n-lorem FOUNDATION

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Nano-rare Patient Colloquium 2025

ASOs Can Be Safely Developed for Nano-rare Patients: Insights from the n-Lorem Experience

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Today's Agenda

- Uniqueness of nano-rare patients
- What is clinical safety and how we measure it
- n-Lorem's Clinical Safety Overview

No ASO-related Serious Adverse Events

The Challenges of Treating and Evaluating Nano-Rare Patients

- Nano-rare patients present with a unique combination of clinical and disease characteristics
  - Severe disease phenotypes
  - Advanced disease
  - Multiple concomitant medications
- Patients expected to experience disease-related adverse events while being treated with an experimental ASO
- Paucity of natural history data
  - Even patients with the same mutation may have different clinical phenotypes and progression rates

Pediatric Patients Present their Own Unique Challenges

- Growth
- Maturation
  - Advancing intellectual capabilities
  - Puberty
  - Emotional growth
  - Social pressures
- Advanced diseases at varying progression rates

Safety Is the Cornerstone of our Mission

- Most important guiding principle:
  - **Develop safe ASOs for patients**
- This comes with great responsibility and accountability
  - Constantly monitoring for safety
  - Performing detailed mechanistic assessments of adverse events
  - Reporting on safety quarterly to Data Safety Monitoring Board
  - Reporting safety assessments and annual updates to FDA
  - Informing investigators and adapting informed consent
  - Sharing information with wider community in a timely manner

Clinical Experience and Expertise Provides the Most Comprehensive Evaluation of Safety

- n-Lorem team has extensive experience in safety monitoring of clinical trials with ASOs in rare diseases
- Extramural DSMB members have deep clinical trial experience and clinical understanding of patients with rare diseases

n-Lorem Team:

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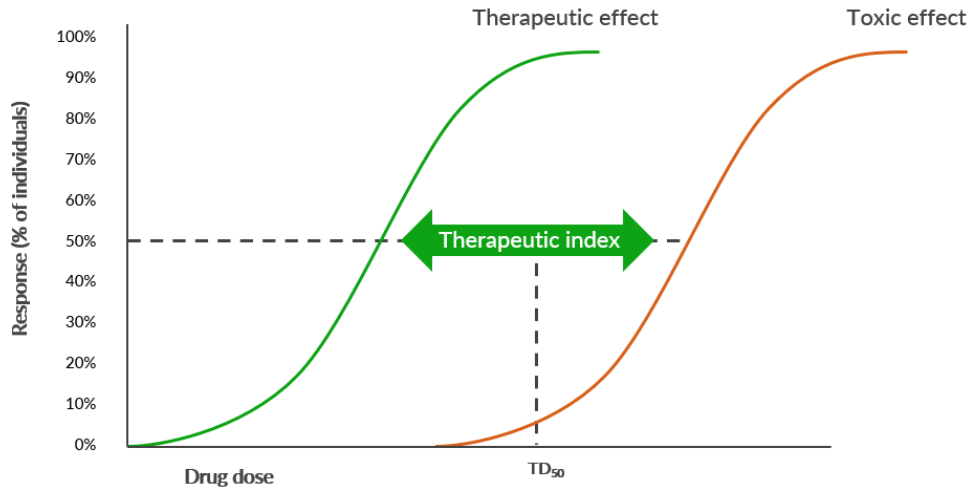
Historical Work on ASOs Provides the Foundation to Built Upon

- Ionis created and advanced ASO technology since 1989
- Ionis has treated several hundred thousand patients in controlled clinical trials
- Ionis has uniquely published databases that integrate all safety observations from NHP to human studies through all controlled clinical trials
- n-Lorem is continuing to advance antisense technology in many ways

Deep Experience with ASO Technology Enhances the Probability of Successful Treatment

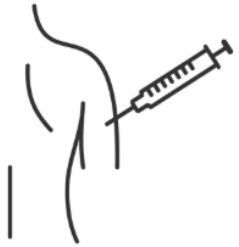
- Desired and undesired effects are both dose-dependent
- We maximize the separation in dose for benefit versus side effects by selecting only optimal ASOs
- Based on past experience with ASOs of the same chemistry, we know the right route of administration, dose range and frequency to use
  - Cautious dose-escalation is a must
- Based on past experience, we know the potential adverse events to look for



