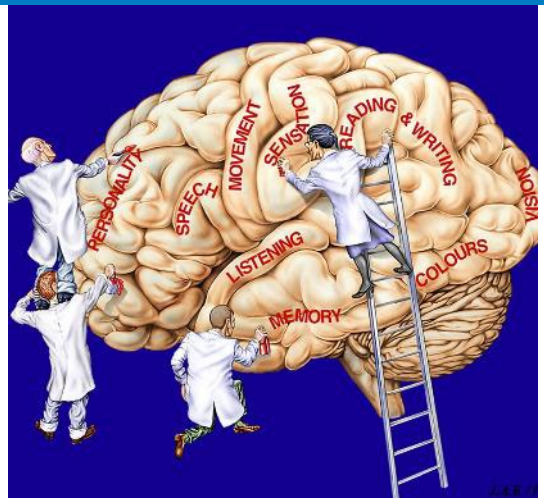
Leiden University Medical Center

CCMO/MEB Science Day May 20, 2026

N-of-1 treatment with antisense oligonucleotides – a Dutch perspective -

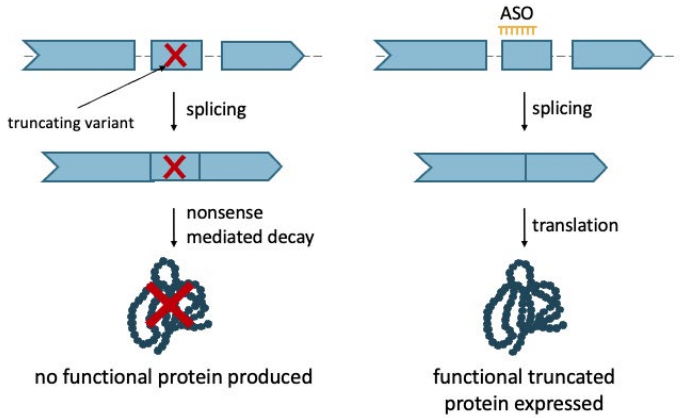
Professor Willeke van Roon-Mom
Department of Human Genetics
LUMC
LEIDEN, THE NETHERLANDS



