Alnylam®

WELCOME TO

R&D DAY

Forward-Looking Statement

Today's presentations contain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. All statements other than historical statements of fact regarding Alnylam's expectations, beliefs, goals, plans or prospects, including, without limitation, statements regarding the potential for Alnylam to identify new potential drug development candidates and advance its research and development programs, including statements regarding the number of programs that Alnylam anticipates having in the clinic by the end of 2025, the number of INDs and CTAs that Alnylam intends to file, the timing of initiation of any of Alnylam's clinical trials, and the achievement of pipeline milestones and data, including relating to ongoing or planned clinical trials of nucresiran, zilebesiran, mivelsrian, ALN-HTT02 and other product candidates; Alnylam's aspiration to become a top-tier biotech company and the planned achievement of its "Alnylam P^{5}x25" goals; Alnylam's growth potential; Alnylam's plans for additional global regulatory filings and its ability to obtain approval for new commercial products or additional indications for its existing products, including AMVUTTRA in ATTR-CM; Alnylam's expectations regarding the safety and efficacy of AMVUTTRA for the treatment of ATTR-CM and the potential for AMVUTTRA to become a first line and/or standard of care treatment for ATTR-CM; the size of the commercial opportunities for Alnylam's current and any future products, and the addressable markets for such products, including AMVUTTRA; the potential attributes, value proposition and product profile of any of Alnylam's products or combination of products and the impact of such products or combination of products on patients; the potential efficacy and safety of any of Alnylam's product candidates; Alnylam's ability to deliver RNAi therapeutics to major tissues and its potential ability to silence any gene in the genome; Alnylam's ability to develop new manufacturing technologies that meet demand, decrease cost, expand capability and have reduced impact on the environment; and Alnylam's projected commercial and financial performance, including the expected range of net product revenues for 2025 and Alnylam's expectation that achievement of its 2025 net product revenue guidance positions it to achieve non-GAAP profitability, should be considered forward-looking statements.

Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation, risks and uncertainties relating to Alnylam's ability to successfully execute on its "Alnylam P^{5}x25" goals; Alnylam's ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of its product candidates; the pre-clinical and clinical results for Alnylam's product candidates; actions or advice of regulatory agencies and Alnylam's ability to obtain and maintain regulatory approval for its product candidates, as well as favorable pricing and reimbursement; successfully launching, marketing and selling Alnylam's approved products globally; delays, interruptions or failures in the manufacture and supply of Alnylam's product candidates or its marketed products; obtaining, maintaining and protecting intellectual property; Alnylam's ability to successfully expand the approved indications for AMVUTTRA; Alnylam's ability to manage its growth and operating expenses through disciplined investment in operations and its ability to achieve a self-sustainable financial profile in the future; Alnylam's ability to maintain strategic business collaborations; Alnylam's dependence on third parties for the development and commercialization of certain products, including Roche, Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the potential risk of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the "Risk Factors" filed with Alnylam's most recent Annual Report on Form 10-K filed with the SEC and in its other SEC filings. In addition, any forward-looking statements represent Alnylam's views only as of the date of this presentation and should not be relied upon as representing Alnylam's views as of any subsequent date. Alnylam explicitly disclaims any obligation, except to the extent required by law, to update any forward-looking statements.

Alnylam

The Leader in RNAi Therapeutics

Outstanding R&D Productivity

- **Proven platform** that has pioneered new class of medicines
- **5** approved medicines

Rich Pipeline with Multiple Blockbuster Opportunities

- **>25 high-value programs** expected in clinic across diverse indications by end of 2025

Leading Commercial Capabilities Driving Strong Performance

- Significant share and consistent growth, including in competitive markets
- **33% YoY** growth in net product revenue

On Track to Deliver on *Alnylam P^{5}x25* Financial Goals

- **≥40% revenue CAGR** expected through YE 2025*
- **Sustainable non-GAAP profitability** expected in 2025

** Since time of inception of "Alnylam P^{5}x25" goals at YE 2020*

Alnylam

2024 Delivered Strong Progress Across the Business

Portfolio & Pipeline

Highly positive HELIOS-B Phase 3 results

Global regulatory filings for **vutrisiran,** PDUFA date March 23, 2025

Positive **nucresiran** (ALN-TTRsc04) Phase 1 data supporting potential for best-in-class profile

Positive initial multi-dose results with **mivelsiran**

Initiated cAPPricorn-1 Phase 2 study in CAA

Positive **zilebesiran** Phase 2 results showing significant additive blood pressure lowering

