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Nano-rare Patient Colloquium 2025

From Decision to Impact: Case-Based Insights into ASO Drug Development for Nano-Rare Patients

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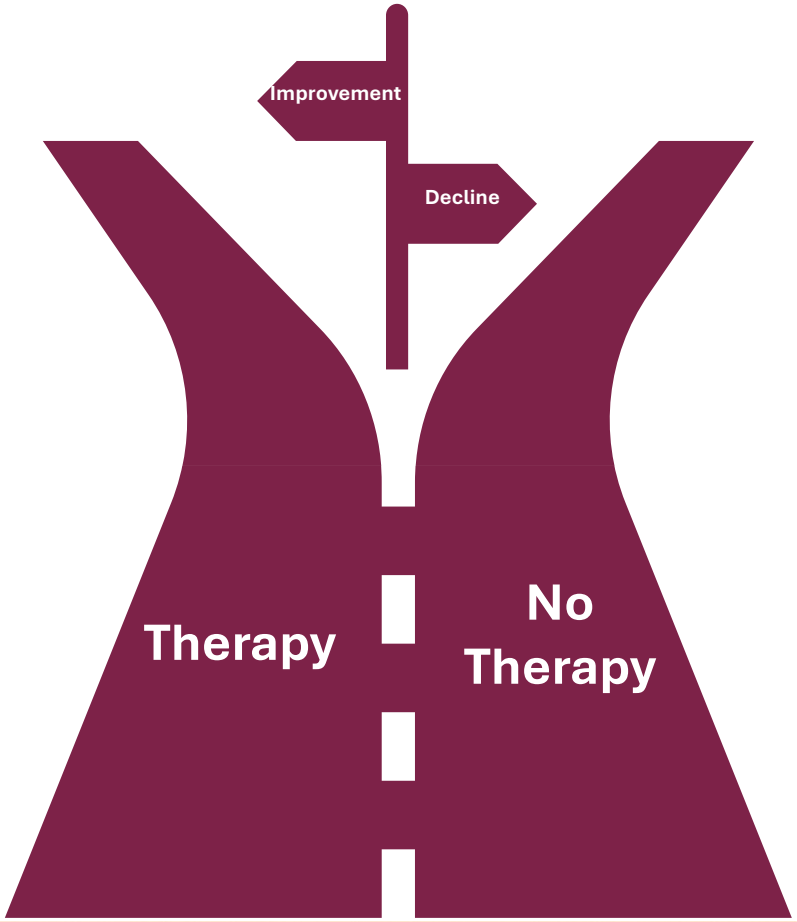
The Stakes are High for Nano-Rare Patients

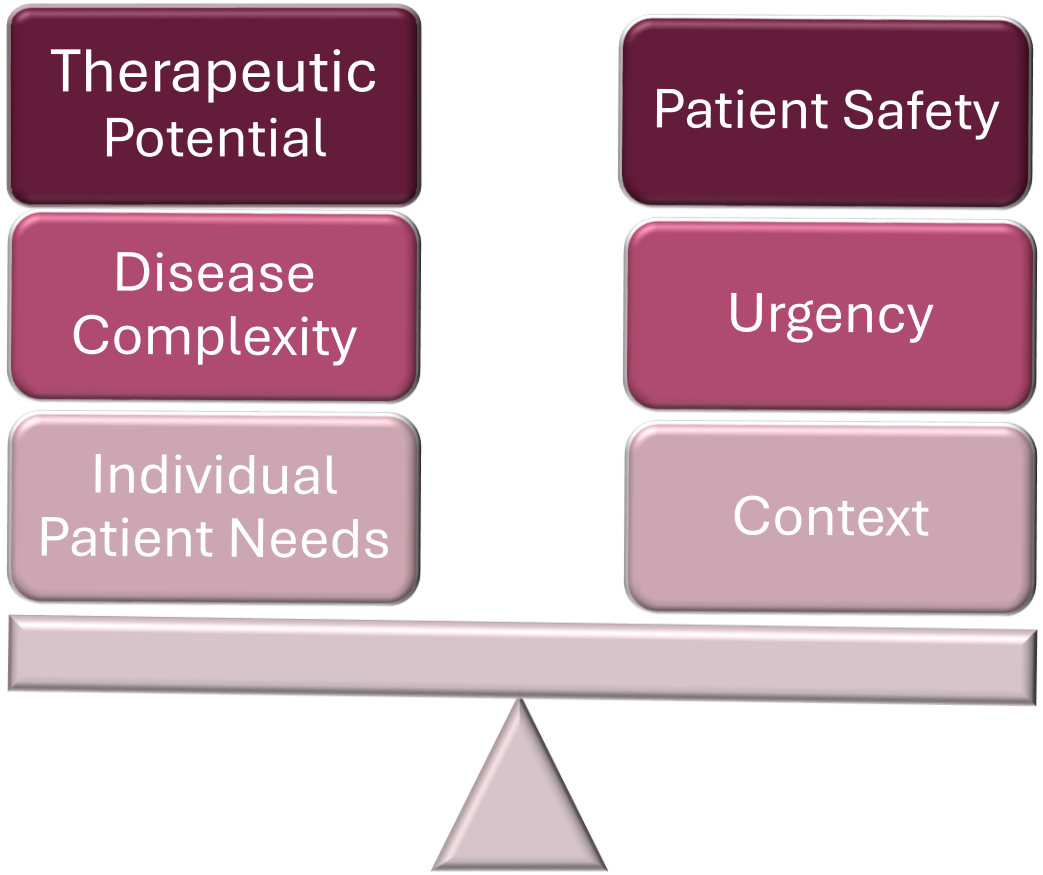
- **No margin for error**: Nano-rare patients have severe, often progressive, and typically advanced disease
- We move to treatment with **less data than typical**
  - Less animal data
  - No normal volunteer data
- **Informed decision-making** can mean the difference between therapy, or no therapy, improvement or decline



