Uncertainty in the development of Orphan drugs

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Alnylam® PHARMACEUTICALS

Alnylam was Founded in 2002 with a Vision to turn RNAi into a New Class of Medicines

First scientific report of RNAi phenomenon in which Napoli and Jorgensen report that violet petunias turned white instead of a deeper violet[1]

Fire and Mello published a paper that reported a potent gene silencing effect in worms and coined the term RNA interference[2]

Alnylam founded with a core focus on developing RNAi therapeutics

Fire and Mello awarded the 2006 Nobel Prize in Physiology or Medicine

Positive results from Phase II ALN-TTR02 (Patisiran)

1) Positive results from APOLLO Phase III ALN-TTR02 (Patisiran)
2) FDA and EMA Regulatory Submissions Completed

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
FDA

FDA approval and EC Marketing Authorisation

1990 | 1998 | 2002 | 2006 | 2013 | 2017 | 2018

16 years of drug development
2.5 billion USD Investment[3]

References: 1. Napoli C, Lemieux C, Jorgensen R. Plant Cell. 1990;2(4):279-289. 2. Fire A, Xu S, Montgomery MK, et al. Nature. 1998;391(6669):806-811. 3. Alnylam calculation based on cumulative spent to date

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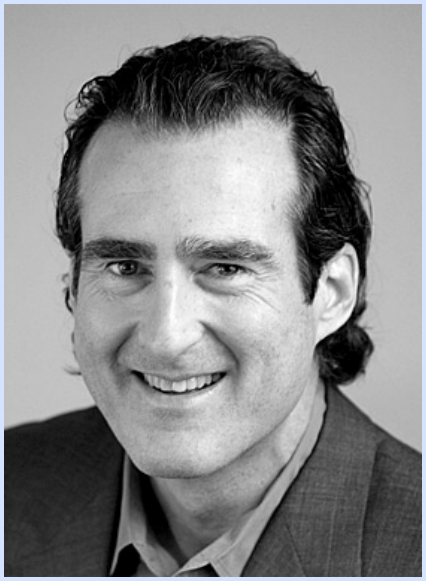
RNAi is Nobel Prize-Winning Technology

Nobel prize in Physiology or Medicine in 2006
was awarded jointly to Andrew Z. Fire and Craig C. Mello for
"their discovery of RNA interference – gene silencing by double-stranded RNA"

