n-lorem FOUNDATION

Your Extraordinary Impact

Creating and Providing Experimental ASO Treatments For Ultra-Rare Patients — For Free, For Life

2020-2021

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Dear n-Lorem Community,

In January of 2020, we announced the establishment of a non-profit foundation with the mission of providing experimental antisense oligonucleotide therapies (ASOs) to patients suffering from ultra-rare disease for free, for life. Despite the extraordinary adversity brought about by the Covid 19 pandemic, I am grateful that we have been able to make rapid progress in our efforts to serve n-of-1 patients. I invite you to discover our impact throughout the pages of the following report.

Before I touch upon n-Lorem's progress, I want to express my deepest gratitude to our founding partners. Ionis Pharmaceuticals has led the creation of the drug discovery technology that makes n-Lorem possible, contributed significant cash donations and many in-kind contributions. We, at n-Lorem, could not help any of these patients without our colleagues at Ionis under the leadership of CEO, Brett Monia. Biogen is also a founding partner and has contributed broadly to n-Lorem's success. In particular, thanks to Michel Vounatsos, CEO for leadership on the n-Lorem board and broad support and Al Sandrock MD, PhD, EVP Research and Development for participation in the Access to Treatment Committee.

Meeting the Extraordinary Demand

When we founded n-Lorem, I imagined that patients would find us slowly and the number of applicants for treatment would be quite modest, but in parallel with establishing n-Lorem, we collaborated with two clinical investigators to treat 14 patients. Even more exciting is the growing demand. As of today, n-lorem has received 80+ patient applications, we have approved more than 30 patients for drug discovery and clinical development of a personalized medicine for each and now have more under review. Our first n-Lorem patients will soon receive treatments. To meet the demand, we have expanded rapidly, and I am thrilled with the quality of the team we have assembled as we discuss later. Many senior industry and academic leaders are donating their time. I think the reasons these busy eminent people are committed to n-Lorem can be summed up with this comment: "these desperate patients depend on us".

Beginning in 2019 well before we formally initiated n-Lorem, we worked closely with the FDA and provided several proposals in response to the FDA's request for public comment about guidance for approaches to the treatment of ultra-rare disease patients. We were therefore greatly encouraged and appreciative when the FDA provided guidance specific for ASO treatment of ultra-rare patients. The guidance was consistent with our recommendations and provides a critical set of directions on how to develop experimental ASOs. We continue to work with the FDA to add other elements of guidance if the FDA determines that even more specific guidance might be helpful. We are deeply appreciative of the rapid provision of guidance that addresses the unique challenges these patients present.

Establishing Quality Systems

Patients with ultra-rare diseases are typically complex and severely ill. It is vital that we do everything possible to assure that only the most appropriate patients are treated and that they are exposed to only prudent risks. (Sadly, no medicine is risk free). To help us make these complex judgements, the Access to Treatment Committee was created and is contributing enormously to our successes. We must know the disease we are treating, why we are treating and that, if successful, the benefit will matter to the patient. Thus each patient has an individual treatment and natural history plan. We must assure that we provide every patient with the very best possible antisense medicine, and our collaboration with Ionis assures that. Finally, we must evaluate our performance and share what we learn with all stakeholders. The quality systems described here are unique and vital.

Establishing a Broad Network of Stakeholders and Contributors

We know that we cannot do this alone. We know that only via a network of all stakeholders can we maximize the value we can provide to our patients. We are, therefore, thrilled with all the stakeholders who have already joined us in our quest to change the futures of these patients and their families. Each of these collaborators and benefactors have also helped us spread the word that n-Lorem can offer immediate hope and rapid experimental treatment to ultra-rare diseases patients.

In just 18 months, the contributions from many different types of stakeholders have exceeded $30 million in cash and significant in-kind donations. Without this generous support, we could not have met the remarkable demand we have experienced. We also believe that this start assures that we can raise the funds we need to meet the growing demand over the long term.

Our vision

We have just begun, but we have an exhilarating long-term vision. As Jefferson said when the Lewis and Clark expedition was formed, we are the corps of discovery. We are pioneering an entirely novel approach to treating patients. We are creating a path and a model for others to follow and it is that leverage that will lead us from helping thousands of patients to millions. We can't do it without you. On behalf of our patients and their families, I thank you. You have chosen to be a part of n-Lorem and, in the long run, that means you will be a contributor to more holistic solutions for these patients in the future.

