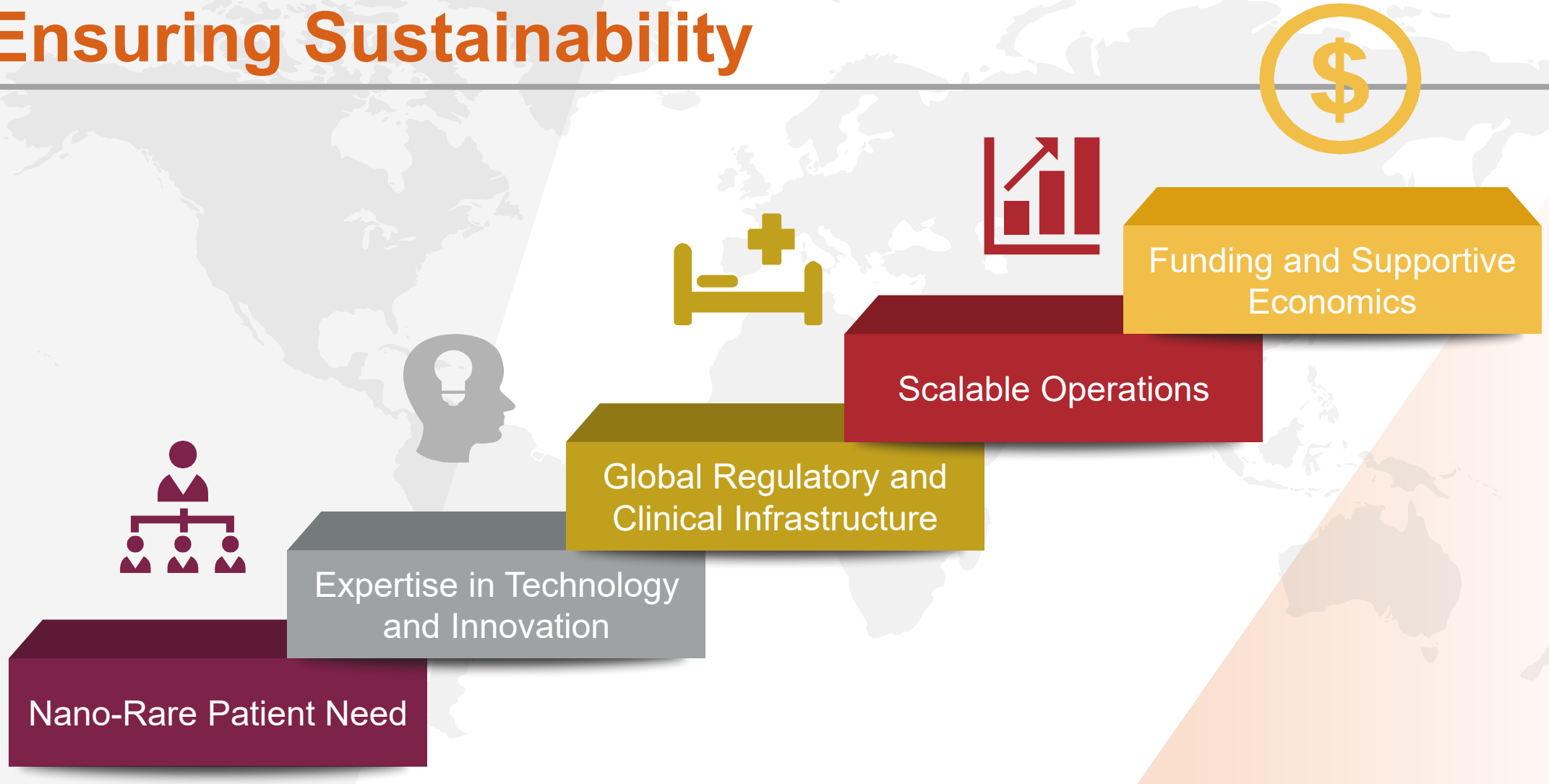
The Future is Bright for the Nano-Rare and Those Dedicated to that Community

Our Nano-rare Patient Research and Treatment Pipeline



>400 Applications Submitted to Date
>200 Patient-directed Drug Discovery Programs to Date
>40 INDs Submitted
5 Divisions of the FDA Supportive

Ensuring Sustainability



Support From Leaders Across All Areas of Drug Discovery, Development and Manufacturing *More than 30 Partners Supporting Nano-rare Patients*

Biotech/Pharma Companies

IONIS

Biogen

ALEXION AstraZeneca Rare Disease

Alnylam Pharmaceuticals

ultragenyx

Takeda

Genomic Sequencing

Children's Mercy Kansas City

COVANCE by labcorp

GeneDx

illumina

PacBio

Disease Focused

ASXL3

FSHD2

MAPK8IP3

Silence ALS

Pre-clinical Toxicology CROs

charles river

KIT Korea Institute of Toxicology

Greenfield Pathology Services, Inc.

Access to Appropriately Characterized Patients and Investigators

Undiagnosed Diseases Network

Other personalized medical centers

Manufacturing

ChemGenes Corporation

cytiva

Hongene Biotech

IDT Integrated DNA Technologies

Nitto Avecia

Clinical Management

parexel

Foundations Grant Organizations

The Conrad Prebys Foundation

TARGET ALS

SOLVE FSHD

Wolverine Foundation

Anonymous Donor

URGenT NIH Grant

Sterile Fill Product

ARGONAUT Manufacturing Services

Nitto Avecia Pharma Services

SCHOTT PHARMA

Other

COMBINED

Cooley

COWEN

STIFEL

J. Wood Capital Advisors

sysnav Health Care

Data Partners

Across Healthcare

Unipr

Conclusions

- Discovery and Development of Individualized ASOs at scale is here
  - Our **integrated operating model** consists of an industrialized, scalable process that enables a new treatment in <2 years for <$1.5M
  - **40 INDs** for 27 unique ASOs have enabled treatment of 50 patients (43 on treatment today) and represent a supportive regulatory environment
- Customized, individualized trials leading to **high-quality data collection** are successfully enabling physicians' treatment decisions and will be used to support regulatory approval paths
- Clinical Data suggests a powerful impact on patient lives
  - Clinical safety and professional management of patients on treatment is the highest priority and has resulted in a **favorable safety profile**
  - >90% of patients with evaluable data show **clinical benefit** according to their unique protocol
- The current focus to ensure sustainability is on fundraising and supporting regulatory progress to drive broader access


Thank you!

Abstract (<300 words)

n-Lorem is a non-profit that discovers, develops, and provides individualized therapies for patients with ultra-rare genetic diseases. Our approach to the clinical operations related to the >40 patients on treatment today with individualized therapies relies on customized within-patient trials, comparing each patient's baseline to on-treatment outcomes, so every patient serves as their own control. This design enables rapid evaluation of therapeutic impact without large cohorts or randomized arms, while maintaining rigorous safety oversight. n-Lorem has observed an excellent safety and tolerability profile and evidence of significant clinical benefit observed in patients on treatment.

This talk will focus on the operational framework that allows these trials to scale. We will cover patient-specific protocols, streamlined data collection and analysis, and coordinated execution across clinical, regulatory, and manufacturing teams. Key operational challenges, including standardizing outcomes, managing variability, and integrating real-world data into endpoints, will also be discussed.

Attendees will gain actionable insights into translating individualized treatment strategies into scalable clinical operations. n-Lorem's model demonstrates that precision medicine can be both patient-centered and operationally efficient, offering a practical roadmap for executing n=1 trials in a controlled, replicable manner.