Andrew Z. Fire



Craig C. Mello

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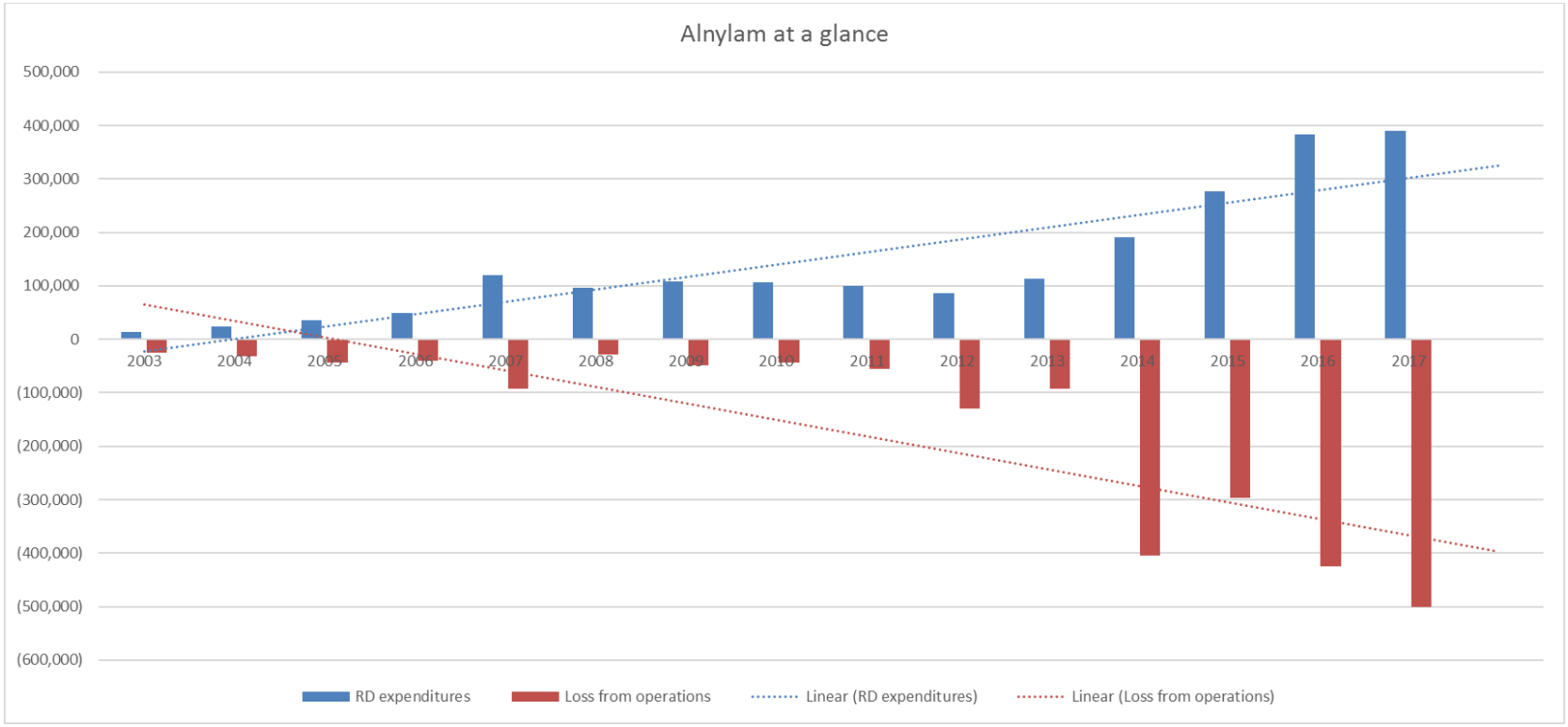
ALNY Value Since Inception

PPS/Market Cap/Enterprise Value/Investment

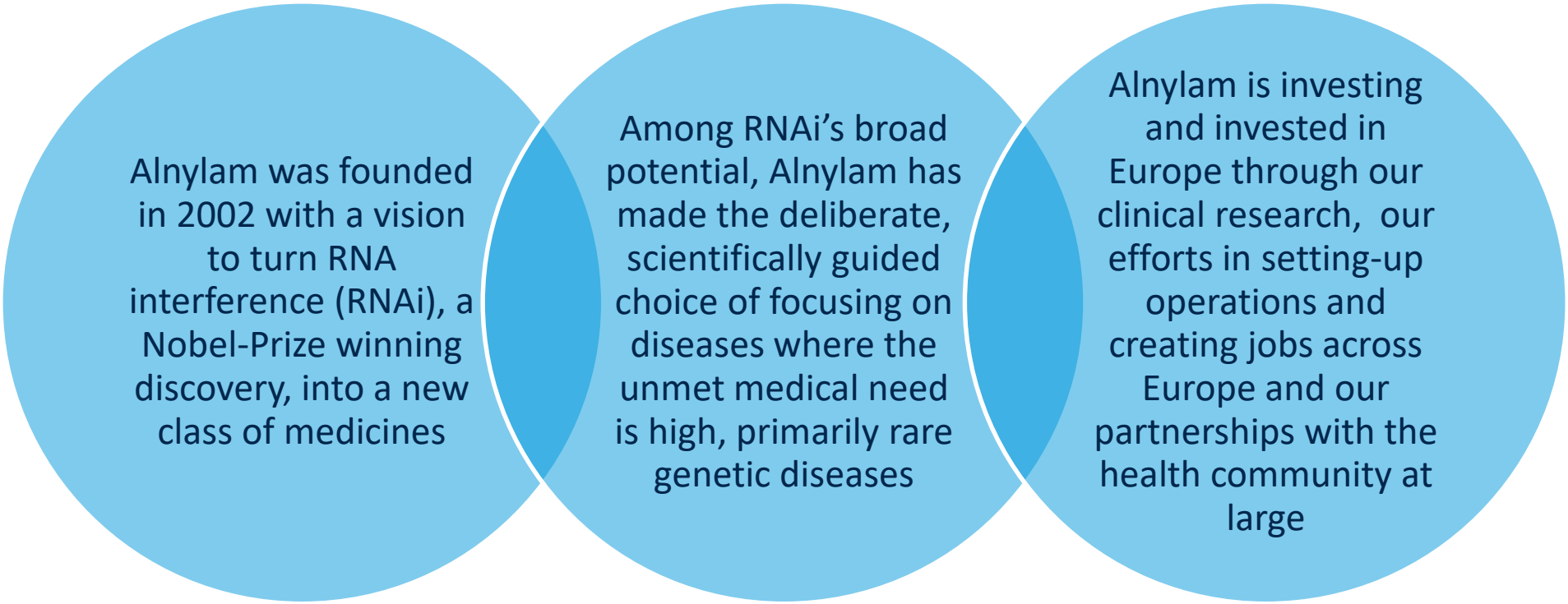
Manufacturers of orphan medicines require intense and sustained financing to support continued innovation