With gratitude,

Stanley T. Crooke, MD, PhD

Founder, CEO and Chairman of the Board

The Dalby Family Story

My name is Kelley Dalby, and I am a mom to three kids: Chase, Connor and Cameron. I have two kids who are healthy and typical in every way, and then I have Connor who has special needs and needs constant attention.

At a few weeks old, I noticed something was off. Connor wasn't sleeping, he wasn't eating, and he was extremely uncomfortable the majority of the time. At eight months old, he began having seizures. We tried anti-epileptic drugs, and nothing was helping. He was having 50 seizures a day—all day all night long.

> *"I felt like I was fighting for so many years for my son, especially in the beginning, and now I'm watching all of these amazing people show up and work on this personalized treatment for one child that could potentially benefit and change the course of his life and our family's life. Just that is enough –* **it's the best feeling, it's hope**.

I found out Connor's mutation was incredibly unique, and he would need his own personalized treatment because his gene mutation was not like the majority of other kids with SCN2A. At this point I started losing hope because I didn't know what else to do. Connor is now 11 years old, and the seizures still get to me. To watch my child have a seizure, and there is nothing I can do to stop it—it breaks my heart every time. I have seen thousands of Connor's seizures.

I feel like I've been fighting for so many years alone with my son for my son, and I wasn't very successful in helping him. At n-Lorem, with what is happening right now, with a team of scientists and doctors and donors, people stepping in and giving their time and energy and making a medication for one child, for my son, to help him and his quality of life and our family—it's still so hard for me to believe and accept that all these people are coming together to help Connor.

Patient Pathway

Our focus is on helping patients with ultra-rare diseases one patient, one family at a time. Each of these patients has a poignant story to tell. Our hearts go out to each of them. They are why we exist. They are our motivation. They are all in need of our best efforts.

n-Lorem encourages all US-based ultra-rare disease patients to submit a proposal for treatment. Our Access to Treatment Committee, which is made up of a range of scientific and medical experts, assesses each patient. Interest has been strong, and the n-Lorem pipeline is expanding rapidly.

While establishing n-Lorem, we had the opportunity to work with two clinical investigators, Neil Shneider, MD, PhD and Tim Yu, MD, PhD to provide experimental ASO treatments to 14 patients. This experience was particularly gratifying and informative as we established the formal systems that are a part of n-Lorem.

Patient
Investigator
& Institution

Genetic
Characterization

n-lorem FOUNDATION

- Analysis of suitability of patients for ASO
- Management of ASO discovery and investigator IND preparation
- Funding
- Evaluation of ASO performance

IONIS

- Experimental ASO discovery
- Preclinical development
- Investigator IND preparation
- Evaluation

