n-lorem FOUNDATION

Transforming Dreams into Reality: Tackling Nano-Rare Diseases

Julie Douville

Executive Director, ASO Discovery and Development

05 October 2024

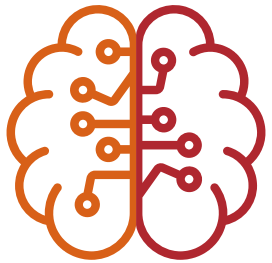
we are nano-rare

n-Lorem's mission is to apply the efficiency, versatility and specificity of antisense oligonucleotide (ASO) technology to charitably provide experimental ASO medicines to treat patients with nano-rare diseases

n-Lorem Then… and Now

January 2020

- **n-Lorem Foundation established**
- **Founding Donors:**
  Ionis, Biogen
  Stan and Rosanne Crooke
- **Patient Assumptions:**
  1-2 applications in year 1
  10-20 applications by year 5
- **n-Lorem managed with volunteers**
- **ASO discovery outsourced**



October 2024

- **Operating at full capacity as a nonprofit biotech organization**
- **Exceptional, mission-driven, hand-picked talent in every function**
- **Processes and systems established**
- **Regulatory engagement entirely favorable**
- **Growing network of partners, reducing $$ per ASO**
- **Growing network of institutional partners for clinical treatment**

n-Lorem Current State

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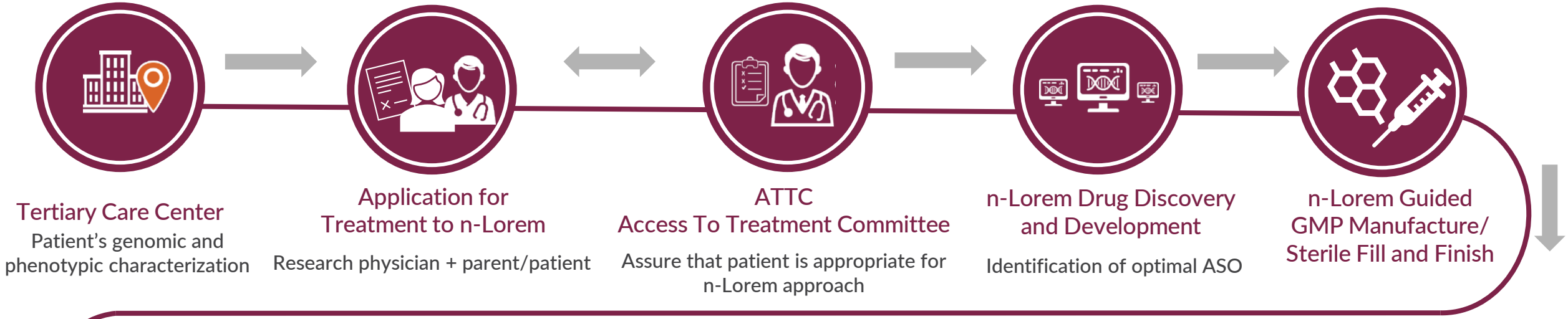
Overview of n-Lorem Process



Tertiary Care Center
Patient's genomic and phenotypic characterization

Application for Treatment to n-Lorem
Research physician + parent/patient

ATTC
Access To Treatment Committee
Assure that patient is appropriate for n-Lorem approach

n-Lorem Drug Discovery and Development
Identification of optimal ASO

n-Lorem Guided GMP Manufacture/ Sterile Fill and Finish

Food and Drug Administration
IND submissions based on FDA guidance for n-of-1 ASOs

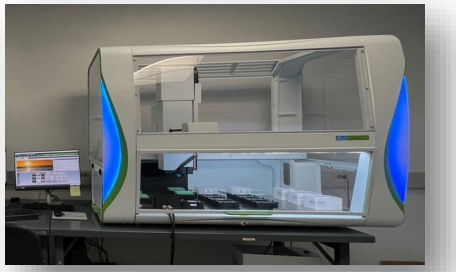
Research and Treatment Centers
Treatment and evaluation begins