Expanded clinical pipeline with **4 proprietary CTAs:**

- ALN-HTT02
- ALN-AGT-REVERSIR
- ALN-6400
- ALN-4324

Financials & Culture

Combined net product revenues: **$1,646 million (33% growth YoY)**

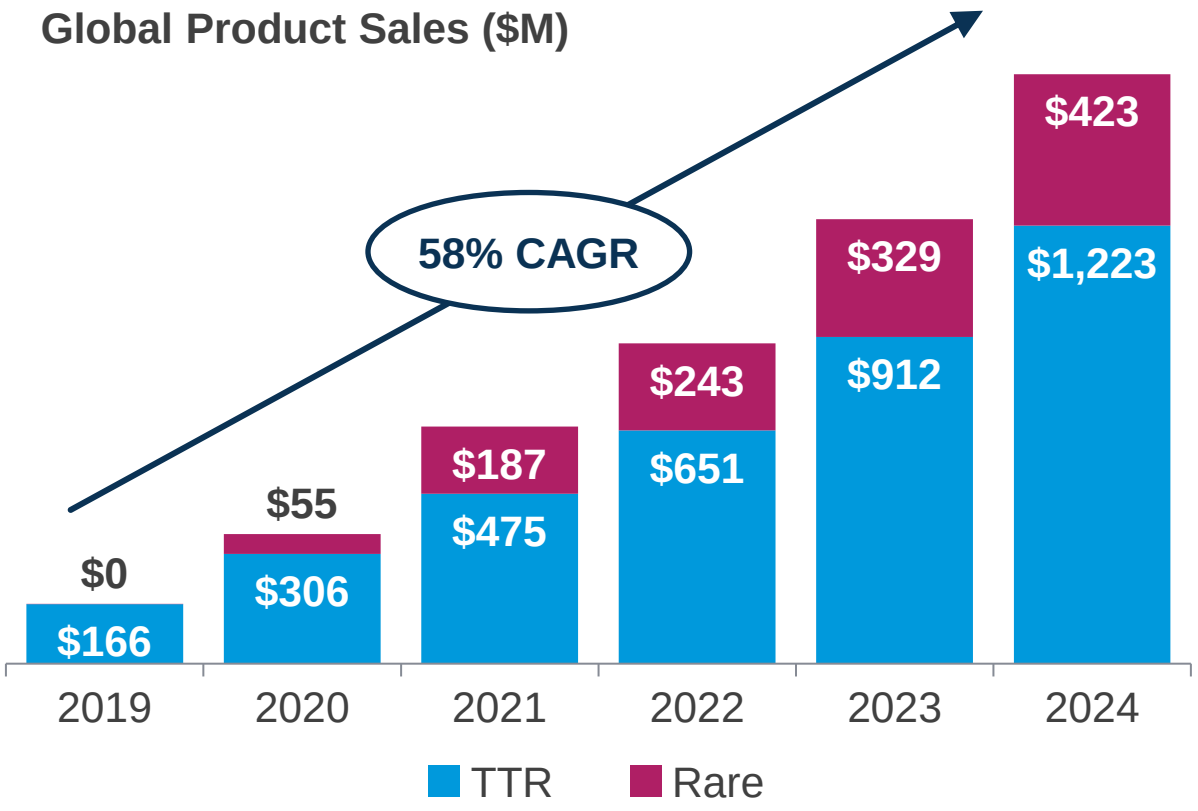
Maintained strong financial position **$2.7 billion in cash** at year-end 2024

Continued recognition of **award-winning culture**

Strong Commercial Performance, ExceptionalGrowth Potential

Transformational Medicines Delivering $1,646 Million in Annual Product Revenues in 2024

Robust 33% 2024 YoY Growth in Total Net Product Revenues



Total TTR

onpattro (patisiran) amvuttra (vutrisiran)

34%

YoY growth in Total TTR revenues

Total Rare

GIVLAARI (givosiran) OXLUMO (lumasiran)

29%

YoY growth in Total Rare revenues

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2025 Net Product Revenue Guidance Positions Company to Achieve Goal of Sustainable Non-GAAP Profitability

	2025 Guidance
Total TTR Product Sales (PN & CM*) (ONPATTRO®, AMVUTTRA®)	$1,600 to $1,725 million
Total Rare Product Sales (GIVLAARI®, OXLUMO®)	$450 to $525 million
Total Combined Product Sales	**$2,050 to $2,250 million**
Non-GAAP Operating Income	**Achieve profitability**

** Guidance assumes FDA approval of the sNDA for vutrisiran for the treatment of adults with ATTR amyloidosis with cardiomyopathy by the March 23, 2025 PDUFA target action date.*