The Stakes are High for Nano-Rare Patients

In the nano-rare ASO space, how decisions are made is as important as the treatment

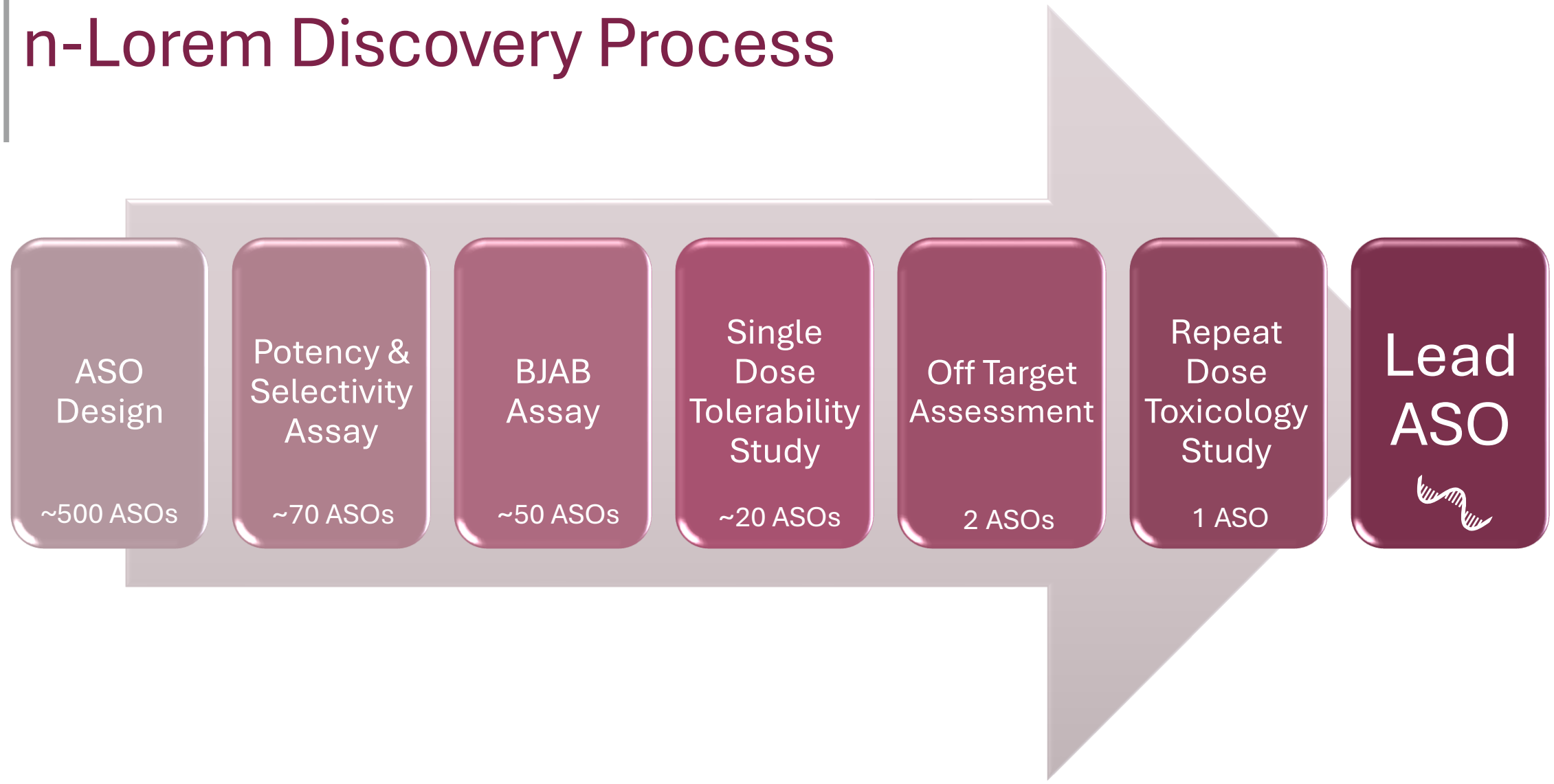
Key Drivers in Decision-Making: A Balancing Act



Integrated, Industrialized Approach to Decision Making

Scientific Expertise	✓	✓
ASO Experience	✓	✗
Drug Development Experience	✓	✗
Growing Experience with Nano-rare	✗	✗
Regulatory Landscape	✗	✓

n-Lorem Discovery Process



What is a Toxicology Study?

90% Success Rate

Toxicology

Identify potential side effects and target organs after semi-chronic dosing, and to help select dose for the clinic

Clinical Observations / General Health
Early indicator of any adverse effects

Functional Assessments
Detect any acute organ-specific side effects

Pathology
Identifies target organs (organ-specific toxicities)

Embedded Quality Control Enhances Potential for Success

Access to Treatment Committee (ATTC)
To advise on whether a patient should be accepted for potential treatment

Research Management Committee (RMC)
To assure the ASO selected to treat a patient meets the highest standards

Study Treatment and Assessment Review (STAR)
To assure the treatment plan is optimal

FDA
To review each investigational new drug (IND) application and assure the ASO and treatment plan meet standards

Institutional Review Board (IRB)
Independent review committee of each medical institution to assure ethical treatment of patients

Data Safety Monitoring Board (DSMB)
To review all clinical safety data on a quarterly basis and determine whether safety profiles of the ASOs are adequate.