Accumulated Clinical ASO Knowledge Defines Parameters for Safety Assessments

- The historical and clinical safety data teaches us
  - What adverse events to be on the lookout for

Inflammation
Cataracts



Flu-like symptoms
Injection site reactions
Liver function

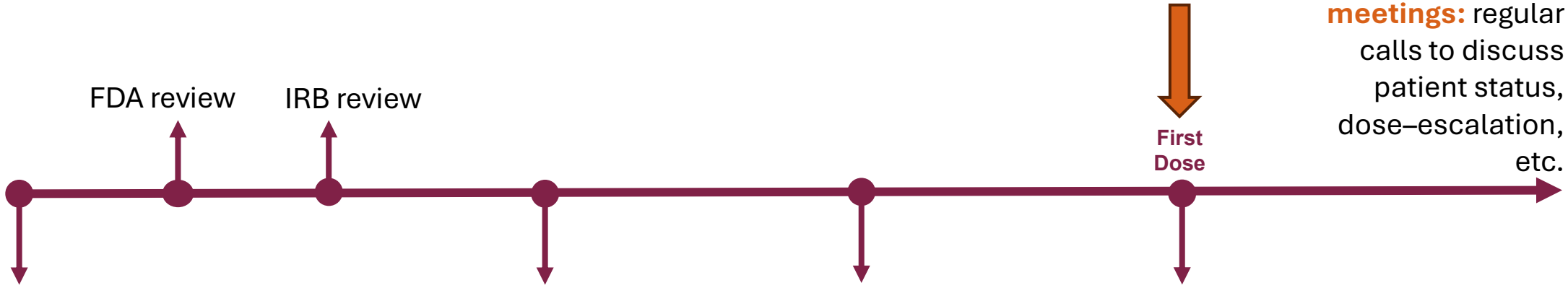
Brain inflammation
Hydrocephalus

  - How to assess these adverse events
    - Physical, neurological and retinal exams
    - Established laboratory values for blood and CSF
    - Imaging
    - Established biomarkers, such as neurofilament

Safety Oversight in n-Lorem Trial
It Takes a Village

Dose day: n-Lorem team on stand-by, awaiting to hear from site

Investigator meetings: regular calls to discuss patient status, dose–escalation, etc.



Protocol development: Safety measures and rules on how to monitor safety

Site initiation visit: n-Lorem team trains clinical site team on study protocol, timing of assessments, study drug preparation, and blood/CSF samples collection

Baseline Visit:
Imaging
Safety blood tests
Physical exam
Neuro exam

Predose:
Safety blood test
Neuro exam
Physical exam

Post-dose: Overnight hospital stay

How is Safety Measured in a Trial?

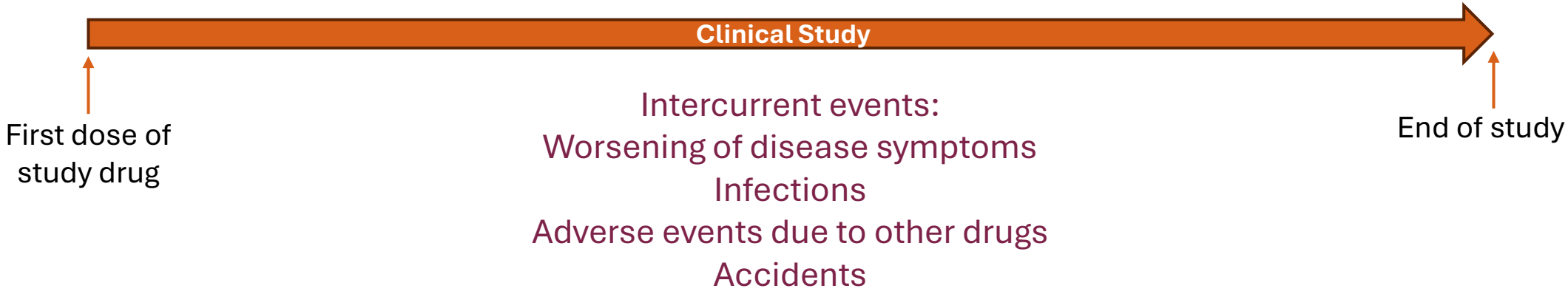
- Definition of ‘safety’ in a clinical trial:
  - systematic evaluation, monitoring, and documentation of any *adverse events*, risks, or unintended consequences associated with the study drug when administered to humans
- Every adverse event is described based on 2 qualifiers
  - Severity
  - Relationship to study drug