Alnylam 2025 Goals

onpattro (patisiran) / amvuttra (vutrisiran) / GIVLAARI (givosiran) / OXLUMO (lumasiran)		Combined Net Product Revenue Guidance $2,050M – $2,250M	**2025**
VUTRISIRAN	ATTR Amyloidosis	U.S. FDA Approval	**PDUFA date March 23, 2025**
		Additional Global Approvals (Japan, EU)	**Q2, Q3**
NUCRESIRAN* **(ALN-TTRsc04)**	ATTR Amyloidosis	Initiate Phase 3 Study in ATTR-CM	**H1**
		Initiate Phase 3 Study in hATTR-PN	**H2**
ZILEBESIRAN*	Hypertension	KARDIA-3 Phase 2 Results	**H2**
		Initiate Phase 3 CVOT	**H2**
MIVELSIRAN*	Cerebral Amyloid Angiopathy and Alzheimer's Disease	Interim Phase 1 Part B Data in EOAD	**H2**
		Initiate Phase 2 Study in AD	**H2**
ALN-6400*	Bleeding Disorders	Initiate Phase 2 Study	**H2**
ADDITIONAL PROGRAMS		File ≥4 New INDs	**2025**
KEY PARTNER-LED PROGRAM MILESTONES			
FITUSIRAN* (Sanofi)	Hemophilia	U.S. FDA Approval	**PDUFA date March 28, 2025**
ELEBSIRAN* (Vir)	Chronic HBV/HDV	Initiate Phase 3 study in HDV	**H1**
		Phase 2 HBV Functional Cure Results	**Q2**
CEMDISIRAN* (Regeneron)	Complement-Mediated Diseases	Phase 3 MG Results	**H2**

** Not approved for any indication and conclusions regarding the safety or effectiveness of these drugs have not been established.*
EOAD = Early Onset Alzheimer's Disease; MG = Myasthenia Gravis

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Alnylam 2025 Goals

onpattro (patisiran) amvuttra (vutrisiran) GIVLAARI (givosiran) OXLUMO (lumasiran)		Combined Net Product Revenue Guidance $2,050M – $2,250M	2025
VUTRISIRAN	ATTR Amyloidosis	U.S. FDA Approval	PDUFA date March 23, 2025
			Q2, Q3
NUCRESIRAN* (ALN-TTRsc04)			H1
			H2
ZILEBESIRAN*			H2
			H2
MIVELSIRAN*			H2
			H2
ALN-6400*			H2
ADDITION			2025
FITUSIRAN* (Sanofi)			PDUFA date March 28, 2025
ELEBSIRAN* (Vir)	Chronic HBV/HDV	Initiate Phase 3 study in HDV	H1
		Phase 2 HBV Functional Cure Results	Q2
CEMDISIRAN* (Regeneron)	Complement-Mediated Diseases	Phase 3 MG Results	H2

6 commercial products (4 WHOLLY OWNED)

3 Phase 3 study starts

Vutrisiran launch in ATTR-CM

≥4 new INDs

KARDIA-3 Phase 2 results

Achieve sustainable non-GAAP profitability

** Not approved for any indication and conclusions regarding the safety or effectiveness of these drugs have not been established.*
EOAD = Early Onset Alzheimer's Disease; MG = Myasthenia Gravis

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Strong Progress Against Ambitious Five-Year Goals

Alnylam P5X25

PATIENTS: Over 0.5 million on Alnylam RNAi therapeutics globally

PRODUCTS: 6+ marketed products in rare and prevalent diseases

PIPELINE: Over 20 clinical programs; 10+ in late stages; 4+ INDs per year

PERFORMANCE: ≥40% revenue CAGR through YE 2025

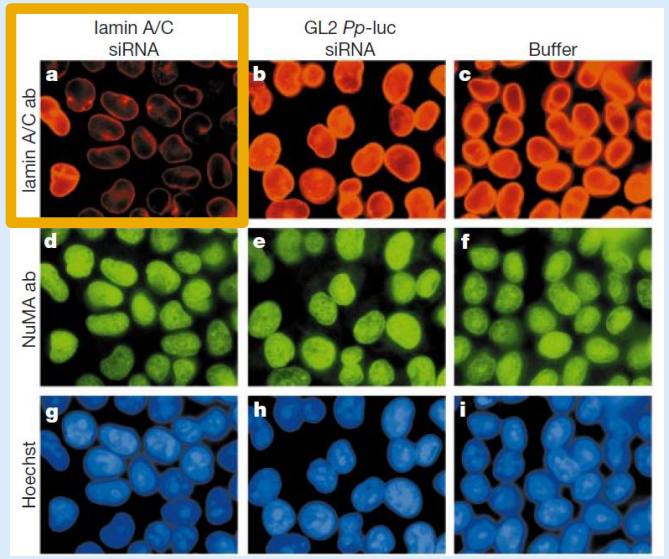
PROFITABILITY: Achieve sustainable non-GAAP profitability within period

Spring-Loaded for Growth

Pushkal Garg, M.D.
Chief Medical Officer

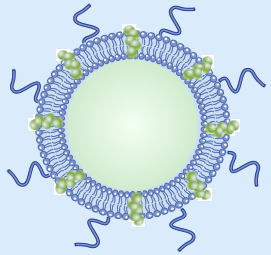
Alnylam – Pioneering a Generational Class of Medicines Based on RNAi