85

Patient Referrals

33

Patients Approved for Drug Development

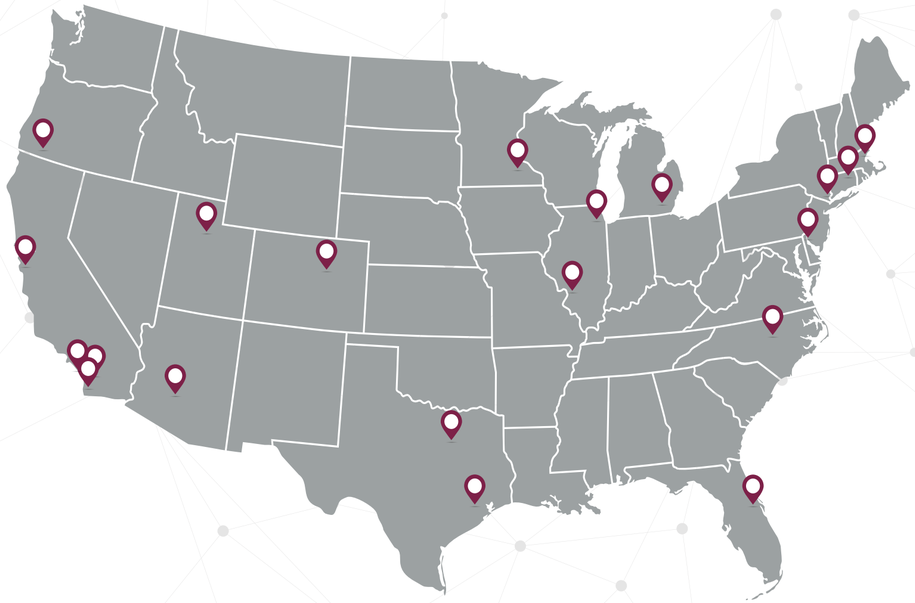
39%

Acceptance Rate

as of August 2021

A Growing Network of Patient Care Collaborators

n-Lorem works collaboratively with treating physicians and medical experts at major medical research and tertiary care centers across the country to ensure the highest level of patient care and access.



Our reach is broad and *continues to expand*.

n-Lorem Volunteer Leadership Team

Our work is only possible through the dedication of Ionis Volunteers. These experienced industry leaders dedicate their time and talent to oversee the critical work of personalized experimental ASO development for n-of-1 patients.

C. Frank Bennett, PhD
Chief Technical Officer

Patrick R. O'Neil, Esq.
Legal Counsel

Walter Singleton, MD
Chief Medical Officer

Matt Buck, JD
Regulatory Affairs

Joseph Gleeson, MD
Vice President Medical Affairs

Brian Birchler
Development Operations

Max Moore
Manufacturing

Scott Henry, PhD
Pre-Clinical Development

"Patients and families impacted by diseases that do not yet have treatments, have continued to be the trailblazers and source of my inspiration. My career has focused on successful development of antisense oligonucleotide medicines, and being able to work with n-Lorem to advance free, lifetime supplies of these medicines to patients who desperately need them, continues to fuel my efforts.

C. Frank Bennett, PhD

"I felt motivated to support n-Lorem following the success of Spinraza which has changed the lives of patients and their parents, and provided many years of happiness for them, correcting the effect of a uniformly fatal mutation. If we at n-Lorem can do this for others, even one patient at a time, it can provide survival and improved health for patients, and hope for the parents and other caregivers.

This is my hope – this is why I support n-Lorem.

Walter Singleton, MD

Volunteer Spotlight: Drug Discovery Team

Volunteers contribute immensely to the scientific work of n-Lorem. Whether it is Joseph Ochaba leading the group in identification of the antisense therapies used to treat n-Lorem patients, Andy Watt leading the primary cell culture screens, or Sue Freier perfecting oligonucleotide design, n-Lorem volunteers provide an abundance of talent, experience, and passion to serve ultra-rare patients.

Photos by Maheen David

Volunteers:

Gemma Bachmann
Scott Henry
Huynh-Hoa Bui
Christine Hoffmaster
Paymaan Jafar-nejad
Holly Kordasiewicz
Liang Liang
Berit Powers

Ionis In-Kind Support:

Ashley Dung
Sue Freier
Stephanie Klein
Joseph Ochaba
Ashley Rivera
Eli Scandalis
LJ Shen
Antony Thomas
Ruben Valas
Andy Watt

FDA Guidance for Treatment of Ultra-Rare Patients with ASOs

A clear regulatory path to treating individual patients is a necessary step to fulfillment of the n-Lorem mission. Building a strong and productive relationship with the FDA is incredibly important to the Foundation.

In April 2021, the FDA issued draft guidance for treatment of severely debilitating or life-threatening diseases by individualized ASO treatment.