Research and Treatment Centers
Individual Patient Data

n-Lorem Clinical Data Analyses
Detailed aggregate analyses

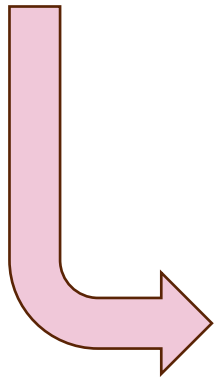
n-Lorem Discovery and Development process

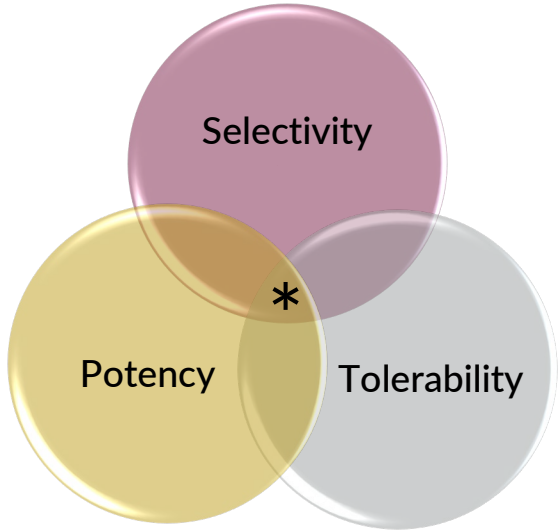
Quality Steps to Develop Safe ASOs for Each Patient



Screening Step
ASO design including in silico off-target assessment
Primary ASO screen
5-point dose response evaluation of multiple ASOs
In vitro off-target analysis
BJAB Assay
Single dose tolerability screen in rodents

400-600 ASO candidates





1 lead ASO

GLP toxicology

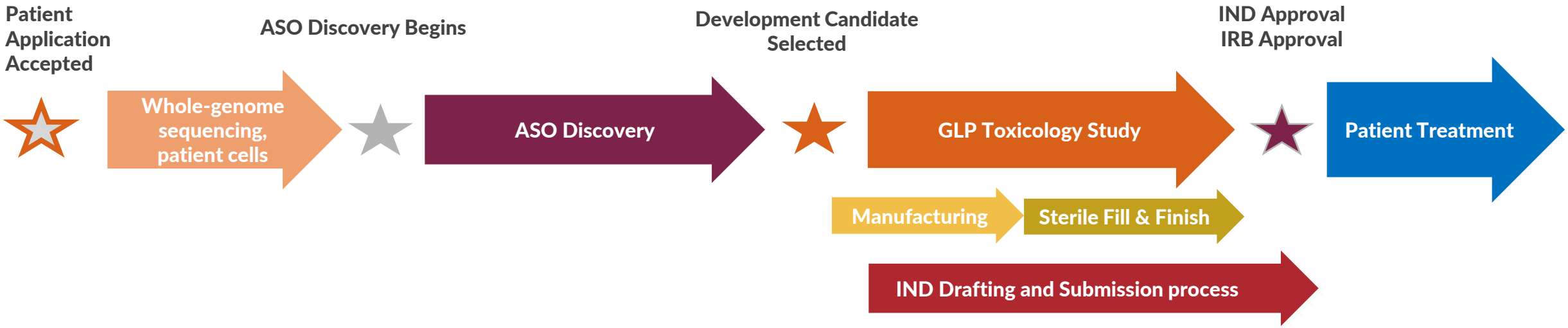
GMP manufacturing

Collaboration with Clinical Sites

Collaboration with investigators starts at case acceptance	Throughout ASO discovery, physicians provide update on patient status	Collaborative development of protocol and ICF	Upon IND approval
• Patient cells and whole genome sequencing required for ASO design and in vitro screening	• Tracking disease progression, potential changes in treatment goals	• Individualized treatment goals tailored to patient phenotype • Slow dose escalation and safety monitoring	• Support site with IRB submission and queries • Train site staff and pharmacy team on protocol • Develop electronic database for clinical data collection

n-Lorem's Parallel Processes Focus on Quality and Speed

Every Day Matters for Our Patients



Clinical Activities

Development of well-defined **Treatment Goals** specific for each patient

Development of **individualized protocol** and informed consent

Development of **patient specific electronic database** to capture pre-and post-treatment clinical data