Antisense oligonucleotides

DCRT Dutch Center for RNA Therapeutics

Canonical exon skipping

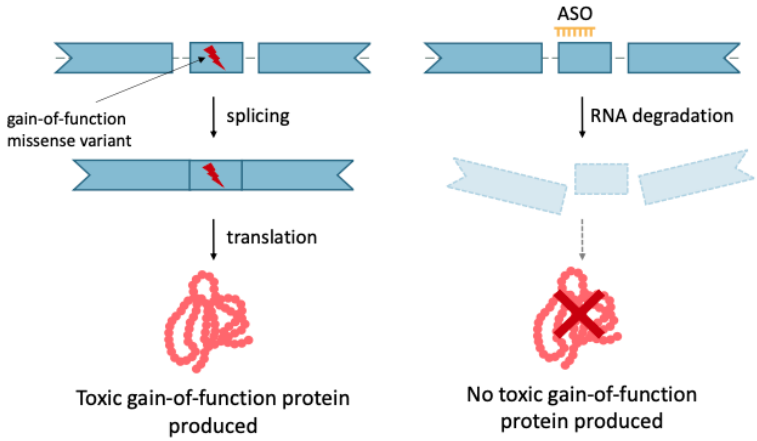


Loss of Function

Gain of Function

Dominant negative

Transcript knockdown



Gain of Function

Current state of the art

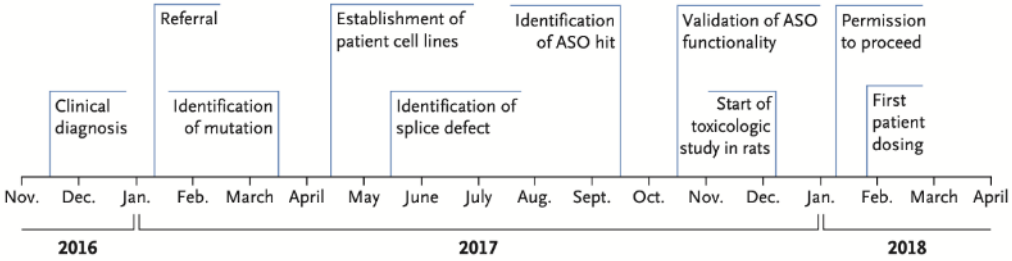
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Patient-Customized Oligonucleotide Therapy for a Rare Genetic Disease

J. Kim, C. Hu, C. Moufawad El Achkar, L.E. Black, J. Douville, A. Larson, M.K. Pendergast, S.F. Goldkind, E.A. Lee, A. Kuniholm, A. Soucy, J. Vaze, N.R. Belur, K. Fredriksen, I. Stojkovska, A. Tsytsykova, M. Armant, R.L. DiDonato, J. Choi, L. Cornelissen, L.M. Pereira, E.F. Augustine, C.A. Genetti, K. Dies, B. Barton, L. Williams, B.D. Goodlett, B.L. Riley, A. Pasternak, E.R. Berry, K.A. Pflock, S. Chu, C. Reed, K. Tyndall, P.B. Agrawal, A.H. Beggs, P.E. Grant, D.K. Urion, R.O. Snyder, S.E. Waisbren, A. Poduri, P.J. Park, A. Patterson, A. Biffi, J.R. Mazzulli, O. Bodamer, C.B. Berde, and T.W. Yu

Milasen: the ultimate personal treatment



Rare diseases – thinking outside the box

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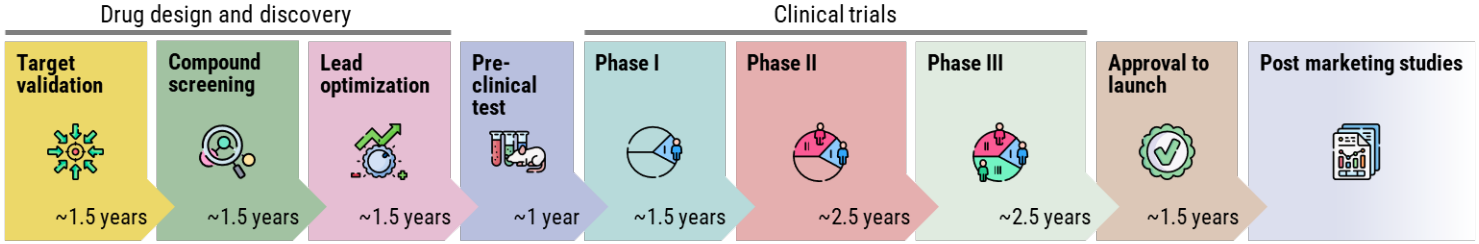
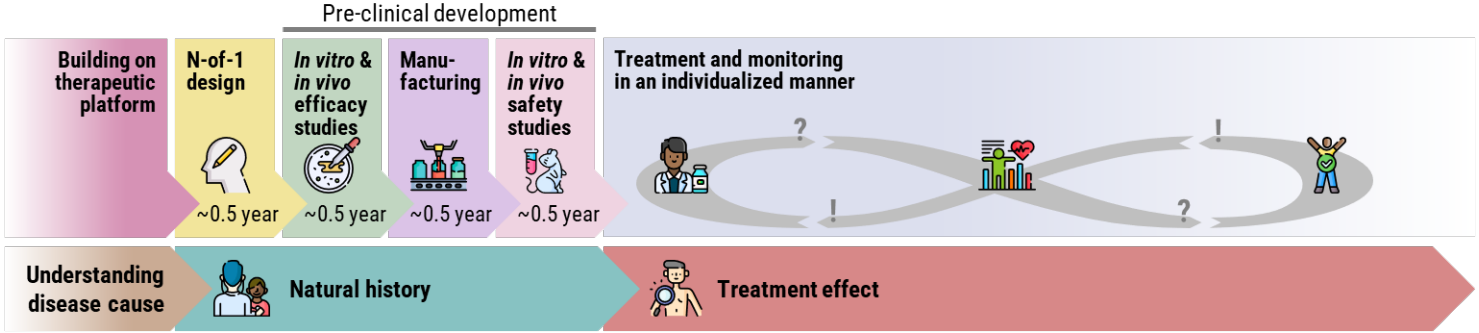
Traditional drug approval process