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Case Study – nL-IKBK-001

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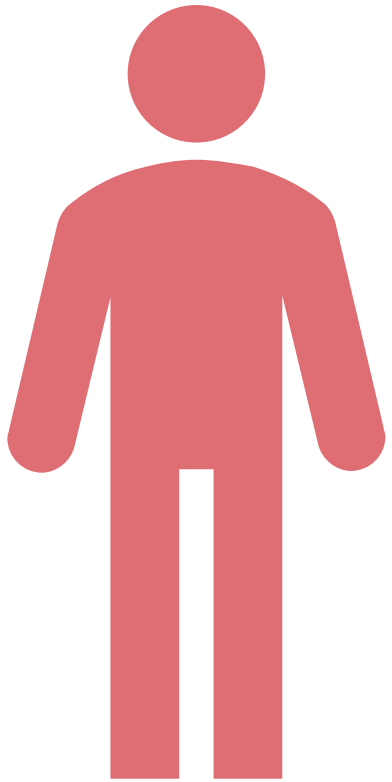
Familial Dysautonomia (FD)

Autosomal recessive hereditary **sensory and autonomic neuropathy**

Causes abnormal **breathing**, **digestion**, **blood pressure** regulation, altered pain and temperature **sensitivity**

Less than 50% of patients survive to **40 years of age**

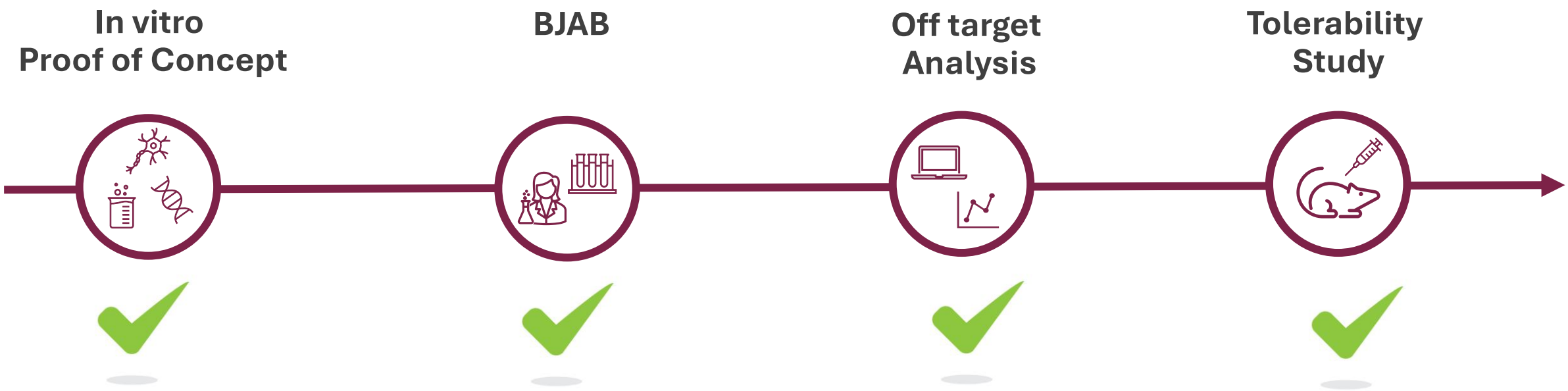


Caused by a single founder point mutation in the **ELP1 gene**

Occurs predominantly in the **Ashkenazi Jewish** population

Results in mRNA degradation and **reduced functional ELP1 protein**

Positive Early Indicators



Based on **positive** discovery data, we moved confidently to the development steps

Learnings from Unexpected Events During Toxicology Study

Dose Administration
(Days 1, 29, 57, 85)

Study conducted as per planned dosing schedule

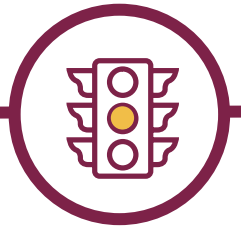
Unexpected Observations

Animals looked unwell after dosing but recovered rapidly

Pathology Review

Evaluation revealed findings of concern

Program Re-evaluated



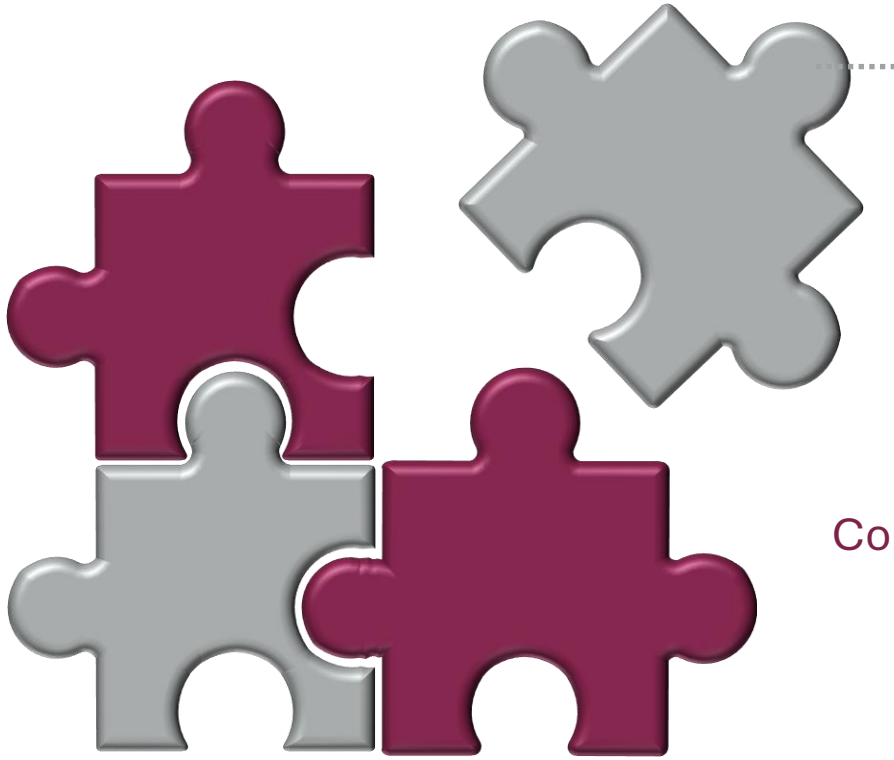
Is there a path forward?