What does that really mean?

Assessing Adverse Events is Frequently Complicated by Intercurrent Events

Adverse Event

Any unfavorable sign, symptom, or disease that occurred during the duration of the study, including occurrences that happen in everyday life



How Is Severity Defined?

- Severity refers to *how much* the adverse event *interferes* with daily activities
- The physician assesses the severity of each adverse event

Mild – easily tolerated, does not interfere with daily activities:
Allergies

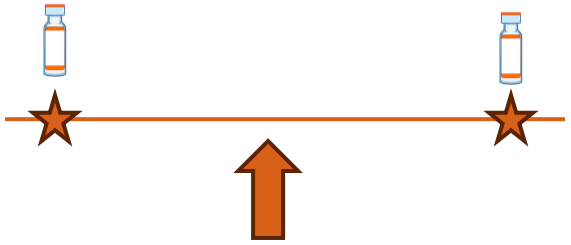
Moderate –results in more discomfort, and causes some interference with functioning:
Fall resulting in broken arm

Severe – incapacitating, interrupting daily activities:
Norovirus infection leading to constant vomiting / diarrhea

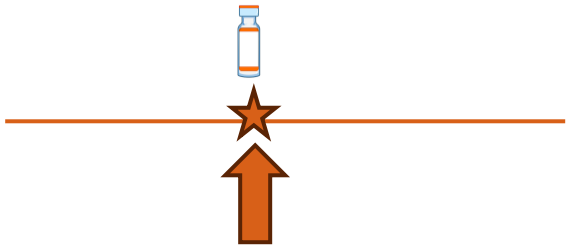
How Is Relationship to ASO Defined?

3 criteria for relationship

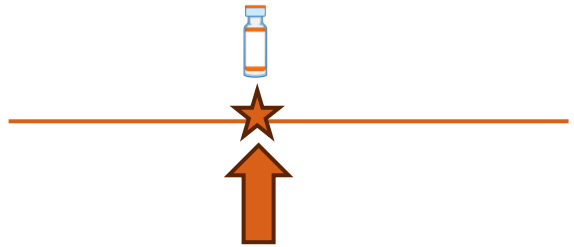
(clinical decision of physician)



Cough



Nausea, vomiting



Local redness and swelling at injection site (subcutaneous admin)

Not related:

No temporal relationships to ASO administration, event is clearly related to other factors

Possibly related:

Reasonable temporal relationship, but could be explained by other reason (patient always feels nauseated after sedation) but cannot rule out ASO

Definitely related:

Strong causal link between ASO and event based on timing, recurrence on all injections, absence of alternative explanations

An Adverse Event Can Also Be Related to the ASO Administration

- The administration procedure, the injection, itself can also lead to untoward events
  - Subcutaneous administration: bruise, pain from needle stick
  - Intrathecal injection: lumbar pain and headache
  - Intravitreal injection: pain and inflammation
- Relationship assessment is the same as for the study drug
  - Not related, possibly related, definitely related
- Mitigation strategies are used to prevent any discomfort, including needle size, pretreatment with medication, post-dose guidance

What Is a Serious Adverse Event?