Collection of clinical data post-treatment / DSMB review

Regulatory Approach

Successes

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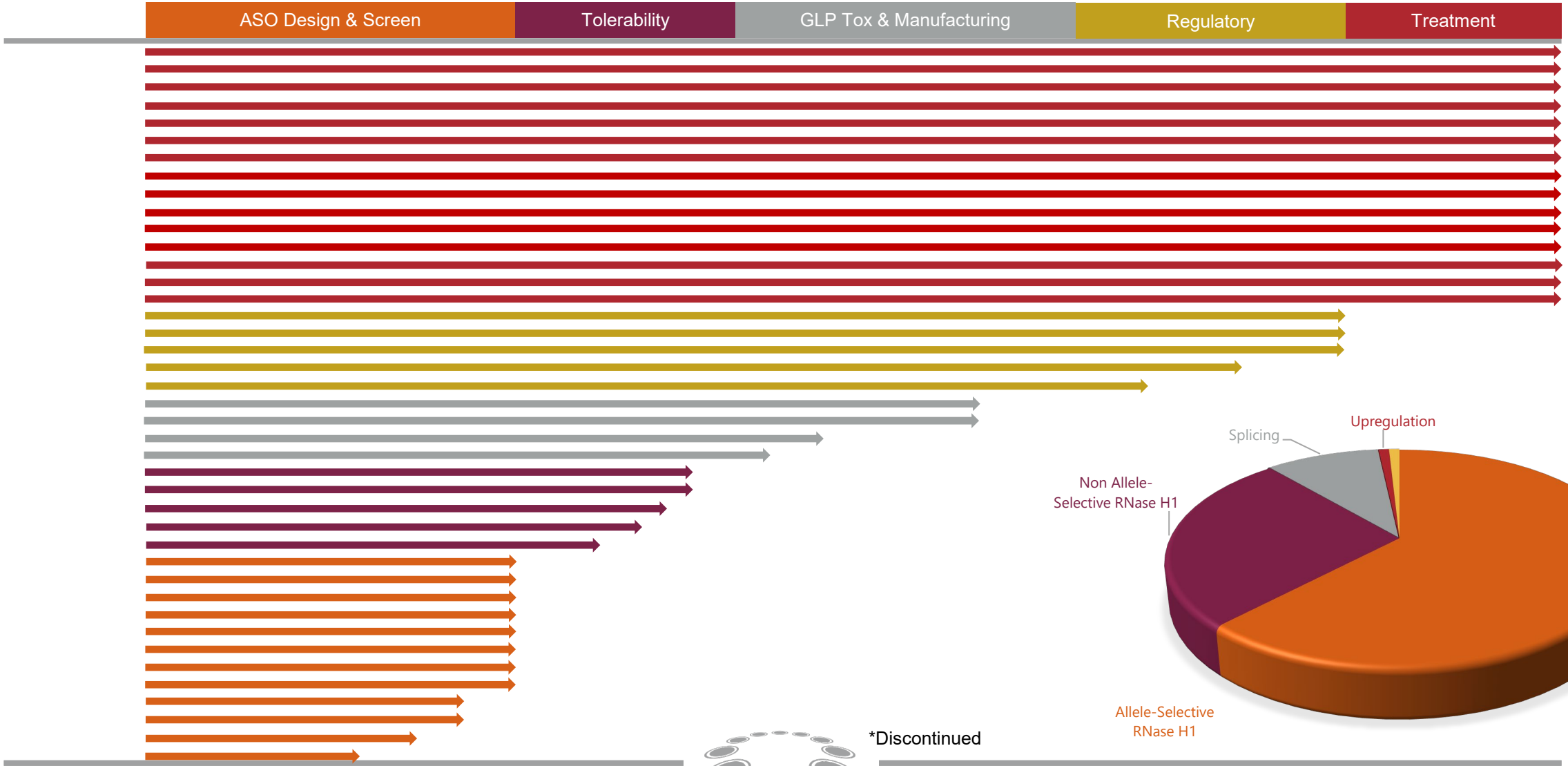
n-Lorem Active Pipeline