Alnylam has invested more than 3 billion USD to date of which 2 billion in R&D, without making any revenues



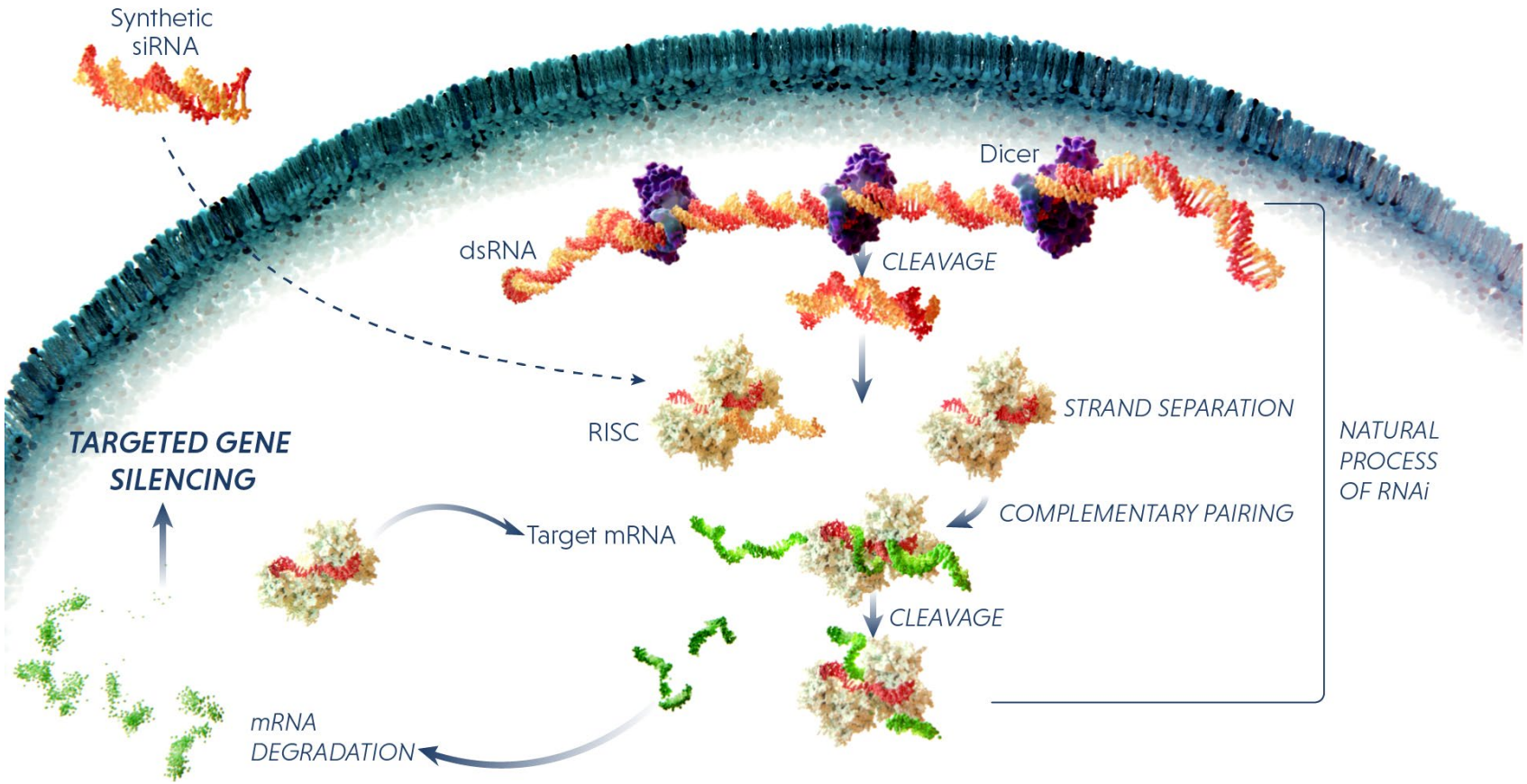
Alnylam Amazing Journey is a Three-Act Play