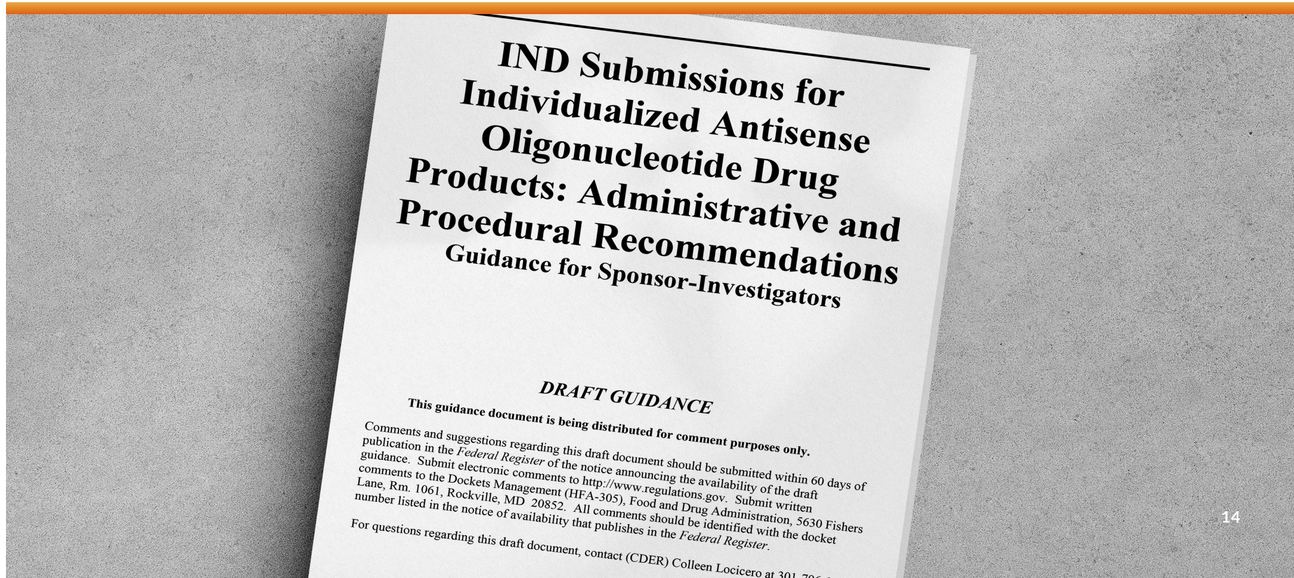
n-Lorem has been in active communication with the FDA since the Foundation's inception. We provided recommendations to the FDA for this guidance in 2020.

Recent draft guidance from the FDA is in accord with n-Lorem's approach to experimental ASO drug development and clinical trials.

The guidance outlines an abbreviated non-clinical toxicology package that provides a clear path to treating patients with experimental ASOs created by Ionis for n-Lorem.

In certain cases, with rapid disease progression, the draft guidance allows human dosing after at least two weeks of toxicology studies. In diseases that progress more slowly, the draft guidance requires a completed three-month toxicology study.

FDA draft guidance explicitly references the chemistries available to n-Lorem as an example of a "well characterized" chemical class. We look forward to receiving further guidance from the FDA on our mutual aim to help ultra-rare patients receive life-changing treatment.



IND Submissions for Individualized Antisense Oligonucleotide Drug Products: Administrative and Procedural Recommendations

Guidance for Sponsor-Investigators

DRAFT GUIDANCE

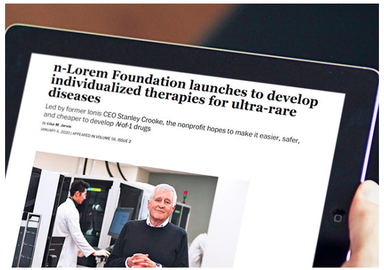
This guidance document is being distributed for comment purposes only.

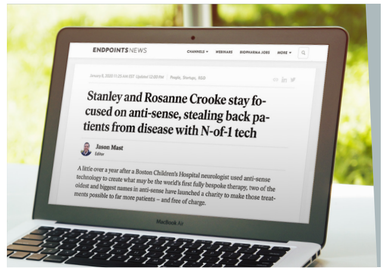
Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Colleen Locicero at 301-796-

Spreading the Word

To ensure that as many patients and physicians as possible are aware that n-Lorem is providing a new opportunity for treatment for free for life, we have invested in extensive media outreach. Here are just a few examples.





230,000+

Social Media Impressions

Quality

Central to n-Lorem's approach to treating n-of-1 patients with personalized ASOs is an unmatched commitment to quality. Our work is possible because we have established robust quality systems to produce treatments and meet the needs of patients.