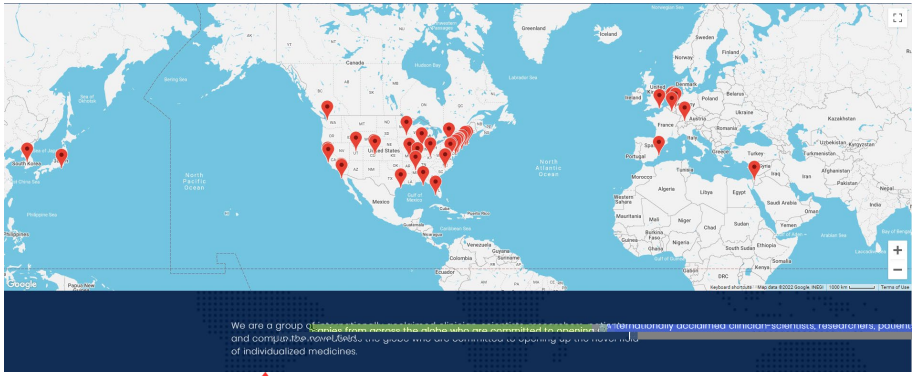


Patient specific N-of-1 treatment



Slide courtesy of IRDIRC N of 1+ task force

Global context



DCRT Dutch Center for RNA Therapeutics

Synofzik 2022 Nucl Acid Ther
Aartsma-Rus 2023 RNA
Schule et al Mol Ther Nucl Acids 2025
Jonker et al 2024 Nat Rev Drug Disc
Jonker et al 2025 Ther Adv Rare Dis

1M 1M

Co-founders
Co-coordinators

Belgrad et al 2025 Nucl Acid Res
Zardetto et al 2024 Hum Mut
Cheerie et al 2025, Am J Hum Gen
Aartsma-Rus et al 2024 Ther Adv Rare Dis
Schule et al 2024 Nat Med
Ehmann et al 2024 Nucl Acid Ther

N=1 COLLABORATIVE

SAB chair/members
Past BOD member
Working group leaders/members
Working group members

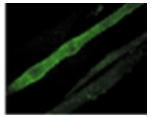
IRDiRC INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Chair IRDIRC N=1 taskforce

EURORDIS European Rare Diseases Research Alliance

WP12-N=1 therapies for eligible rare disease patients

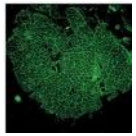
Timeline and EU historical context n=few ASO therapies



ASO induced dystrophin restoration in Duchenne myotubes

2001

First publication on exon skipping ASO design



ASO induced dystrophin restoration in patients after local injection

2005

2007

ASO splice restoration for genetic retinal disease

Methods on exon skipping book published including chapter on ASO design

2012

EMA ICH Concept paper S12: Nonclinical biodistribution considerations for gene therapy products