Study revealed unexpected findings despite transient clinical recovery, indicating the need for **additional optimization** before progressing

Experience Helps us Move Towards Resolution

ASO levels in tissues **higher than expected**

Additional calculations confirmed a **lower dose** would be **efficacious** in the clinic



Ensure FDA alignment via Pre-IND meeting

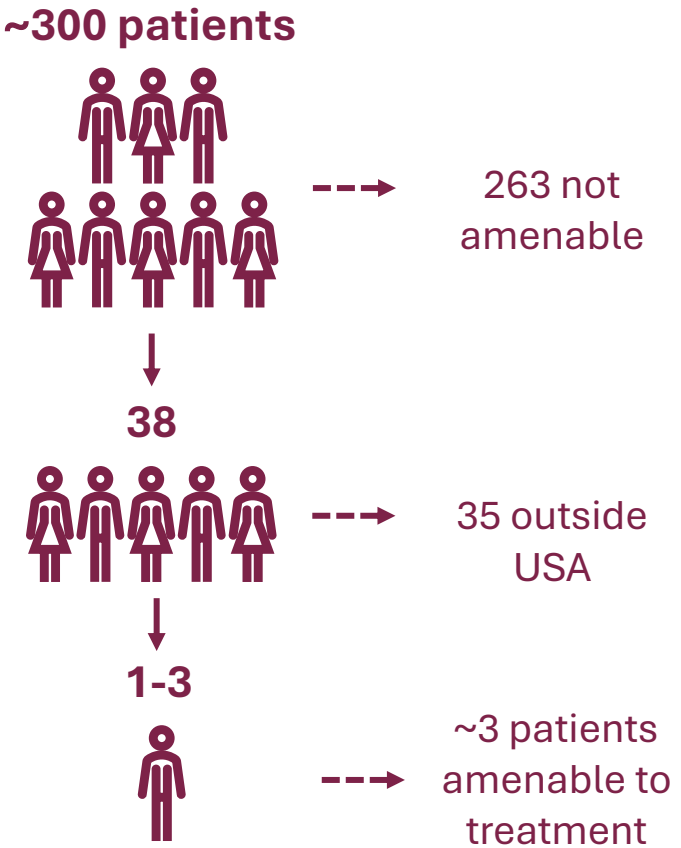
Conduct an **additional study**?

Non-GLP
Small cohort
Limited endpoints

FDA Regulatory Engagement : New Hurdle

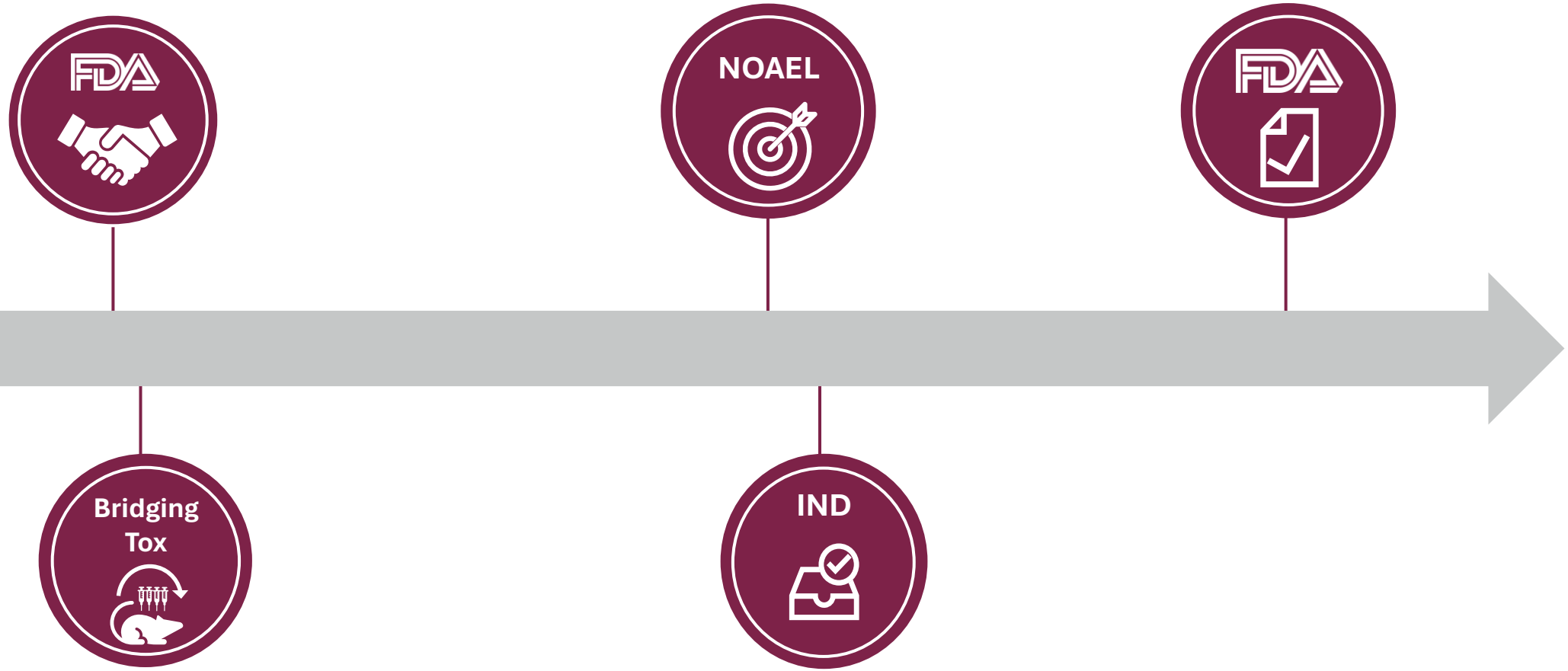
FDA Regulatory Engagement : New Hurdle

- **This indication is not n=1**
- The majority of the population is **not eligible/amenable** for treatment based on exclusion criteria
  - Beyond age of amenability, disease progression, comorbidities
  - Genetic prescreening and awareness have greatly reduced new cases
  - Geographical location
- Overall: **1-3 patients** in the USA are **amenable** to treatment
- Indication not compatible with full development program



FDA agreed!