- A ‘severe’ adverse event is not necessarily a ‘serious AE’
- A Serious Adverse Event (SAE) is a regulatory term and is an adverse event that in the view of the physician meets any of the following criteria
  - Results in death
  - Is life-threatening, or poses immediate risk of death
  - Requires inpatient hospitalization or prolongation of existing hospitalization
  - Results in persistent or significant disability/incapacity
- If deemed possibly or definitely related to study drug, and the event is unexpected, n-Lorem is required to submit a safety report to the FDA for SAEs
  - Specific timelines based on the event

Safety Oversight in Clinical Development Has Many Layers

- Key committees support the design and treatment with safe ASOs
  - RMC – ascertains the best ASO is chosen for the final GLP toxicology study
  - FDA – reviews nonclinical, manufacturing data and safety monitoring plan prior to first dose in humans
  - IRB – reviews the clinical protocol to ascertain ethical treatment of patients
  - DSMB – provides quarterly review of safety data of patients on treatment
- n-Lorem has regulatory requirements with the FDA
  - Annual safety report is submitted to the FDA for each IND
  - Safety reports throughout the study for unexpected events
- Safety assessments are made in the context of the disease
  - Benefit / risk balance of treating versus not treating
  - Discussion with the physicians at every step

Informing the Community on New ASO-related Findings

Type of communication	Audience
Regulatory Safety Update	FDA
Safety Bulletin	Treating Physicians
Amendment to the informed consent	Patients
Safety Updates	Larger community

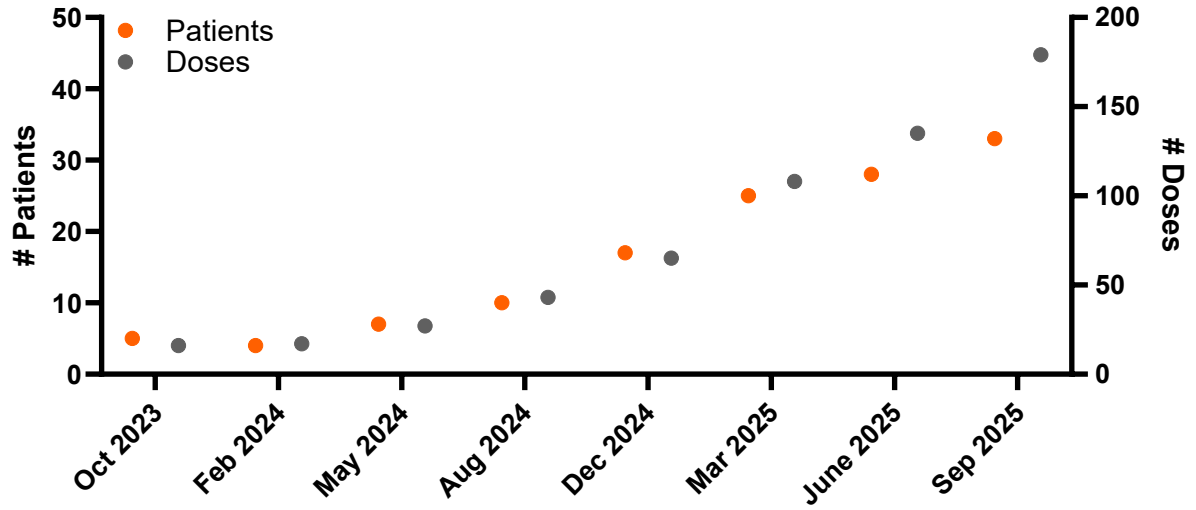
Fundamental Concepts Recap

- Extreme importance of ASO experience and clinical trial experience
- n-Lorem treats every patient, even if severely progressed at baseline
- Safety is tracked diligently in every trial
  - Close collaboration between the physicians and n-Lorem
- Adverse events are unfavorable events that occur during the study
  - These events may or may not be due to the ASO
  - These events are often due to the underlying disease
- n-Lorem has reporting responsibilities to the FDA
  - Annual safety reports
- n-Lorem has responsibility to share clinical results with the community – so here we go!

n-Lorem's Safety Database is Scalable to Accommodate Increasing Numbers of Patients on Treatment

- As September 2025
  - 32 patients on active treatment with 18 different ASOs
    - >180 doses given
    - ~30.7 patient years of treatment
  - First patient treated for almost **3 years**
  - 10 patients treated for > 1 year
  - Age range of treated patients: 3 years – 70 years