Nusinersen approved for SMA

2017

Milasen treatment started

2018

OTS N-of-1+ taskforce established

Milasen story presented at conferences

2019

N=1 collaborative

DCRT Dutch Center for RNA Therapeutics

Feb 2020

FDA Draft guidance nonclinical testing individualized ASOs

1M 1M

2021

German patient treated with Atipeksen Boston -> Tubingen

CEP290 ASO induced improvement of visual acuity

2022

Tofersen approved for SOD1 ALS

FDA Plausible mechanism framework

Preparation of Dutch regulatory informed n=few protocol

2023

2026

DISCOVERY | DRUG APPROVAL | N=FEW | SUSTAINABILITY

Adapted from Aartsma-Rus et al Ther Adv Dis 2024

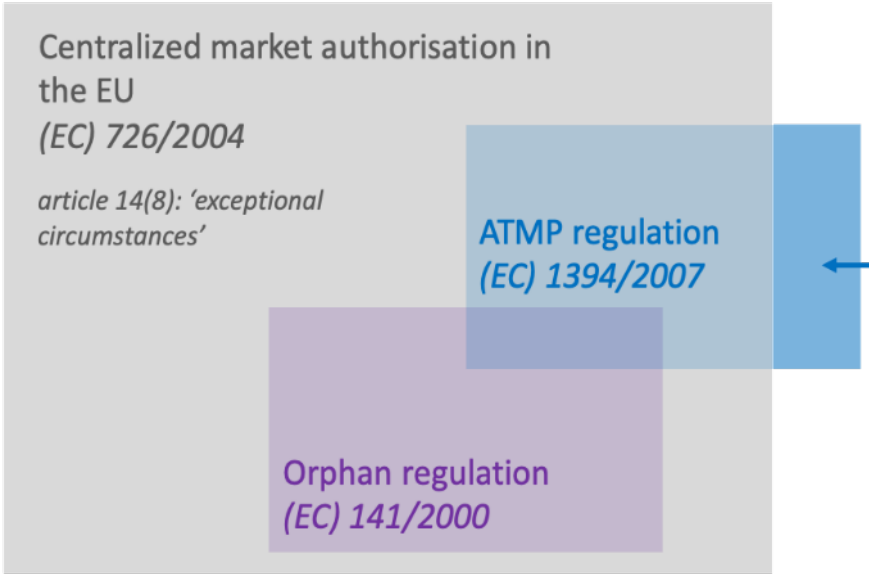
Regulatory challenges in Europe
Access options for patient-specific ASOs

Unlicensed access options for groups of patients

Clinical trial
(EC) 2001/83 Article 3(3)

Compassionate use
(EC) 726/2004 Article 83

- groups of patients with chronically or seriously debilitating or life-threatening disease
- medicinal product is undergoing clinical trial or subject of a marketing authorization application



Unlicensed access options for single patients

Hospital exemption
(EC) 1394/2007 Article 28(2)

- ATMP custom-made for an individual patient; not routinely produced
- administered in a hospital setting under exclusive responsibility of a medical practitioner
- produced and administered in the same member state
- manufacturing authorised by a competent authority of the member state
- quality standards equivalent to (EC) 726/2004

Named patient use
(EC) 2001/83 Article 5(1)

- to fulfill special needs
- purely therapeutic considerations

The Dutch Center for RNA Therapeutics

DCRT Dutch Center for RNA Therapeutics

- The Dutch Center for RNA Therapeutics (DCRT) is a non-profit consortium consisting of 5 UMCs
- The aim is to develop tailor-made RNA (ASO) treatments for patients with nano-rare germline mutations focused on eye, brain and skin disorders

Board of directors

Annemieke Aartsma-Rus

LUMC

Rob Collin

Radboudumc

Ype Elgersma

Erasmus MC

Willeke van Roon-Mom

LUMC

Jan Veldink

UMC Utrecht

Peter van den Akker

umcg

Wouter van Rheenen

UMC Utrecht

DCRT@lumc.nl

Antisense therapy in NL (EU) - advice

MEB

- No MEB dossier needed
- No EMA approval needed
- MEB has expert panels that can advice on all aspects of N=1 ASO therapy
- Go to EMA for more advice, larger expert panels and more experience with RNA therapies