Based on Nobel-Prize winning science, focused on rare genetic diseases, invested and investing in Europe



RNA Interference (RNAi): Mechanism of Action

RNAi potentially enables selective and durable silencing of any gene by targeting mRNA for degradation and prevents the expression of proteins and their function in disease



dsRNA, double-stranded RNA; mRNA, messenger RNA; RISC, RNA-induced silencing complex; siRNA, small interfering RNA

Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Hepatic Infectious Diseases
- CNS Diseases

		HUMAN POC[1]	ORPHAN DESIGNATION	PRIME DESGINATION	EARLY STAGE *(IND or CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 4)*	REGISTRATION/ COMMERCIAL[3]
Patisiran	*hATTR Amyloidosis*[2]	✓	●				●
Givosiran	*Acute Hepatic Porphyria*	✓	●	●			●
Fitusiran	*Hemophilia and Rare Bleeding Disorders*	✓				●	
Inclisiran	*Hypercholesterolemia*	✓				●	
Lumasiran	*Primary Hyperoxaluria Type 1*	✓	●	●		●	
Vutrisiran	*ATTR Amyloidosis*	✓	●			●	
Cemdisiran	*Complement-Mediated Diseases*	✓			●		
ALN-AAT02	*Alpha-1 Liver Disease*				●		
ALN-HBV02 (VIR-2218)	*Hepatitis B Virus Infection*				●		

[1] POC, proof of concept – defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies
[2] Approved in the U.S. for the polyneuropathy of hATTR amyloidosis in adults, and in the EU for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy
[3] Includes marketing application submissions
As of December 2018