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n-Lorem Accomplishments

- Application Review Metrics to date
  - **~300 applications reviewed**
  - ~150 were accepted
- Discovery Metrics to date
  - 14 are ongoing
  - 38 programs are completed
- Nonclinical Development Metrics to date
  - 5 are ongoing
  - 14 programs are completed

n-Lorem Accomplishments

- Regulatory Metrics to date
  - **21** INDs submitted to **4** FDA divisions in ~2 years – 20 approved
    - 1 under review
    - 29 patients covered
- Clinical Metrics to date
  - **15** patients dosed – 13 CNS, 1 eye, 1 liver
  - Between 1-10 doses given per patient
  - 4 patients treated for 12+ months
- Safety Metrics to date
  - **No ASO-related Serious Adverse Event**
  - **No ASO-related Adverse Event**
- Efficacy Metrics to date
  - 7/7 evaluable patients show evidence of clinically important benefit
  - Other patients too early in the treatment process to evaluate

Ongoing Clinical Programs and ASO Strategy

Programs with Approved Investigational New Drug (IND) Applications

Treatment

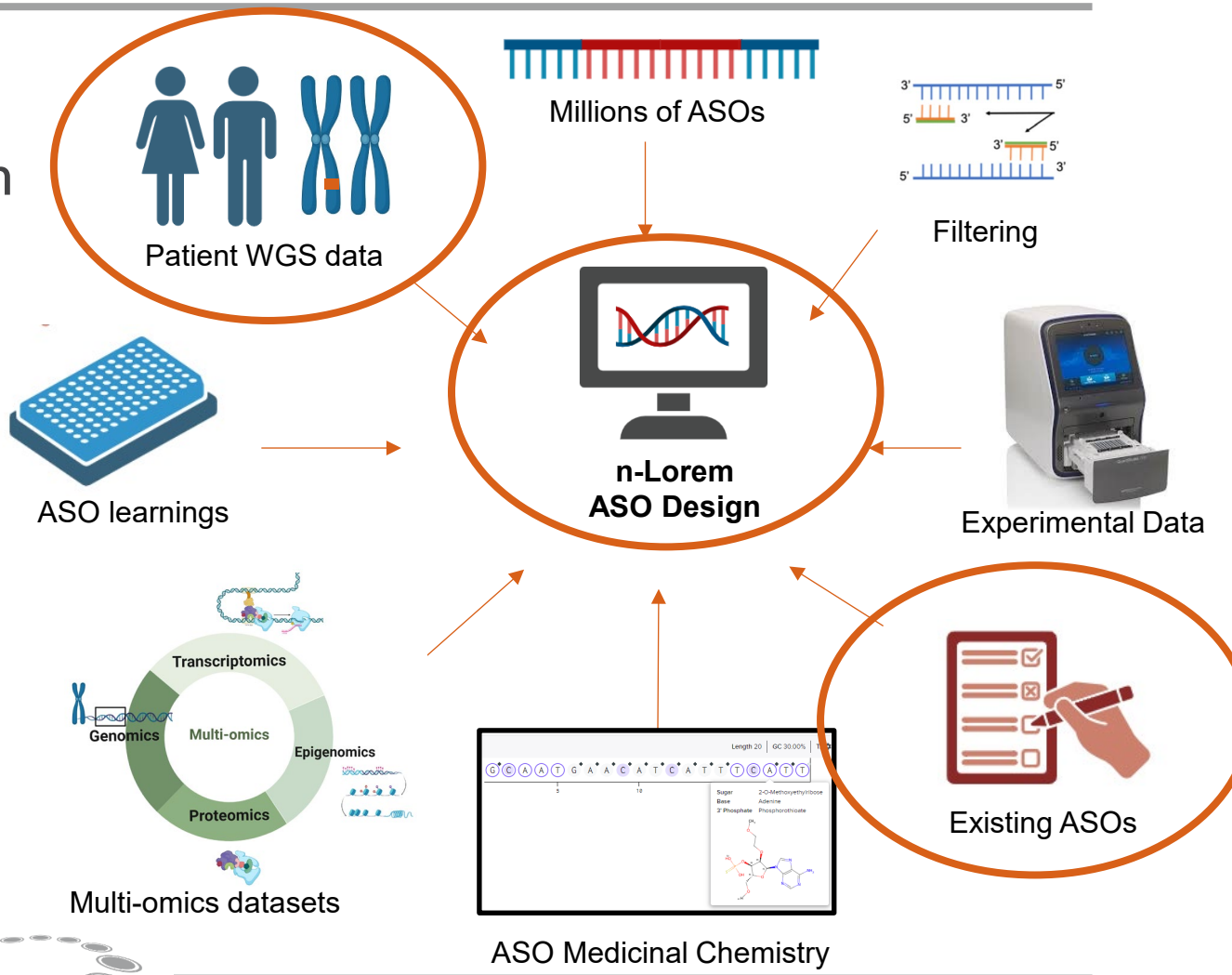
- 10 ASO Programs, 13 Patients

Patient	Route	ASO Strategy	First dose	# of doses given