EMA

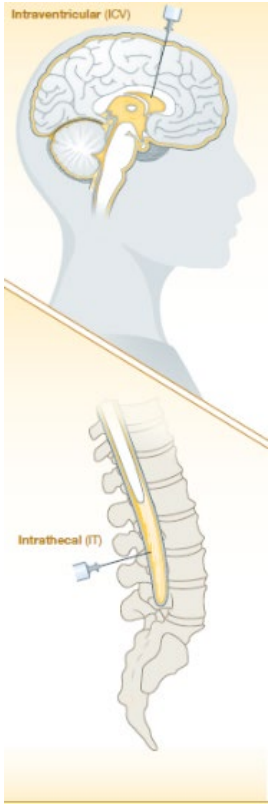
- Innovative Taskforce (ITF) /Scientific Advice (SA) meeting
- No EMA approval needed
- No registered drug
- Named patient setting
- N=1 ASO therapy does not fall under ‘hospital exemption’, it is not an ATMP (Advanced therapy medicinal products)
- Expert opinion on:
  - Tox studies
  - Registry patient safety
  - Treatment protocol

National Healthcare Institute

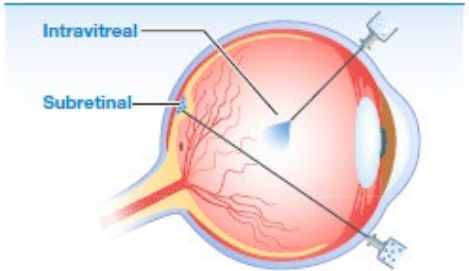
- How much proof is needed to show treatment effect?
- How much will the development of one N=1 ASO therapy cost?
- Is it cost-effective?
- Reimbursement?

Personalized antisense therapies in the EU

DCRT Dutch Center for RNA Therapeutics



- Mutations must be very rare (n=1/n=few)
- Antisense oligonucleotides (ASOs) must have EMA/FDA approved chemical modifications (optimized preclinical, tox and ASO production protocols)
- Local method of delivery proven effective and safe (brain/eye/liver)
- Patient must have benefit from treatment
- The treatment will always be experimental
- Named-patient setting: no regulatory approval
- Experimental drug
- Clinician and pharmacist are responsible
- Application filed with the inspection for health care (IGJ)



Hammond *et al.*, EMBO Mol Med (2021)13:e13243

DCRT- complementary expertise

DCRT Dutch Center for RNA Therapeutics

LUMC

- Neurodegenerative diseases
- Non-GLP toxicity assays (in vitro/in vivo)
- European implementation n=few ASO treatments (ERDERA, 1M1M)
- Leading role in global n=few developments (N1C), IRDIRC taskforce), co-lead in MMM ITN network for n=1 ASO treatment development

Erasmus MC

- Neurodevelopmental disorders (incl. epilepsy)
- iPSC - and mouse models
- Non-GLP toxicity assays (in vitro/in vivo)
- Leader of PSIDER-TAILORED program for development of a pipeline for n=1 ASO treatment

- Preclinical ASO design and testing
- Collaboration with Pharma on ASO development
- iPSC modelling
- ASO trials

RadboudUMC

- Inherited retinal disease, including Usher syndrome
- Non-GLP toxicity assays (in vitro & in vivo)
- Academic spin-off biotech
- Regulatory expertise (Therapy Accelerator for Rare Diseases)

UMCU

- Clinical expertise in administering ASO treatments >100 patients/year (Tofersen/ Nusinersen).
- Expertise in working with the ODAP protocol and Coverage Lock policy (sluis procedure)
- Expertise in submitting CCMO clinical trial protocols for novel gene-based treatments

UMCG

- Genetic skin conditions, neuro-metabolic and cardiac diseases
- Advanced disease models
- NL and EU accredited Centers of Expertise for Genetic Skin, Heart, Metabolic conditions

DCRT- Where are we now?