Program now Back on Track



From Concept to Clinic

News and Breakthroughs

Gene Therapy for Familial Dysautonomia: The dawn of an era

On June 20, 2024, the field of familial dysautonomia (FD) research reached a groundbreaking milestone.

A young patient with FD received the first dose of an antisense oligonucleotide (ASO), a drug designed to correct the genetic defect underlying FD. This marks the beginning of a new era of genetic therapy for this devastating condition.

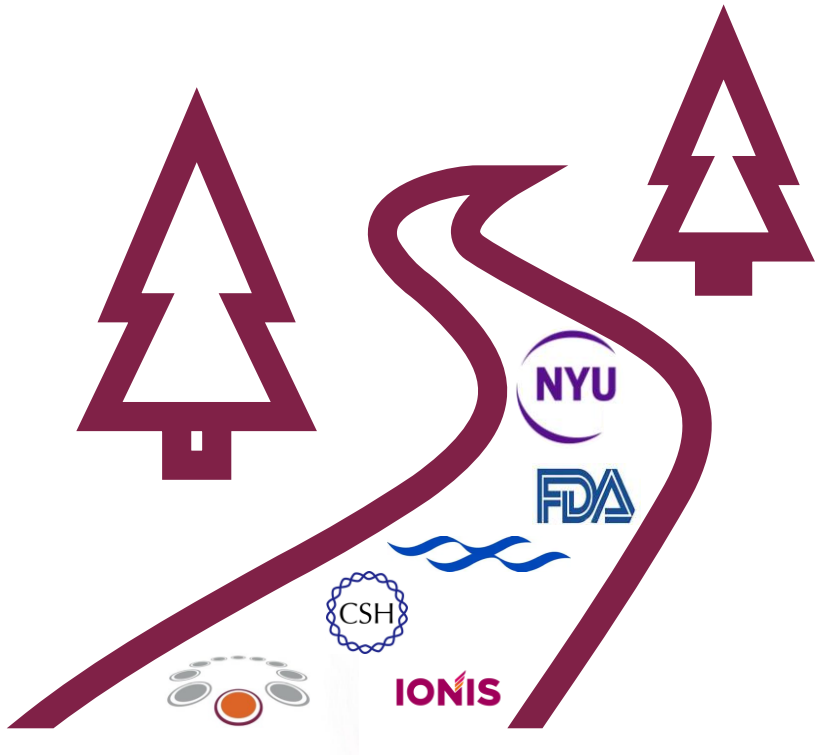
Drs. Horacio Kaufmann and Alejandra Gonzalez-Duarte

Significantly Improved Clinical Status at 9 Month

- Improvements noted in:
  - Gait
  - Temperature and vibration perception
  - Quality of life
  - Nerve fiber density
  - ELP1 levels
  - Neurofilament levels

Expanding our Mission, One Patient at a Time

- IND has been amended to include a second patient with a similar phenotype
- The first patient has now received 6 doses, and the second patient has received 3 doses, which have all been well tolerated
- The treating team has identified a few more patients both in and outside of the USA, and is working with n-Lorem to navigate the logistical aspects



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Case Study – nL-TARDB-003

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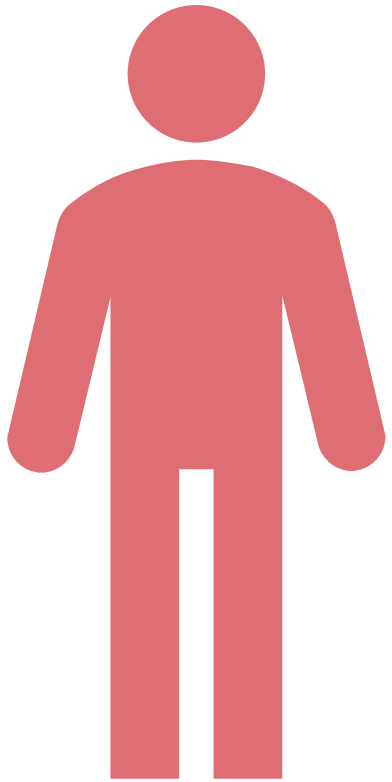
TARDBP-Associated ALS

Typically **autosomal dominant**, accounting for 2-5% of familial ALS

Characterized by **progressive motor neuron disease** leading to weakness, muscle wasting, spasticity, and loss of motor function