RNA Interference



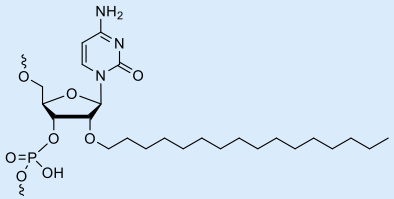
Elbashir et al., Nature, 411: 494-98 (2001)

State-of-the-Art Delivery



LNPs

GalNAC



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Building a Portfolio of RNAi Therapeutics with Transformational Patient Impact

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Alnylam – Pioneering a Generational Class of Medicines Based on RNAi

Silence *any* gene in genome

Upstream of today's medicines

Catalytic mechanism

Highly potent

Highly specific and reversible

Infrequent administration

Building a Portfolio of RNAi Therapeutics with Transformational Patient Impact

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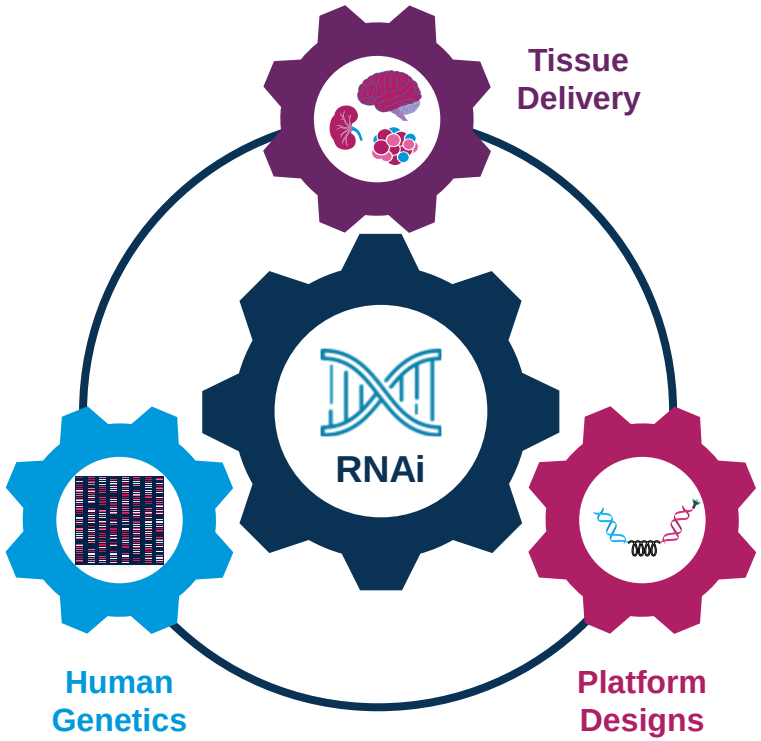
Five Marketed Products Based on our Technology & Approach

Track Record of Successful Execution

1. Alnylam formed a collaboration to develop inclisiran with The Medicines Company in 2013; Novartis completed acquisition of The Medicines Company in 2020

Our Disciplined R&D Strategy is Building a High-Yielding Portfolio of RNAi Therapeutics to Transform Human Disease

Sustainable Innovation Engine



Guided by

Strategic Principles

- Address diseases with high morbidity & mortality
- Pursue high conviction targets
  - Strong biologic rationale, informed by human genetics
- Potential to halt or reverse disease, and be best-in-class
- Drive to clear clinical proof-of-concept
- Encouraging market opportunity and access dynamics

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Alnylam Will Primarily Focus on Organic Innovation

Funding Tomorrow's Breakthroughs

- Disciplined R&D investment is **hugely value-creating** given above average success rates
- Wealth of targets allows us to **advance only the best opportunities**
- Growing opportunity to invest in **wholly-owned internal programs**
- Alnylam is in a privileged position to **create transformational medicines**

Why We're Poised to Deliver

- **RNAi pioneer** with sustainable product engine
- **Deep science** & disease knowledge to prioritize opportunities
- **Proven track record** of successful end-to-end execution

Continued Use of Value-Creating Partnerships

Genetics
Finding promising targets across global populations

Technology
Accessing new innovation to expand frontiers of opportunity

Programs
Enhancing productivity and building capabilities with global partners

biobank uk

Our Future Health

All of Us Research Program

discoverme South Africa

PeptiDream

ADIMAB

Novartis

Regeneron

Roche

sanofi

Alnylam will continue to partner selectively to expand and accelerate our patient impact