DCRT
Dutch Center for RNA Therapeutics

ARPP21

GMF2

FAR1

UNC13A

ABCA4

Standardization between institutes- modular framework

Develop individual antisense oligonucleotides targeting unique DNA variants for CNS/eye disorders

Fixed modules:
Unique ASO sequence but identical backbone, chemistry, drug product, PK behavior, class specific safety expectations

Variable modules:
Sequence specific toxicity
Disease specific aspects, clinical protocol and assessment

'Platform protocol' to combine individual treatments under one framework

Registration and collection of data to proof safety, efficacy and treatment effect. Use data to learn and make the next individual ASO therapy better

Standardization between institutes- modular framework

Develop individual antisense oligonucleotides targeting unique DNA variants for CNS/eye disorders

Fixed modules:
Unique ASO sequence but identical backbone, chemist
manufacturing, PK behavior, class specifi

specific toxicity
specific aspects, clinical read out parameters

Master protocol to combine individual treatments under one standardized clinical design

Registration and collection of data to proof safety, efficacy and treatment effect. Use data to learn and make the next individual ASO therapy better

March 2026
'n-of-1' working party of the Dutch Medicines Regulatory Network'

Writing protocol 1 and 2: the beginning of a Dutch platform?

DCRT N-of-few meeting, *March 25, 2026 – UMC Utecht*

Rob Collin (RadboudUMC) *–Carel Hoyng (RadboudUMC) - Lonneke Duijkers (RadboudUMC) – Karin Ruijtenbeek (RadboudUMC) -* ***Annelot van Esbroeck (EMC)*** *– Ype Elgersma (EMC) – Rosan Lechner (EMC) – Lianne Beuk (EMC) – Willeke van Roon-Mom (LUMC) –Dyah Karjosukarso (LUMC) – Renske Wadman (UMCU) – Ewout Groen (UMCU) - Jan Veldink (UMCU) – Wouter van Rheenen (UMCU) – Ludo van der pol (UMCU) – Camshi Vangoor (UMCU) – Dennis Bos (UMCG) – Tommy Bunte - Peter van den Akker (UMCG)*

Summary / main conclusions:

- Using approved individual gene therapy CCMO protocols as example
- Tailoring is key: start from 2 used-cases, before moving towards master protocol
- Ideal approach lies between formal clinical trial and named-patient basis → ‘named-patient plus’
- Assessment of quality and quantity of preclinical efficacy and safety data, now mostly lies with researchers
- Who will give the final ‘go’ decision / ‘clearance’
- Establish a sustainable financial model and reimbursement

Action plan

- Interactions with N-of-1 working party to outline the regulatory route
- Options for academic GMP manufacturing and Fill & Finish
- Involve patients and patient-organizations; shared decision-making and incorporating their vision and wishes in the study design
- Meeting with business developers for financial sustainability of academic n=few RNA therapies

Making individualized medicines routine

We are here

Proof of concept: custom, individualized treatments are possible, but still experimental & $$$

Repeatability, Standardization Learning

Rigorously establishing safety, benefit/risk

Regulatory acceptance & streamlining

Reimbursement & payer coverage

Scale

Equity & Accessibility

Goal: children w/ orphan genetic diseases receive custom genetic medicines as standard of care

Major challenges to get to the FiH n=few ASO study in NL

- What is the best regulatory approach – how to scale up the named-patient approach → 'named-patient plus'? One at a time is not efficient
- Uniform assessment of quality and quantity of preclinical efficacy and safety data
- Who will give the final 'go' decision / 'clearance'
- Establishment of a sustainable development pipeline - commercial, non-profit, other?
- Sharing of information and knowledge is key – successes and failures
- Establishment of a sustainable financial model and reimbursement

Acknowledgements

DCRT -NL

- Annemieke Aartsma-Rus
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- Rob Collin
- Ype Elgersma
- Annelot van Esbroeck-Weevers
- Pauline de Graaf
- Dyah Karsjosukarso
- Wouter van Rheenen
- Karin Ruijtenbeek
- Jan Veldink
- Erwin van Wijk