https://doi.org/10.1038/s41591-023-02335-2

Personalized antisense oligonucleotides 'for free, for life' — the n-Lorem Foundation

In 2017, results from a clinical trial of the antisense oligonucleotide (ASO) nusinersen demonstrated potent effects in motor milestone responses and event-free survival in infants with spinal muscular atrophy, prompting early termination of the trial[1]. ASOs represent a powerful drug platform, but because of their exquisitely specific binding to RNA nucleotides, most potential disease-altering ASOs would likely never be profitable for pharmaceutical companies. With nearly 7,000 single-gene disorders[2] and many more pathogenic mutations known in humans, the potential space for personalized ASOs is enormous[3]. Patient advocates have started connecting with research groups offering personalized ASOs and other disease-altering therapies, and are finding promising preclinical and clinical evidence of benefit in '*n*-of-1' trials[4]. The challenge will be to scale personalized ASOs as drugs, to impact disease outcomes where possible and to learn which diseases do and do not show benefit if the effect of the mutation is reversed.

The n-Lorem Foundation was established in 2020 with the mission to apply the efficiency, versatility and specificity of ASO technology to charitably provide experimental medicines to treat patients with ultra-rare diseases. n-Lorem is committed to providing these ASOs to the patients for whom they are designed 'for free, for life', focusing on severely debilitating or life-threatening conditions for which there are ≤30 patients who could benefit from a drug. This is both an ethical and practical approach considering the risk/benefit ratio, and is mandated by US Food and Drug Administration (FDA) guidelines[5].

In the simplest model, an ASO can correct certain splicing defects to reactivate a gene that is genetically silenced, or silence a gene whose products result in toxicity. Because ASOs can be developed and administered relatively quickly, what we learn from these rare patients could educate the medical profession on which diseases can show substantial clinical improvement with corrective therapy, and which are too far progressed to expect positive outcomes. This could potentially extend to individuals with subclinical disease based upon cascade genetic testing.

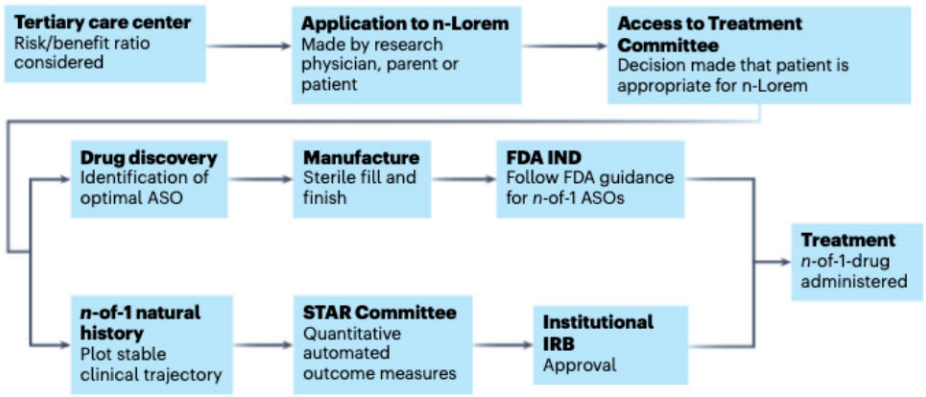

Fig. 1 | n-Lorem workflow from the tertiary care center to treatment. Patients are nominated by a physician at a tertiary care center, and then the Access to Treatment Committee evaluates the patient for the program. If the patient is accepted, the work then bifurcates into two parallel paths: (1) drug discovery, manufacture and FDA Investigational New Drug (IND) processes; and (2) *n*-of-1 natural history, Study Treatment and Assessment Review (STAR) Committee feedback to develop quantitative outcomes, and Institutional Review Board (IRB) input for ethical approval and patient consent.

Personalized ASOs are designed to treat a mutation rather than the resulting disease. ASOs can deliver clinical benefit by silencing dominantly acting toxic gain-of-function mutations; targeting splicing defects to restore protein production; or targeting unique genetic vulnerabilities such as microRNAs, upstream open reading frames or naturally occurring antisense transcripts (Table 1). n-Lorem has developed a workflow to first assess the mutation and clinical status and then simultaneously develop the drug and suitable outcome measures (Fig. 1).

Since n-Lorem's inception, 194 patients have been nominated, and 95 patients accepted (Table 1), after full review by the Access to Treatment Committee. So far, no patient meeting eligibility has been declined if it was thought that the patient could benefit from an ASO. Decisions to decline are most often based on lack of feasibility for ASOs to correct a genetic mutation, on inability to access the target tissue or on the judgment that a disease is too far progressed. Physicians in countries other than the United States have expressed interesting in joining the effort, and so far, conversations with partners in other nations suggest that similar paths might be acceptable.