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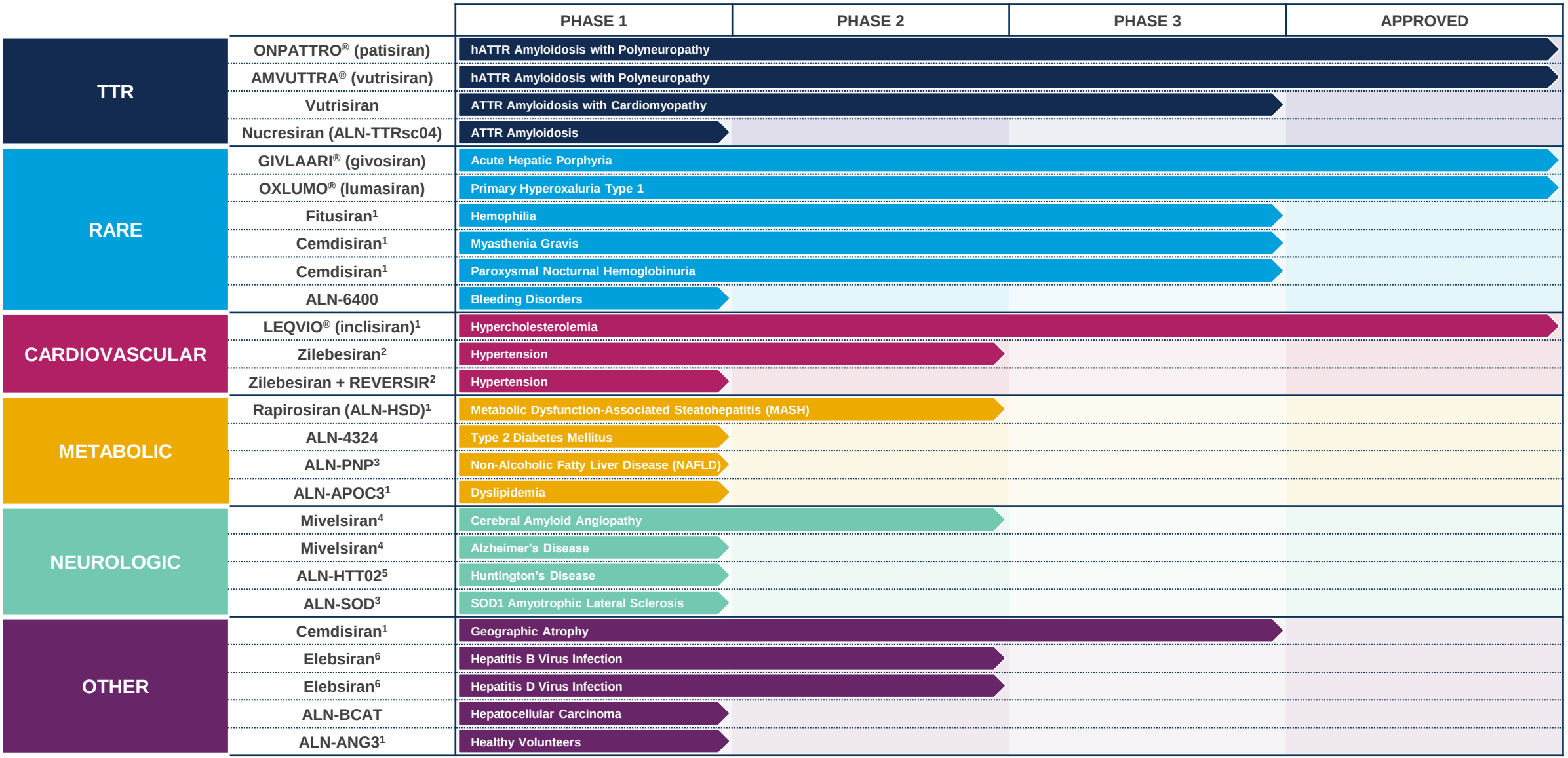
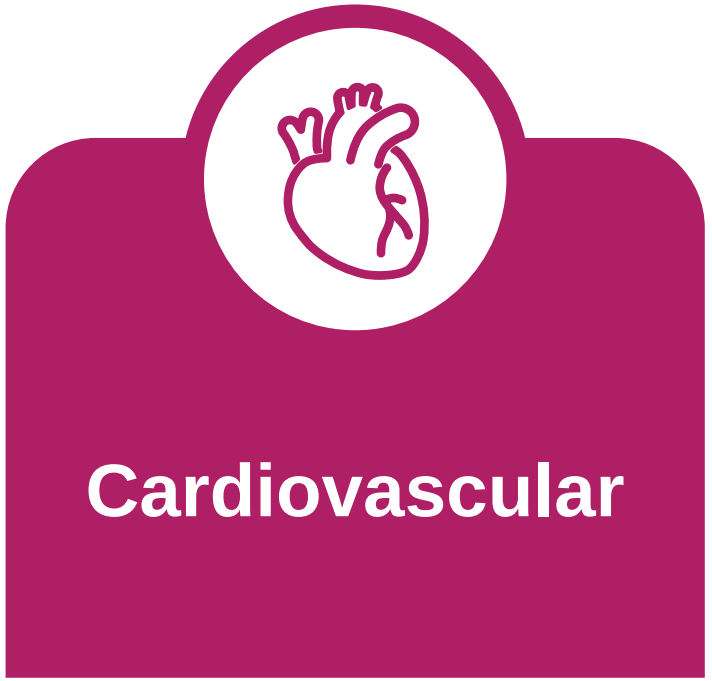
Robust and High-Value Pipeline of RNAi Therapeutics