nL00255 – KIF1A	IT	Allele Selective	October 2022	10
nL00068 – SAA1	SC	Non-Allele Selective	November 2023	10
nL00333 – SCN2A	IT	Allele Selective	June 2023	8
nL00180 – FLVCR1	IVT	Splicing	August 2023	4 R eye; 2 L eye
nL00001 – SCN2A	IT	Allele Selective	March 2024	4
nL01183 – ATN1	IT	Non-Allele Selective	February 2024	4
nL00010 – CHCHD10	IT	Non-Allele Selective	April 2024	3
nL00037 – KIF1A	IT	Allele Selective	May 2024	3
nL00808 – ELP1	IT	Splicing	June 2024	2
nL00152 – CHCHD10	IT	Non-Allele Selective	June 2024	3
nL00214 – TUBB4A	IT	Non-Allele Selective	September 2024	1
nL98087 – hnRNPH2	IT	Non-Allele Selective	September 2024	1
nL00250 – CHCHD10	IT	Non-Allele Selective	October 2024	1

Two patients discontinued treatment as their disease progressed and they could no longer travel to the clinic.

Using AI to Create Libraries of AS ASOs

- Some target genes are repeat offenders
- Multiple rounds of screening focused on different SNPs dependent on each patient's WGS, each identifying a different lead ASO candidate
- This results in having a library of ASOs available 'off the shelf' for future patients presenting with a similar SNP pattern
  - 2 ASOs for SCN2A
  - 5+ ASOs for TARDBP
  - 3+ ASOs for KIF1A