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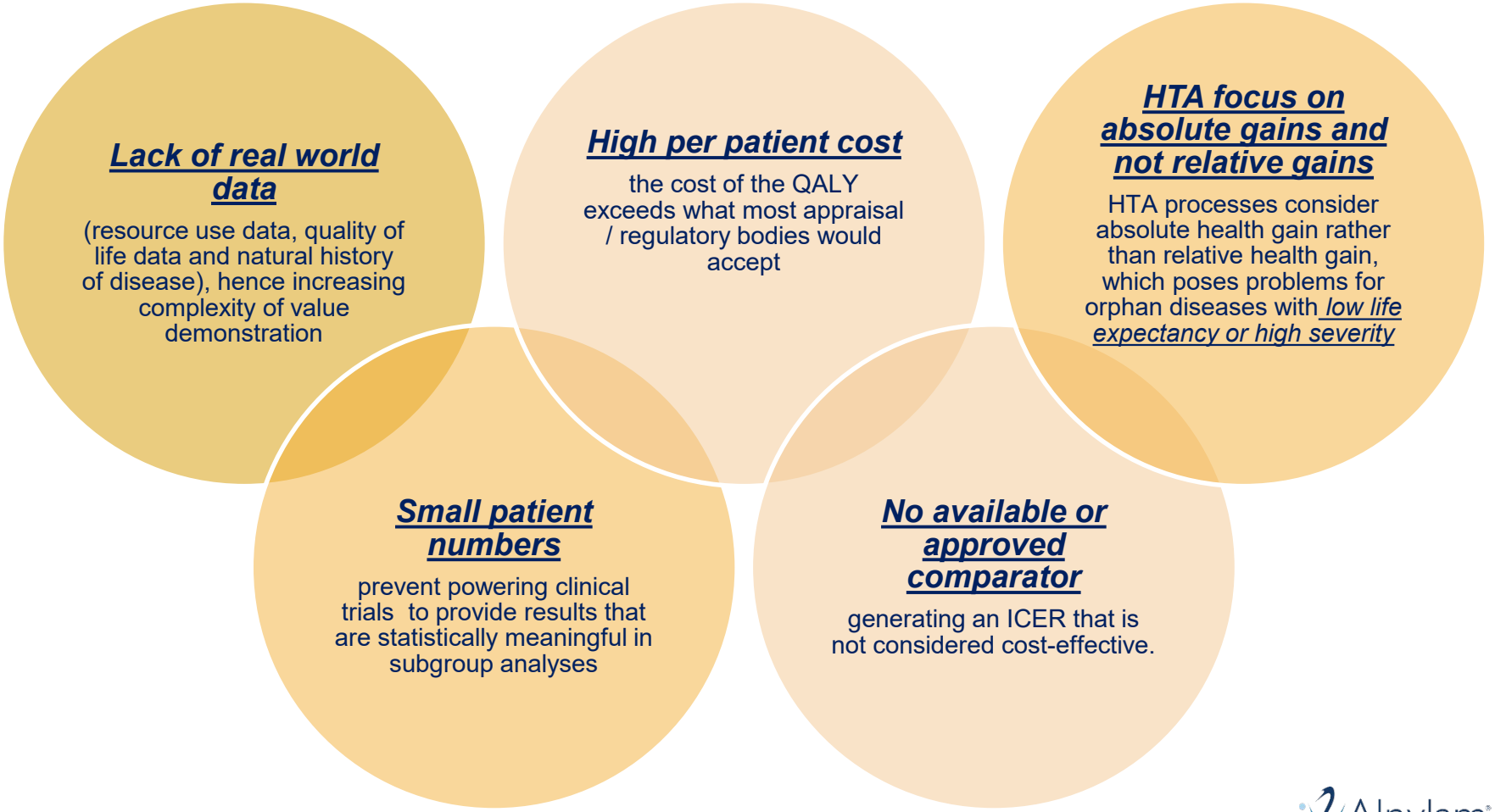
HTA – the Olympic Games of Orphan Drugs

HTA agency requirements pose significant challenges to the assessment of orphan medicines



ATTR Amyloidosis

Rare, progressively debilitating, and often fatal disease

Caused by misfolded TTR protein that accumulates as amyloid deposits in multiple tissues including heart, nerves, and GI tract[1]