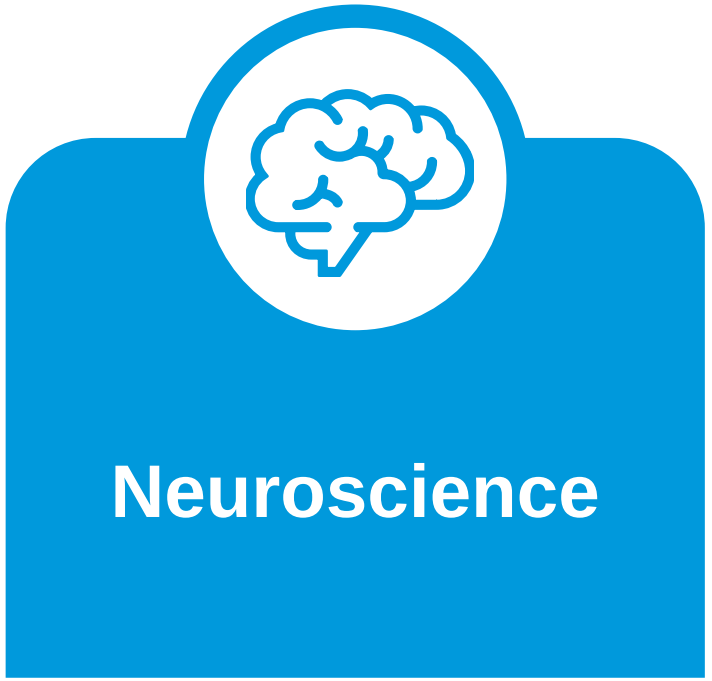


** Vutrisiran and fitusiran are under regulatory review. [1] Out-licensed with milestones and/or royalties; [2] Partnered, Alnylam-led development with U.S. profit split and milestones/royalties ex-U.S.; [3] Partner-led with profit split; [4] Product developed as part of collaboration with Regeneron [5] Partnered, Alnylam-led with profit split; [6] Partner-led with Alnylam option for profit split*

Key Near- to Midterm Growth Drivers

Potential For Three Blockbuster Franchises





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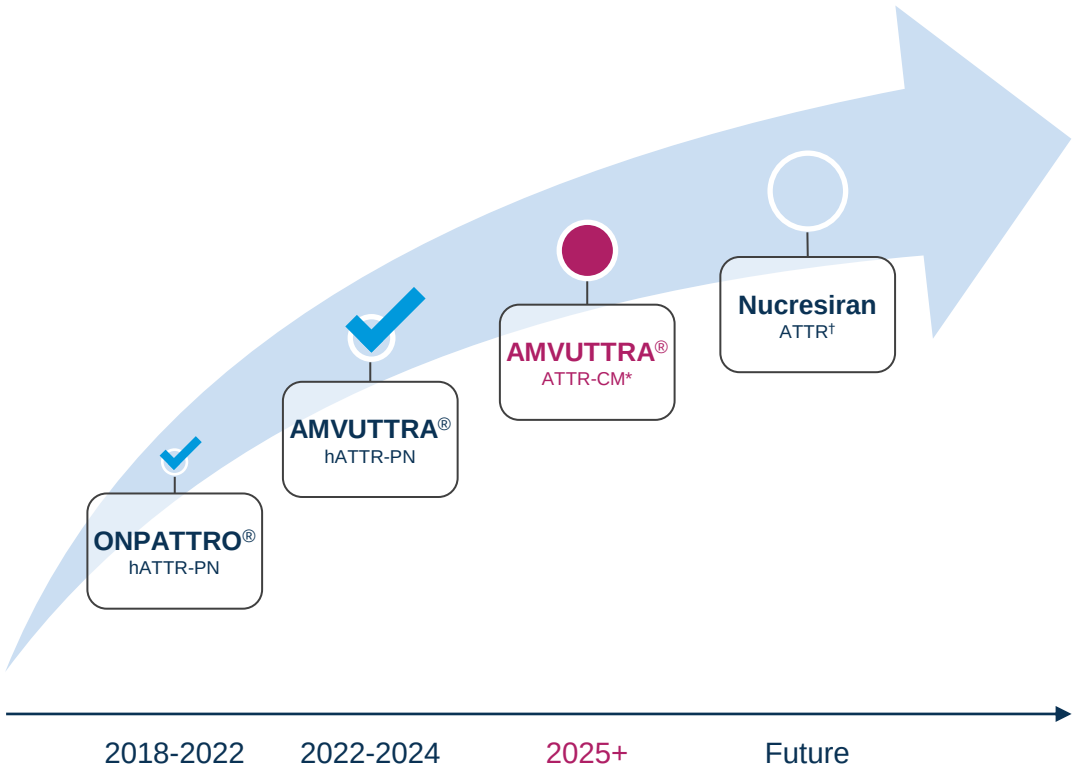
Building on Our Leadership in ATTR Amyloidosis