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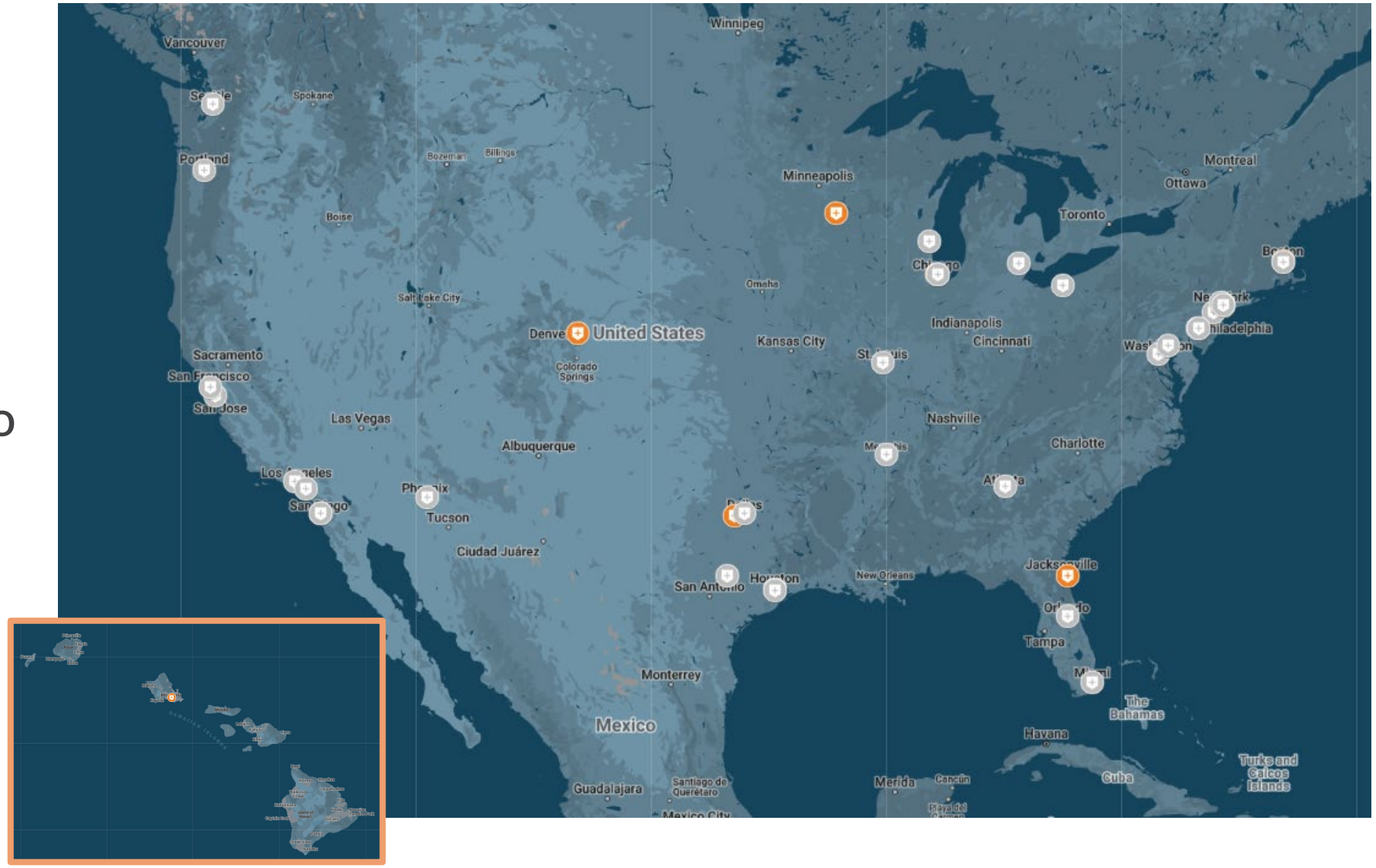
US Institutional Footprint Allows for Local Treatment

- Footprint of collaborating institutions allows for large catchment area
- There is still work to be done to ensure patient access to institutions able to treat them



Moving Beyond n = 1

- Different reasons can push the transition from n=1 to n=few or many
  - Known prevalence increases as WGS becomes more available
  - Demand emerges once treatment becomes available
  - Strategy changes from allele-selective to non allele selective
  - SNPs used to design ASOs are commonly present
- No published guidance to treat more than 1-2 patients
- n-Lorem held proactive discussions with the FDA

Moving Beyond n = 1

- Typically the FDA would require additional animal studies
- n-Lorem proposed to dose one patient, collect data to demonstrate safety, then dose additional patients cautiously
- Response from the FDA has been favorable to date

We now have 5 different ASOs approved to each treat 2 to 9 patients

Conclusions

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What about the future?

- ASO quality remains top focus
- Continue to optimize the ASO Discovery and Development process and grow the partner network
- Continually increase and improve capacity and scalability through partnership and internal growth
- Pursue basic research on molecular mechanisms to broaden the type and number of patients' mutations we can target
- Expand outside the US
- Establish centers of excellence to facilitate access to ASO treatments

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Support From Leaders Across 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

La Jolla Labs

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

KreaMedica Your Partner in Drug Development

IPST

Greenfield Pathology Services, Inc.

Access to Appropriately Characterized Patients and Investigators

UDN 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

danaher

Sterile Fill Product

ARGONAUT MANUFACTURING SERVICES

Nitto Avecia Pharma Services

Other

COMBINED

Cooley

COWEN

STIFEL

J. WOOD CAPITAL ADVISORS

sysnav HEALTH CARE

Data Partners

Across Healthcare

Unipr

Questions?

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Register at nlorem.org

Nano-rare Patient Colloquium 2024

Oct. 30-31, 2024
Cambridge, Massachusetts
Boston Marriott Cambridge

Hosted by: Biogen