Hereditary ATTR (hATTR) Amyloidosis

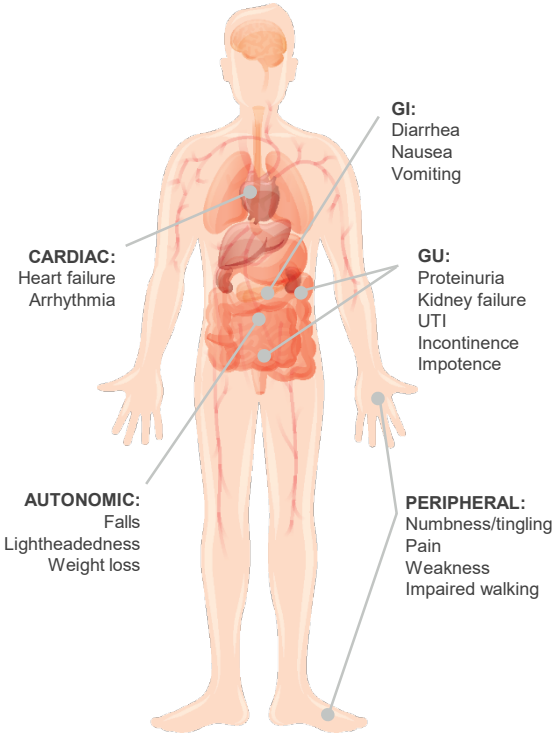
~50,000

patients worldwide*

Wild-Type ATTR (wtATTR) Amyloidosis

~200,000 – 300,000

patients worldwide



1 Coelho T, et al. N Engl J Med. 2013;369(9):819-829

* Ando et al., Orphanet J Rare Dis, 2013; Ruberg et al., Circulation, 2012

Acute Hepatic Porphyrias

Givosiran

Description

Family of ultra-rare orphan diseases causing incapacitating and potentially fatal attacks, leading to frequent hospitalizations and chronic pain

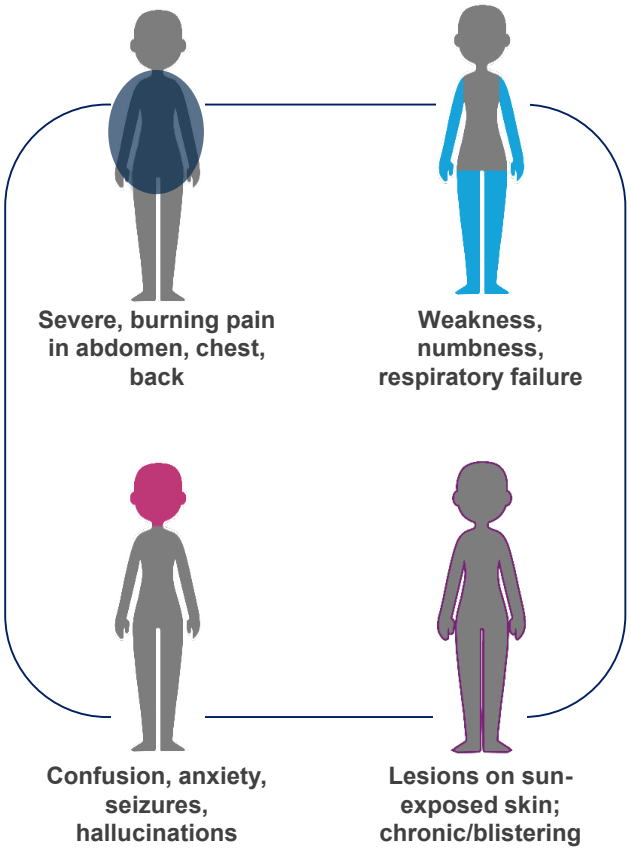
Predominantly

female,

commonly misdiagnosed

Patient Population*

~5,000	~1,000
Patients with **sporadic attacks** in U.S./EU	Patients with **recurrent attacks** in U.S./EU



* ORPHANET; The Porphyria Consortium

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Primary Hyperoxaluria Type 1