A Durable, Blockbuster Franchise



John Vest, M.D.

- Review the broad impact of vutrisiran on ATTR-CM, as demonstrated in the HELIOS-B study
- Share updated survival data & preview ACC presentations
- Update on regulatory status
- Outline Phase 3 development plans for nucresiran in ATTR-CM and hATTR-PN

**Pending regulatory approval*
†investigational therapy in development

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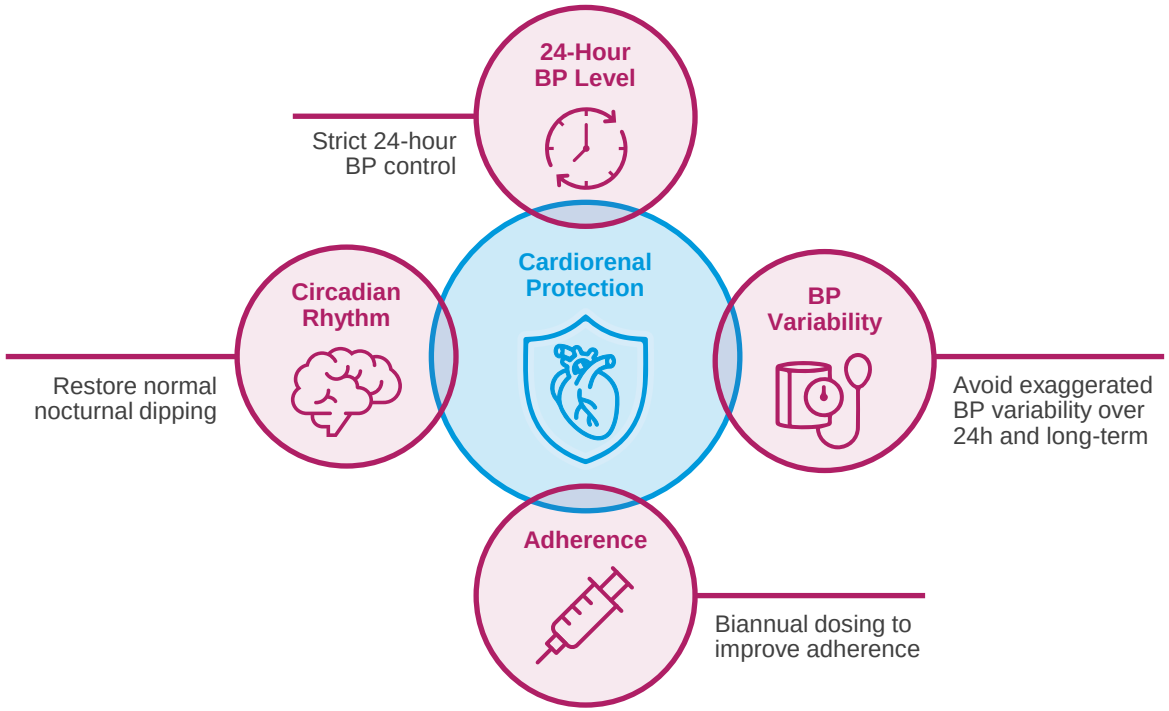
Reimagining Hypertension & Atherosclerotic Cardiovascular Disease

