A Novel Integrated Operational Model for the Nano-Rare

Sarah Glass, PhD
Chief Operating Officer
Bringing it all together: 
Our mission, Our science, Our medicine

- n-Lorem exists to treat nano-rare patients, provide hope to the hopeless and help to the helpless
- ASO technology makes n-Lorem feasible
- Leveraging experience across a range of ASO strategies and target organs broadens the number of patients that can be helped
- Identifying an optimal ASO follows a very specific process, is done in a high-quality manner and involves complex decision-making throughout
- Every patient requires a customized treatment protocol and committed physician/ institution
- Data collection from the point of patient symptom onset through clinical treatment is of the utmost importance
- The FDA has created a supportive regulatory environment centered around the guidance documents for antisense oligonucleotides
HOW?
Time is Critical – Patients Need Treatment Today

Drug Discovery & Development: Standard vs. n-Lorem

- **Standard drug discovery to commercialization**:
  - 5 – 10 years Drug Discovery
  - > 20 years Commercialization
  - > $2 Billion

- **n-Lorem ASO drug discovery to treatment**:
  - ~1.5 years Drug Discovery
  - Drug Development
  - Investigator IND
  - 12 – 15 years Drug Development
  - ~ $1.3 Million

**The only approach with FDA guidance for nano-rare patients**

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**2023 Nano-rare Patient Colloquium**

Hosted by [Biogen]
Standard R&D is Not Suitable for Individualized Treatments

- Focused on the drug and patient population’s phenotype(s)
- Single protocol for entire study population designed to achieve statistical significance
- Regulatory path varies per program with core requirements
- Primary drivers may be financials or corporate strategy

- Focused on a single patient’s genotype and unique phenotype
- Per-patient protocols designed to assess ability of the ASO to improve the patient’s clinical phenotype
- FDA-defined path for Individualized ASOs
- Primary drivers are quality and efficiency
n-Lorem Integrated Operational Model
A Shift in Mindset: Refining >30 years of Antisense and >80 years of Drug Development Experience for the Nano-Rare

- Exceptional hand-picked talent in each function with >80 years of experience in rare disease drug discovery and development
- Successful industrialization at n-Lorem requires a different way of thinking for our internal team and partners accustomed to standard drug development

- Biotech-esque: defined core accountabilities yet ability / willingness to wear many hats
- Communication = listening + sharing
- Every behavior, decision, action is with the patient front of mind
The n-Lorem Integrated Operational Model

- Concisely-defined yet nimble **quality processes** and systems
- Succinct **Project Management solution** for maintaining forward progress of portfolio of ~100 patients’ ASO programs
- Patients play a role in **every step** of the process

**Application evaluation and feasibility (10)**

- **ATTC**= Access to Treatment Committee
- **STAR**= Study Treatment and Assessment Review
- **RMC**= Research Management Committee
- **DSMB**= Data Safety Monitoring Board

**ASO Discovery and Optimization (~60)**

**Preclinical Development (>10)**

**Regulatory Stages (>5)**

**Clinical Study and Treatment (7)**

Frequent engagement with physicians and FDA before and throughout treatment
Success of the Integrated Model Measured by Key Patient-Centered Outcomes

- Seamless, transparent and multidirectional interfaces between roles and processes
- Continual learning and improvement for every patient due to the iterated processes
- Assessing benefit/risk of each ASO program in real-time as the ASO and patient phenotype progress
n-Lorem’s ASO Discovery & Development Process is Unique and Designed for Individual Patients’ Needs

- **Concurrent activities** when possible
- **Expedite** advancement of drug development according to patient’s clinical progression
- Unique patient program and timelines **driven by the ASO strategy and complexity**

**ASO Discovery Begins**
- Whole-genome sequencing, patient cells*

**Development Candidate Selected**
- ASO Discovery
- GLP Toxicology

**IND Submission & IRB Approval**
- Patient Treatment
- Manufacturing
- Sterile Fill & Finish
- IND Drafting and Submission process

*Whole-genome sequencing, patient cells*
Customizing Each Patient’s ASO Program in Real-Time

ASO Discovery Mechanism/Strategies Evolve To Find Optimized ASO

- Target expression not sufficient in patient cells requiring acquisition and growth of a different cell-type
- New data leads to a change in ASO strategy (allele-selective → non allele-selective)
- First attempt to identify an optimal ASO is unsuccessful, uncovers a potential alternative; begin with ASO design again
- First attempt to identify an optimal ASO is unsuccessful and necessitates additional research