The path to developing an optimal ASO benefits from three decades of prior industry experience through n-Lorem's partner, Ionis Pharmaceuticals[6]. n-Lorem screens a minimum of several hundred ASOs per target if possible, through first single-dose and then multi-dose potency experiments in culture. ASOs showing undesirable or inflammatory properties are excluded[7], with 20–30 lead compounds moving into rodent tolerability studies, using benchmarks established by the FDA, followed by an investigational new drug-enabling good laboratory practice toxicology study with the optimal candidate. The final drug is manufactured and shipped to the hospital pharmacy for dosing. Importantly, n-Lorem retains no intellectual property for these drugs, and freely shares reagents and data with academic labs.

FDA regulatory documents set a clear path for ASO approval for ultra-rare, severely debilitating or life-threatening disease, including administrative guidance, chemistry, manufacturing, control recommendations, the nonclinical package and clinical

Table 1 | Nominations to n-Lorem to date

		Number of patients
n-Lorem nominations	Patients nominated	194
	Patients accepted	95
	Patients declined or 'on hold'	99
	Unique genes nominated	118
Types of mutation	Toxic gain of function	87
	Creation of novel splice site	5
	Exploratory	5
Proposed primary clinical endpoints	Reduction in seizures	35
	Improved motor function	27
	Improved cognition	25
	Reduction in liver enzymes	1
	Improved retinal visual function	1

Note that these numbers do not sum to the total number of nominations because of instances where two or more patients with the same mutation are nominated.

recommendations[5]. Safety is paramount, with guidelines clearly defined for each of these aspects. n-Lorem has constituted a Data Safety Monitoring Committee to evaluate interim clinical results and adverse events. The home institution of the treating physician manages the institutional review board process.

Designing and manufacturing drugs 'for free, for life' is certainly not a common model. Costs per program are estimated at US$800,000, not including hospital and care-team expenses. n-Lorem believes that these costs are justified in part by future expected clinical benefit, as well as by the knowledge to be gained. The goodwill evoked by n-Lorem has generated philanthropy and in-kind donations from industry partners. The future might see support from governments, insurers and private sources to sustain this model.

Expected side effects are dependent in part upon the route of administration and are generally minimal. Risk due to intrathecal drug administration by lumbar puncture may be higher than those from systemic dosing, given the recent association with hydrocephalus in two children treated with a personalized ASO for *KCNT1* mutations[8]. Given the very low incidence of hydrocephalus reported for nusinersen and tominersen (the latter designed for Huntington disease)[9,10], it may be that the *KCNT1* ASO had particularly undesirable qualities. Although hydrocephalus has not been observed in our patients so far, n-Lorem has voluntarily alerted investigators about this potential serious adverse event, with recommendation for careful monitoring.

A major challenge for *n*-of-1 clinical trials is proving clinical benefit in the absence of a control arm. To ensure that all ASO programs adopt meaningful outcomes, n-Lorem created the Study Treatment and Assessment Review (STAR) committee. STAR ensures primary and secondary endpoints are fit for purpose (Table 1). For some diseases there are established rating scales, but for others, quantitative assessments are selected for each patient. These include outcomes that do not require observer input or are 'measured by machine', such as automated electrographic spike detection on electroencephalogram. The *n*-of-1 natural history study begins upon a patient's acceptance to the program and continues through the end of the first year of treatment, at which point STAR assesses whether to continue treatment and to support peer-reviewed manuscript publication. Currently, 3 patients have been dosed with n-Lorem drugs and another 5 are scheduled for 2023, with a 5-year goal of 200 patients under treatment.

Parity across socioeconomic status is a critical part of n-Lorem's mission. Although providing personalized treatments for free may seem to obviate issues of parity, there are many considerations to ensure that the technology does not benefit only the well-connected. To some degree, the requirement for genome sequencing may already present barriers to the underinsured, under-represented or under-resourced, and moreover, often only the well-connected learn of opportunities such as n-Lorem. n-Lorem continues to seek ways to evaluate and eliminate potential biases in patient selection, ensuring that all have equal access to experimental therapy.

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Published online: 11 May 2023

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Competing interests

J.G.G. is a consultant for Neurocrine, Shire-Takeda and Ionis Pharmaceuticals. J.F.B. is a full-time employee of Ionis Pharmaceuticals. S.T.C. holds founder stock in Ionis Pharmaceuticals.