- Steady increase in the number of patients on treatment
  - Combination of new ASOs being developed and more patients being treated with an existing ASO

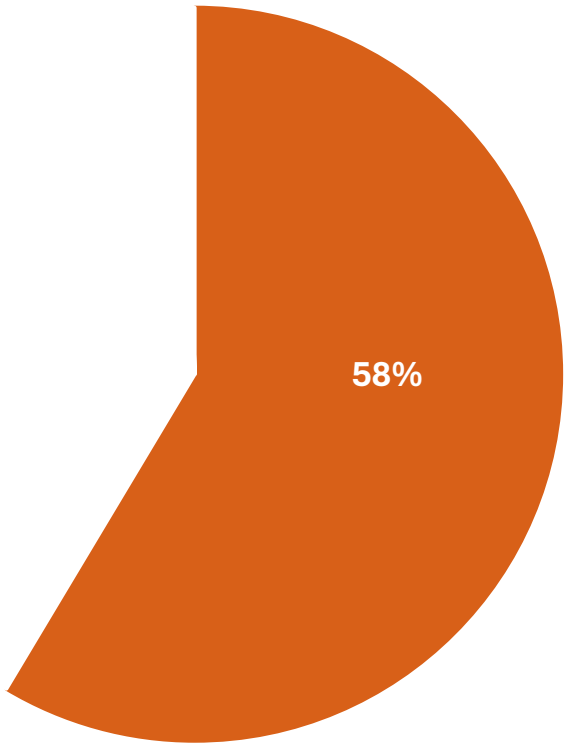


32 Patients Across a Range of Disorders Are on Treatment Today

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

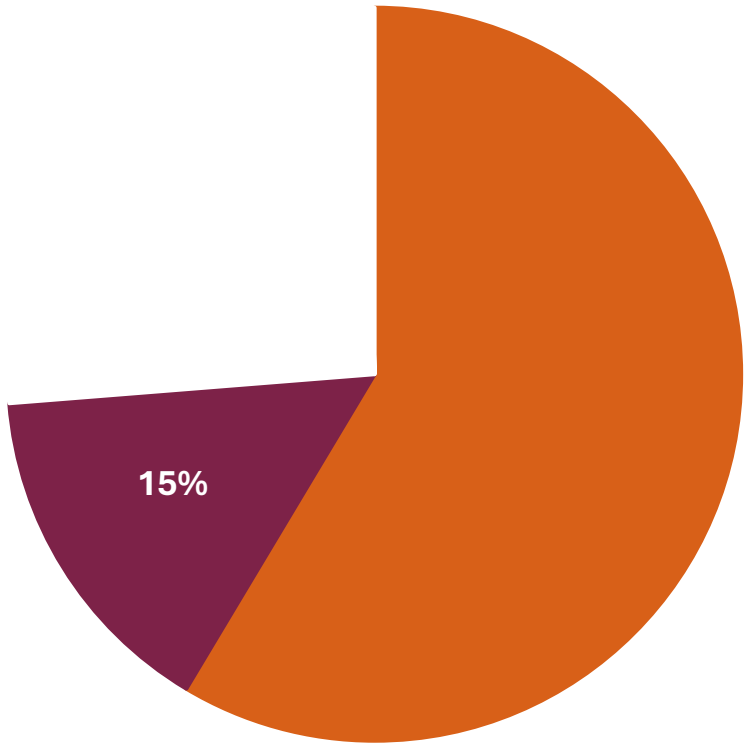
No ASO-related Serious Adverse Events

The Large Majority of Adverse Events Is not Related to Either ASO or Injection Procedure