Survival typically **2–5 years** from onset

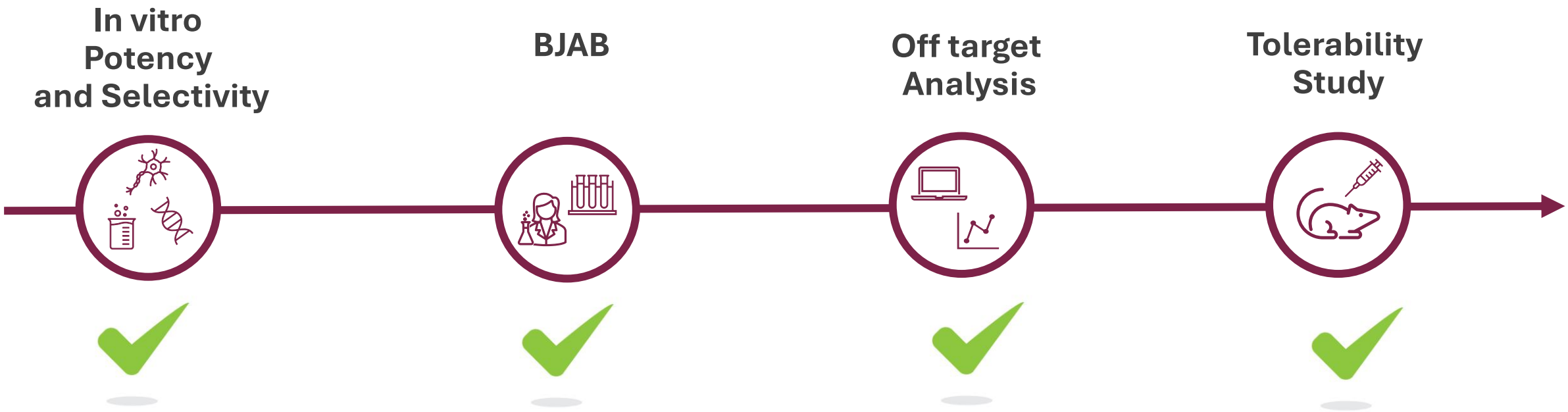


Caused by mutations in **TARDBP** gene, encoding TDP-43

Onset is usually around **40-60 years of age**

Accumulation of **cytoplasmic TDP-43 inclusions** in motor neurons and glial cells is a hallmark of the pathology

Positive Early Indicators



Based on **positive** discovery data, we moved confidently to the development steps

Importance of Repeat Dosing in Toxicology Assesment

Dose Administration
(Days 1, 29, 57, 85)

Study conducted as per planned dosing schedule

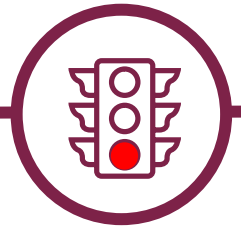
Worsening Observations

Clinical condition of the animals worsened after repeated dosing

Pathology Review

Evaluation revealed findings of concern

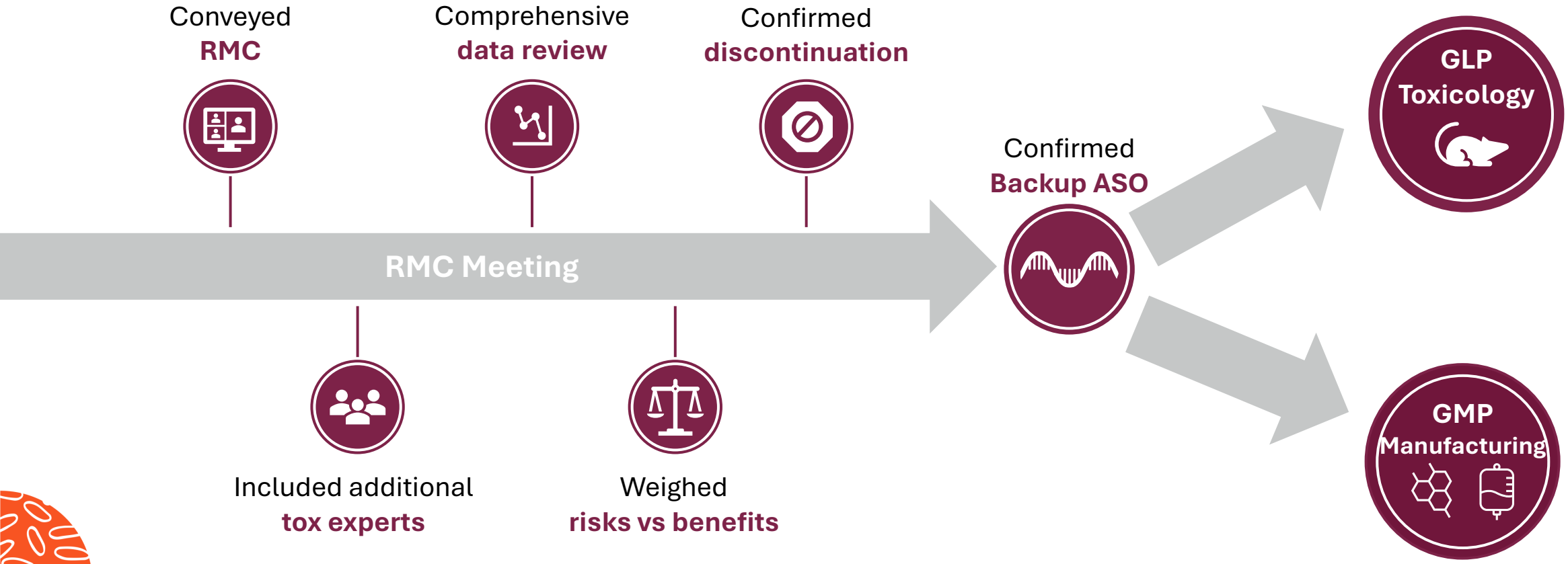
Program Re-evaluated



Is there a path forward?

Study revealed **extensive and concerning toxicities**, prompting in-depth discussions on the program's path forward

Expertise Driving Responsible Decisions



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Case Study – nL-PACS1-001

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PACS1 Syndrome (Schuurs-Hoeijmakers)