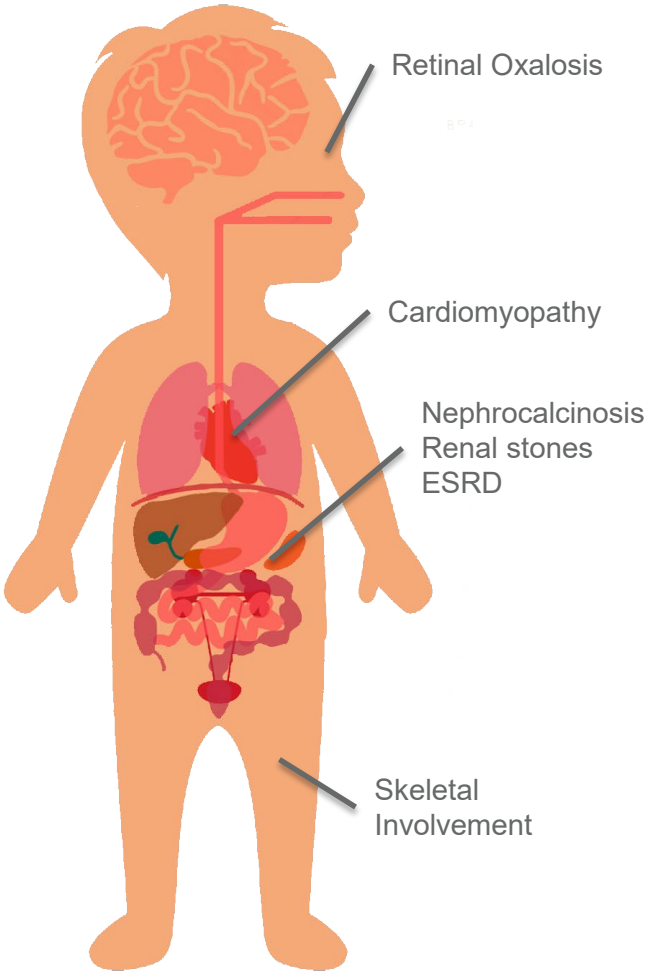
Lumasiran

Description

Rare autosomal recessive disorder of increased oxalate synthesis resulting in kidney stones and renal failure, with subsequent oxalate accumulation in extra-renal tissues

Onset generally
pediatric,
very limited treatment options

Patient Population
~3-5,000
U.S./EU



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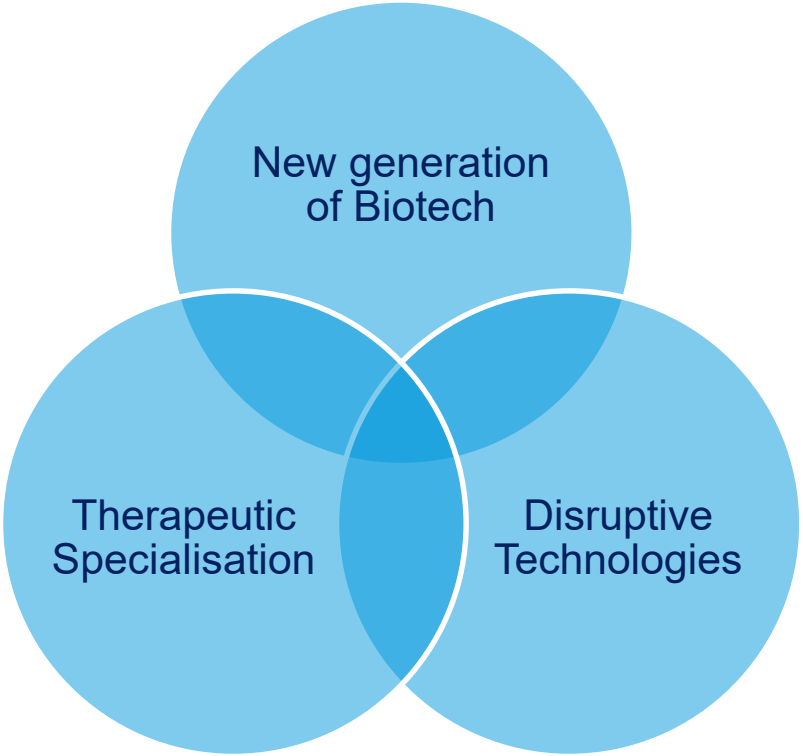
We are living a revolution in Life Sciences