Examples:
- Ear infection
- Constipation
- Pneumonia

The Injection Procedure Itself Will Lead to Some Adverse Events



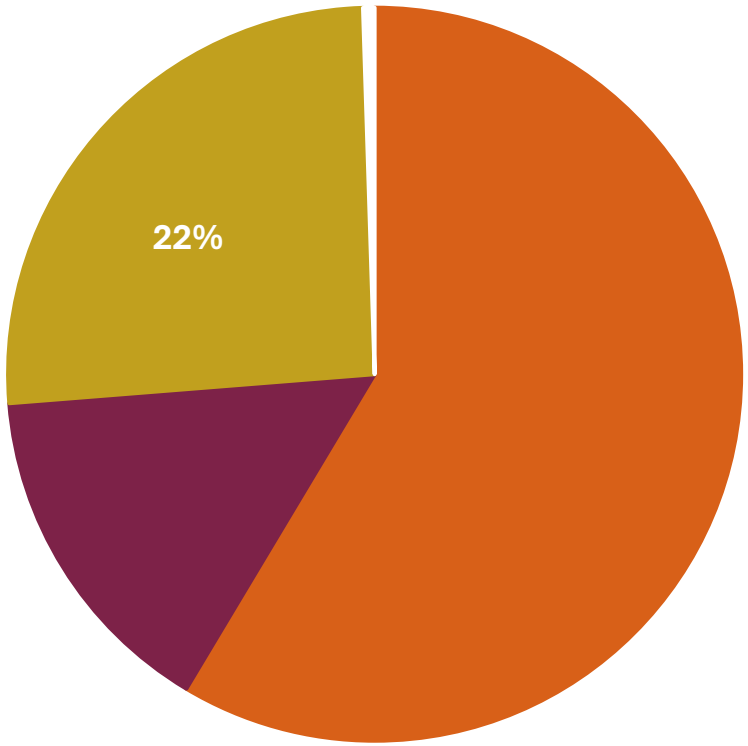
Examples:

- Lower back pain
- Soreness in back

A 4th of All Adverse Events Are “Possibly” related to the ASO and/or the Injection

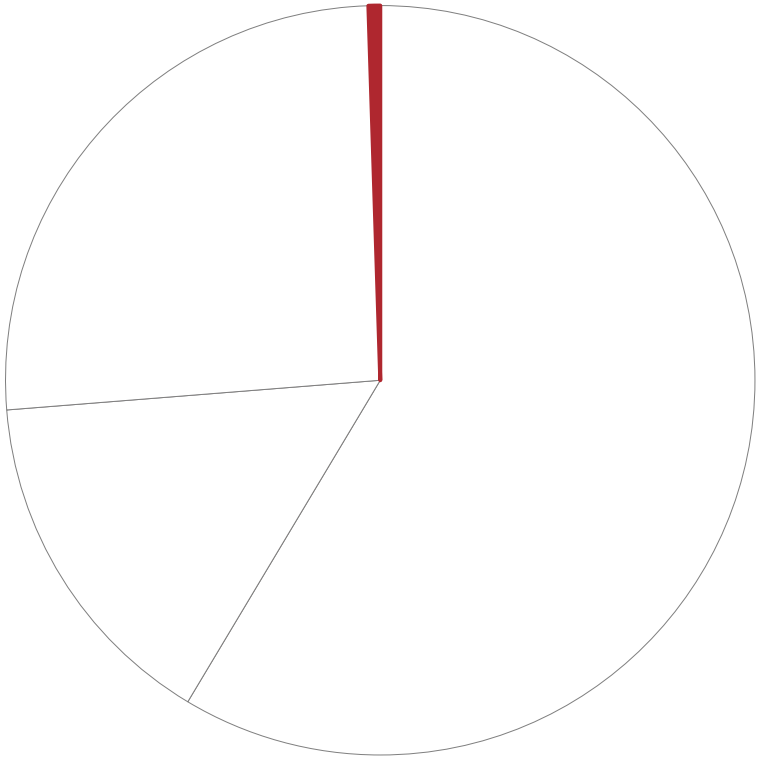
Remember these are events that cannot be separated temporally, but we track them over time.

For example, if vomiting happens every time a patient is anesthetized whether they receive the ASO, that is clearly due to the anesthesia.



Examples:
- Eye pain
- Vomiting

Only One ASO-related Adverse Event



What About that One Adverse Event?