Clinical Features

Spectrum of **neurodevelopmental delays**

Structural **brain abnormalities**

25% **autism spectrum disorder**

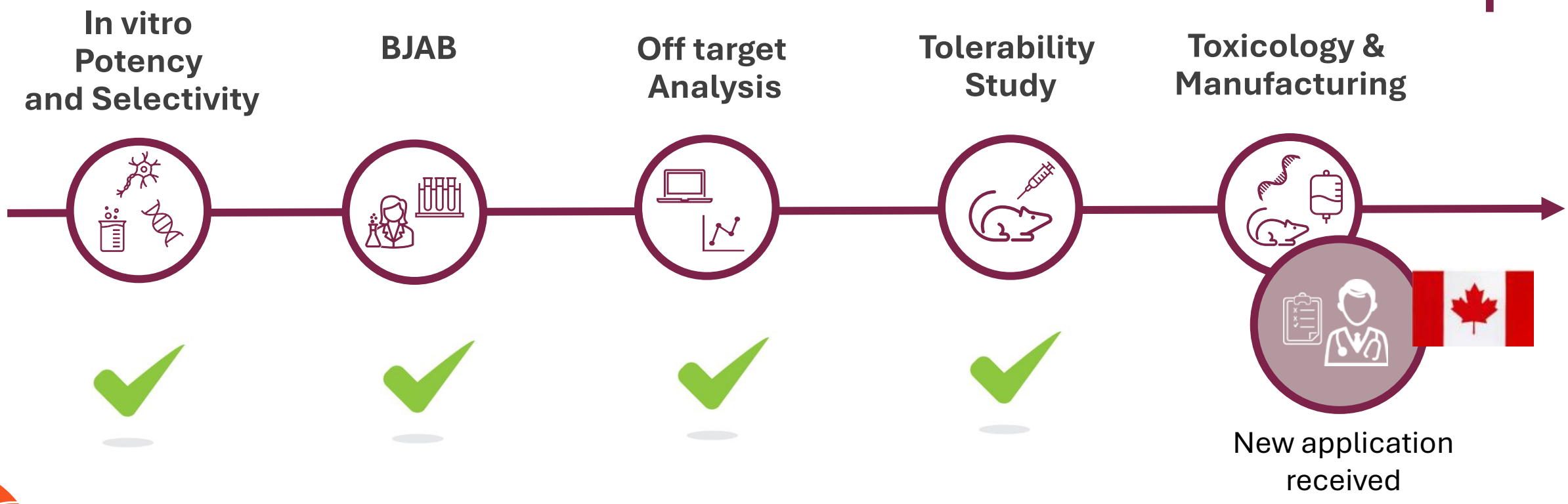
Additional congenital **heart and ocular abnormalities**

Driven by **toxic gain of function** mutation in the **PACS1** gene

Nearly all cases linked to the recurrent missense mutation **R203W**

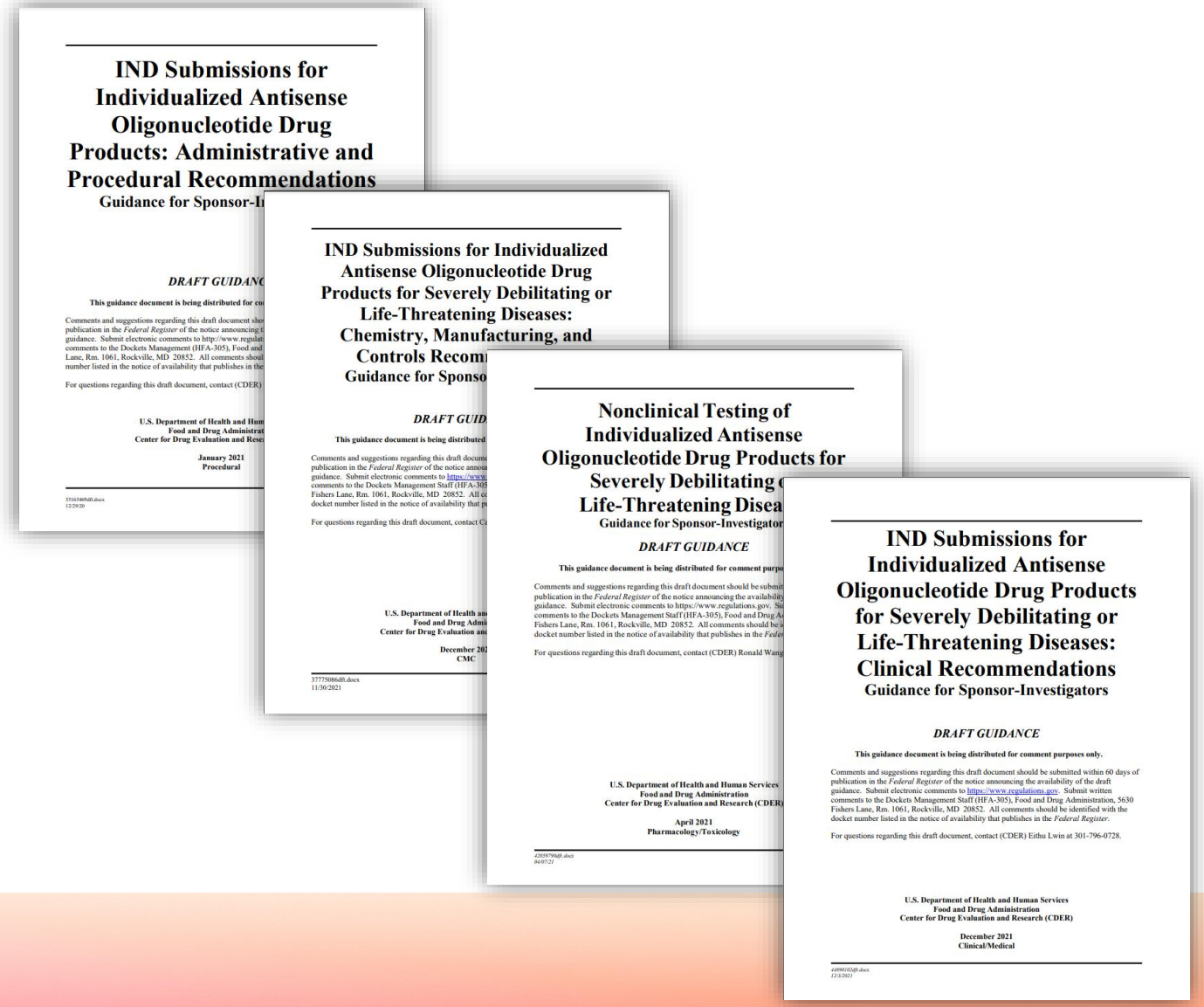
n-Lorem accepted **2 patient** applications in 2020