The first step in establishing our quality systems lies in our risk/benefit treatment decision process. The Foundation's process ensures patient confidentiality in partnership with the clinical investigator. The patient application to n-Lorem is extremely rigorous and must be undertaken by clinical experts and practitioners in concert with the patient and in many cases the patient's family. Our Access to Treatment Committee (ATTC) comprises world-class physicians, geneticist, bioethicists, and patient advocates as well as experts in conducting clinical trials and ASO technology. The Committee deliberates on each application and makes recommendations according to multiple factors.

n-Lorem ensures quality ASO discovery processes by leveraging three decades of Ionis Pharmaceuticals experience. Simply no other entity on the globe has this kind of deep knowledge and experience with developing the highest quality ASOs. Thanks to the generosity of Ionis, n-Lorem is able to access the company's deep experience making it possible to investigate multiple post-binding mechanisms and ASO designs and multiple routes of delivery. Importantly, since all ASOs of the same chemical class behave similarly, the fact that Ionis has published analyses of databases that integrate all safety observations from animal models through all controlled clinical trials for all the major ASO chemical classes, allows us to estimate the appropriate dose and schedule dose to use.

We are then alert to potential side effects, which makes it feasible to conduct clinical trials while exposing patients to only prudent risks. The ASO is then manufactured meeting the highest quality standards, and n-Lorem then helps the investigator prepare an investigator-initiated Investigational New Drug application.

n-Lorem has also developed critical quality methods of evaluation. These include pre-treatment documentation of the patient's natural history as well as a unique pre-defined treatment plan for each patient that include clearly defined primary and secondary treatment goals and methods to measure those treatment goals clinically.

Finally, n-Lorem is dedicated to absolute transparency of our findings and outcomes and the publication of results annually and we will present them at annual investigator meetings to ensure that all stakeholders benefit from all that is learned.

Photo by Evan Crooke and Asa Shin

Corporate Sponsors

As the first and only non-profit organization to offer personalized experimental ASO treatment to patients with ultra-rare diseases, n-Lorem relies on the generous support of its collaborators.

In its first year, n-Lorem has greatly exceeded our initial expectations and is moving forward with treatment of more than 30 patients. The successful launch of the Foundation has created life-changing opportunities for collaboration and philanthropic investment in providing hope and treatment for desperate patients. On behalf of the patients we serve, we thank all of the corporate sponsors who partner with n-Lorem to make our work possible.

We are deeply grateful to n-Lorem founding donor Ionis Pharmaceuticals. Ionis provides financial support, as well as, essential expertise during every stage of the drug development process. n-Lorem's strong partnership with Ionis makes it possible to provide personalized experimental ASOs for ultra-rare patients for free, for life, while continuing to evaluate the performance of each ASO. Ionis employees volunteer their time in this endeavor to make n-Lorem's mission a reality. n-Lorem is also extremely appreciative of Biogen, which is also an important founding donor with a deep commitment to the ultra-rare disease patient.

n-Lorem is very grateful for to our numerous additional corporate sponsors who contribute to every step in the process of developing treatments for ultra-rare patients. This includes services such as genomic sequencing, toxicology studies, and manufacturing at no cost or via steep discounts.

This combination of financial, in-kind and direct support make up the pillars that enable n-Lorem to meet our important goals and provide for numerous desperately needy patients.

Thanks to the generosity of spirit inherent in the biotechnology and pharmaceutical industry, we have been able to meet the growing demand with the very highest quality imbedded in every step in the process leading to patient treatment. This means that n-Lorem can move as rapidly as possible to create new treatments while also doing so at as low a cost as possible. This ensures every dollar is spent efficiently in treating all patients for free, for life.

> "Today, we have the science to treat some of the rarest diseases in the world, and these patients deserve treatments. We are proud to partner with n-Lorem, a first-of-its-kind organization that is using a proven technology to develop treatments for patients with these ultra-rare diseases for the first time.
>
> **Emil D. Kakkis, M.D., Ph.D.**
> *CEO and President of Ultragenyx Pharmaceutical*

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Your Generosity Makes n-Lorem Possible. Thank You.

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* *In memoriam*

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Yanfeng Wang
Teresa White
Patricia Wu

We can do more together.

n-Lorem Foundation is the first and only non-profit organization on a mission to provide personalized antisense oligonucleotide (ASO) treatment for patients affected by ultra-rare diseases (1 to 30 patients, worldwide) – for free, for life. To learn more or donate, please visit **www.nlorem.org.**

Claire Grezemkovsky

Director of Philanthropy

n-Lorem Foundation
2888 Loker Avenue East
Carlsbad CA 92010

(760) 552-7113

Claire.grezemkovsky@nlorem.org

@nloremfoundation **@n_lorem** **@n-Lorem Foundation**