- Our KIF1A patient who has been treated for 3 years has experienced **fevers** post-dose with the last 6 doses
- This patient has shown significant clinical benefit since the beginning of treatment, and is still benefitting from the ASO to date
- Of note, KIF1A disease is associated with fevers in 46% of patients
  - While the fevers post-dose are different, the disease may predispose the patient to fevers in certain situations
- We have performed detailed analyses to understand the cause of these fevers, and assess the safety of continuing treatment

(Boyle et al., Human Genetics and Genomics Advances, 2021)

Previous Knowledge Emphasized the Importance of Evaluating this Adverse Event in Detail

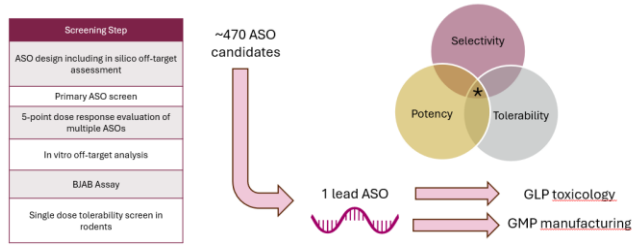
- To determine if inflammation or immune activation was underlying the fevers, we assessed cytokines and complement proteins in the CSF
- Previous work by Ionis has shown that in monkeys the alternative complement pathway can be activated by ASOs given subcutaneously
- Results in our patient
  - Cytokines were not elevated
  - In this patient, some measures of the classical complement pathway were elevated which has not been seen before with ASOs
    - However, it is important to realize that no normal values of complement proteins have been published in pediatric patients, complicating the assessment of severity of this signal
- We believe that this may be a novel ASO-KIF1A disease interaction

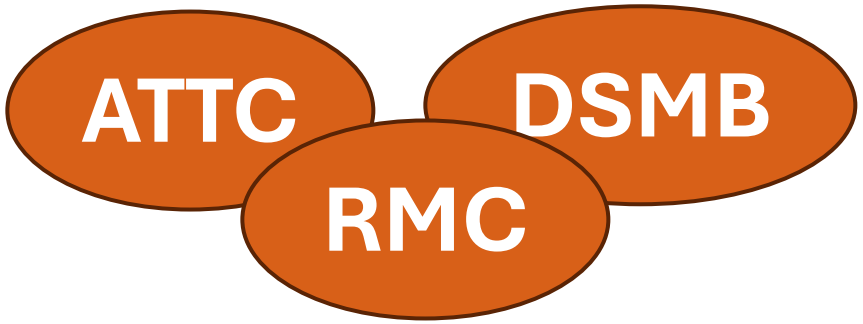
We Have Concluded that Treatment Can Be Monitored and Should Proceed

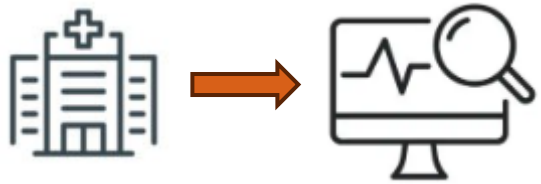
- Importantly, another patient being treated with the same ASO is not exhibiting any fevers post-dose
  - We consider it safe to initiate treatment in additional patients
- We have developed a monitoring plan with the treating physician that has been evaluated and accepted by the FDA and includes
  - Observing the opening pressure and not dosing if too high
  - Continuing assessment of these analytes
  - Pre-treating the patient with steroids
  - MRI if deemed clinically necessary
- All appropriate audiences have been informed
  - Safety Updates – n-Lorem

Excellent Safety Profile Is not an Accident…

- …it is the product of
  - Selection of only optimal ASOs via a rigorous process
  - Deep experience with antisense technology
  - Deep experience in drug development
  - Multiple expert committees
  - Professional management of patients by n-Lorem and the treating physicians







Conclusion

- n-Lorem is treating by far the largest number of nano-rare patients with individualized ASOs and we have an excellent safety and tolerability record
  - CNS, eye, kidney, liver
  - Different routes of administration: SC, IT, IVT
- We are collaborating closely with the treating physicians and monitoring safety on an ongoing basis
- We are deeply committed in sharing safety information with the community as swiftly as possible

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thank you

Thank you to all our investigators and all site staff for your diligence in treating your patients!

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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