This momentum hold promises for science, innovation, health and the economy

New entrants and **pre-commercial** companies, **limited portfolio and revenues**, high research intensity and rapid expansion



Increased focus on developing game-changing treatments for **rare and severe diseases** or **well-defined and severe high-need indications** within more prevalent condition

Novel approaches to treating diseases by addressing their **underlying genetic causes, through technologies** such as gene editing, CAR-T, gene silencing, gene addition

Key role played by NL public institutions and authorities in attracting companies like Alnylam

Alnylam takes pride of its partnership with authorities

Alnylam PHARMACEUTICALS · amsterdam business · Health~Holland SHARED CHALLENGES, SMART SOLUTIONS · INVEST IN HOLLAND · Holland.

Invitation

To celebrate the opening of its Amsterdam office, Alnylam Pharmaceuticals, together with amsterdam inbusiness, Health~Holland and the Invest in Holland Network, has the honour to invite you to a high-level event on:

'Building a Life Sciences Powerhouse in the Netherlands'

Groundbreaking innovation in practice: the example of RNA interference

amsterdam business · Health~Holland SHARED CHALLENGES, SMART SOLUTIONS · INVEST IN HOLLAND · Holland. · Alnylam PHARMACEUTICALS

Alnylam Pharmaceuticals groeit in Nederland en opent nieuw kantoor in Amsterdam

├ Komst toonaangevend RNAi biotechbedrijf bevestigt ontwikkeling life sciences hub in Nederland –

fd. het financieele dagblad

BIOTECHNOLOGIE

Biotechbedrijf Alnylam opent kantoor in Amsterdam

Het Amerikaanse biotechbedrijf Alnylam Pharmaceuticals zet de stap naar Europa met de opening van een kantoor in Amsterdam. Dat heeft de

Alnylam @Alnylam · Oct 25

Hello Holland! We are pleased to announce the opening of our new #Amsterdam office & we'll be marking the occasion by co-sponsoring an event: "Building a #LifeSciences Powerhouse in the Netherlands" with @HealthHolland @nfiaholland on 30 October. #LifeSciencesNL #investinholland

Alnylam Pharmaceuticals will benefit from the EMA relocating from London to Amsterdam | Jerry Lampen/AFP via Getty Images

Q and A with rare disease drugmaker Alnylam Pharmaceuticals

The EU recently approved the first-ever RNA interference treatment developed by Alnylam, which offers promise for other rare diseases.

By KATIE JENNINGS | 10/30/18, 6:30 AM CET

ELSEVIER WEEKBLAD

IN DE CIJFERS

Blij met farmaceut op de Zuidas

FLEURIËTTE VAN DE VELDE

Zag bij evenement hoe de overheid zich inspant om buitenlandse bedrijven naar Nederland te halen.

Welcome in the Netherlands! Het Amerikaanse biofarmaceutische bedrijf Alnylam, dat zijn Europese kantoor in Amsterdam vestigt, krijgt een warm onthaal van de Nederlandse overheid, zo bleek tijdens een bijeenkomst ter viering van de opening van het kantoor aan de Zuidas.

Liefst drie instanties deden mee aan de organisatie van dit *high level event* in het Muziektheater aan het IJ: Amsterdam inbusiness ('het buitenlandse investeringsagentschap van de Amsterdam Metropolitan Area'), Health-Holland (de Nederlandse topsector Life Sciences & Health), dat innovatie in deze sector stimuleert, en Invest in Holland, dat zich inspant om bui-