Whole-genome sequencing, patient cells* → ASO Discovery → Development Candidate Selected → IND Submission & IRB Approval

- ASO Discovery Ends
- Development Candidate Selected
- IND Submission & IRB Approval

Patient Data Collection (WGS, Natural History and Treatment) → IND Drafting and Submission process → Patient Treatment

Manufacturing → Sterile Fill & Finish

*Whole-genome sequencing, patient cells
Customizing Each Patient’s ASO Program in Real-Time
Integrating Intramural and Extramural activities to Maximize Speed

- Finding in GLP toxicity study suggests the need to pursue the back-up
- Timing of GLP toxicity interim report in alignment with IND submission
- Shipping multiple ASO lead candidates to CRO to eliminate potential delay of GLP study start
- Scaling up for long-term treatment necessitates manufacturing of diluent
- Timing of sterile fill not aligned with needs of the patient - identify institution with compounding pharmacy

<table>
<thead>
<tr>
<th>ASO Discovery Begins</th>
<th>Development Candidate Selected</th>
<th>IND Submission &amp; IRB Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole-genome sequencing, patient cells*</td>
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</tr>
</tbody>
</table>

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Customizing Each Patient’s ASO Program in Real-Time
Patient Treatment/ Regulatory To Administer Optimized ASO

- Institutions inability to treat upon availability of an individualized ASO
- Physician movement to different institution leading to IND transfer/ relocation of treatment administration
- Requirement to update protocol/ outcome assessments based on FDA feedback
- Establish dual institution data collection for patient with treatment administered at a different institution than assessments taken

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Manufacturing
Sterile Fill & Finish

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**IND Drafting and Submission process**

*Whole-genome sequencing, patient cells*
Integrated Operational Model: Conclusions

- Antisense and Drug Development experience synergized
- Systems focused on quality
- Patient-focused flexibility to meet needs of each individual and respond to data
- Successfully industrializing the process
- Today: >225 applications, ~100 patients accepted, >60 active development programs and 9 INDs submitted; will continue to expand the volume and value of knowledge gained
Exporting the n-Lorem Model with a Commitment to Quality and Collaboration
Exporting the Model to Help More Nano-rare Patients

- Precisely-defined core elements
- Training for partners integrates antisense and drug development
- Customized model according to the partners’ existing capabilities, mission and goals

Talent and experience, equipment, facilities

Defined ASO discovery & development process

Robust data collection and platform

Integrated Research & Development Committee

- All interested institutions/ physicians/ scientists are potential partners
Additional Existing and Growing Collaborations

- **9 Partners in Excellence**
  - Physician and Institution **committed** to treating a patient with an n-Lorem ASO

- **St. Jude Research Hospital**
  - Collaboration to accelerate the development of optimized experimental ASOs for pediatric patients with extremely rare genetic neurological disorders

- **N of 1 Collaborative**
  - **Professional society** of international physicians and scientists bringing together the academic individualized treatment community

- **Global Collaborations**
  - Canada
  - Genomics England
  - Others in early discussions- Israel, Australia, Europe/ 1M1M
As n-Lorem Establishes more Partnerships, more Nano-Rare Patients Can Be Treated with Quality ASOs.
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Data Collection and Sharing: Defined and Implemented

- Expansion of the model leads to **gains in knowledge**
- Sharing this information is key and is possible through **standardized data collection**
- Sharing data amongst partners and throughout the scientific community will be **multi-faceted**
  - Peer-reviewed Scientific publications
  - Patient ASO programs case reports
  - Clinical data platform with access according to patient's consent
  - Presentations
  - Annual nano-rare colloquium
  - Podcast series
  - Website
We Know How to Do This- and Are Doing It.

- Successfully industrialized a **novel process** for operationalizing individualized ASO discovery, development, manufacturing and treatment
- Closely **integrated functions** make operationalizing the n-Lorem portfolio feasible
- Concise yet nimble processes allow teams to **quickly customize in real-time** according to individual patient / physician / institution needs
- Collaborating with various institutions / organizations to **export model** will enable the treatment of many more nano-rare patients
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