Smooth Progression Through the Steps



Defined Regulatory Path in the US

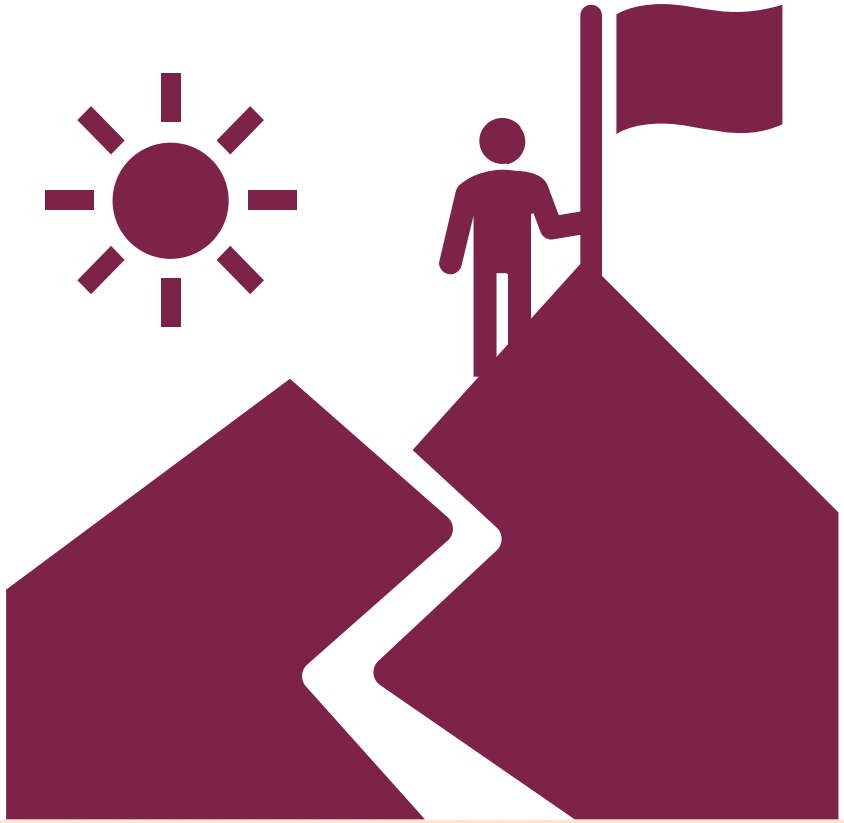
- The FDA has issued specific guidance documents to map the development of individualized ASOs for severely debilitating or life threatening diseases
- No other country has an equivalent path



Exploring New Ground: From Local to Global

- Began with a US IND submission for the first 2 patients
- Built on this foundation to prepare a Canadian CTA, appending the US IND package
- Positioned the case as a collaborative opportunity with Health Canada — to help an individual patient today while opening the door for future Canadian patients

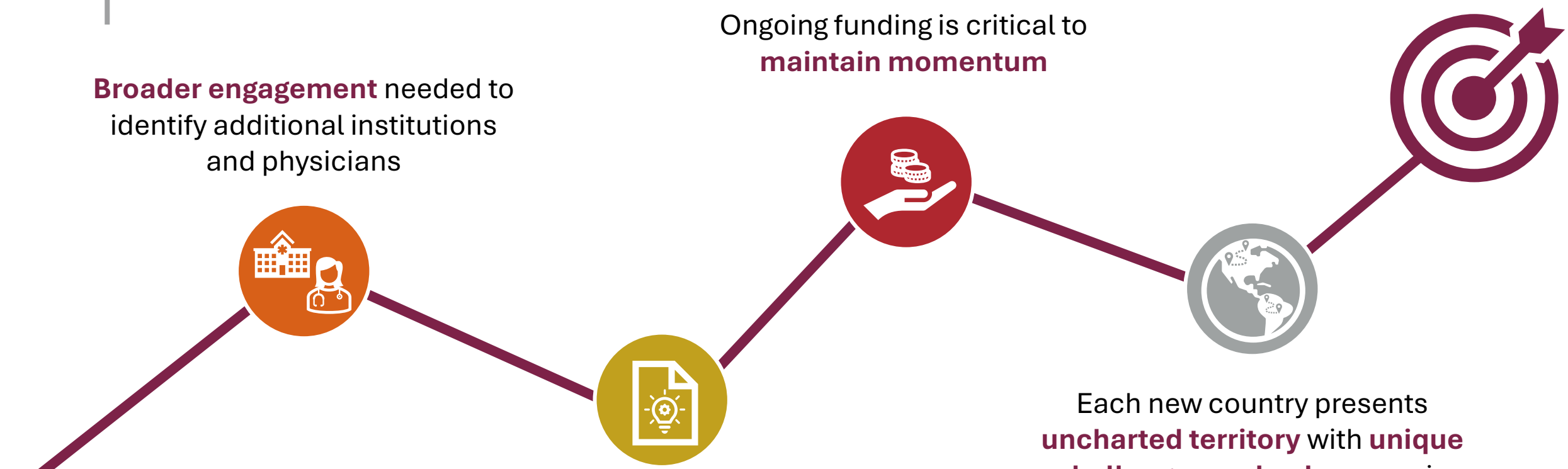
A Step Forward Beyond the US



A Milestone, With More Ahead

Broader engagement needed to identify additional institutions and physicians

Ongoing funding is critical to **maintain momentum**



Health Canada's stance on a **new ASO program** without parallel FDA approval remains unclear

Each new country presents **uncharted territory** with **unique challenges and unknowns**, in addition to the particularities of each patient program

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Key Learnings and Take Home Message

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Key Learnings

- Importance of **informed decisions** in shaping therapy trajectory
- Balancing **scientific data** with **real-world patient** context
- **Flexibility & adaptation** under uncertainty

Experience Matters Because It Informs Judgement

Conclusions

- Every decision is **patient-specific** and **context-dependent**
- Expertise is the **safety net** – scientific, ASO, drug development, clinical and regulatory
- One-size-fits-all does not work when addressing nano-rare conditions, requiring **innovative thinking and flexibility**
- Impact is measured in **lives of patients** and their families changed, and not just in molecules made