Addressing the #1 Preventable Cause of ASCVD, Affecting >60 Million Adults



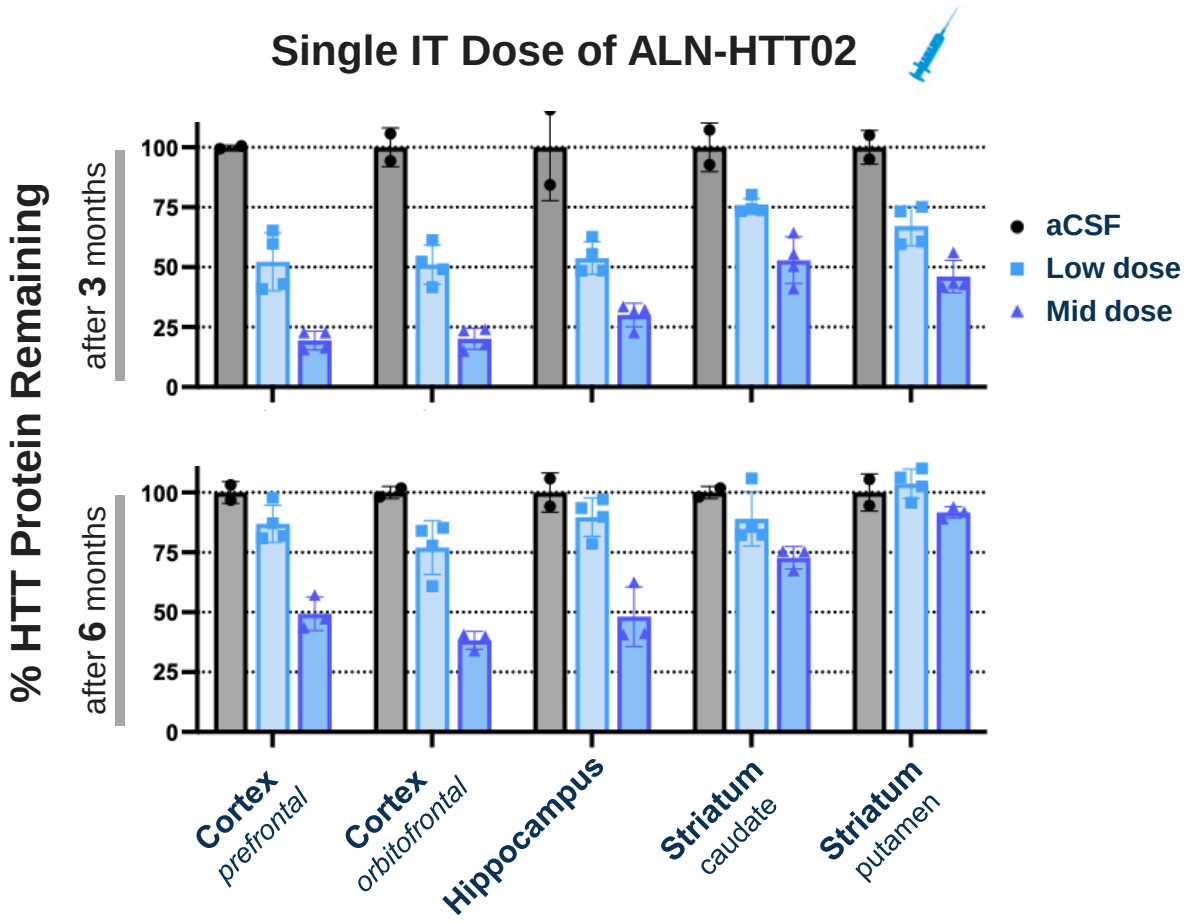
Therapeutic Goal to Improve Quantity and Quality of Blood Pressure Control

Simon Fox, Ph.D.

- Review Phase 2 data indicating potential to offer continuous blood pressure control with every 6-month dosing
- Discuss implications of KARDIA-3 results
- Share design of the global Phase 3 CVOT, to start in 2H 2025
- Outline value proposition

RNAi Therapeutics to Transform the Treatment of Neurologic Diseases

Tremendous Unmet Need for Disease Modifying Therapies



Julia Shirvan, M.D., Ph.D. & Kevin Sloan, Ph.D.

Mivelsiran

- Review updated Phase 1 data in EOAD patients
- Share new preclinical data supporting potential in CAA & ongoing Phase 2 study
- Discuss plans to advance into Phase 2 AD study

ALN-HTT02

- Provide biologic rationale for Huntington's program with unique exon 1 targeting approach
- Review Phase 1 study design

Professor Sarah J. Tabrizi, M.D., Ph.D. FMedSci FRS, UCL

aCSF, artificial cerebrospinal fluid; HTT, huntingtin

1. Sloan K, et al. Oral Presentation at the European Huntington's Disease Network and Enroll-HD 2024 Meeting. September 12-14, 2024. Strasbourg, France (recording available online at EHDN.org).

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Key Mid- to Long-Term Growth Drivers

Emerging Disease Areas

New Tissues & Platform Technology

Evolving Our R&D Operating Model to Continuously Push the Boundaries of RNAi Innovation

>20 Medicines In Development, Including Multiple Potential Blockbusters

Our Keys to Success

- **Agile, content-driven leadership**
- **Enhancing probability of success** via disease & target knowledge and innovative clinical trial design
- **Seamless integration** across R&D
- **Award-winning, patient-centric culture**

And We Continue to Build

- Improved **oligonucleotide** throughput
- Enhanced clinical trial **efficiency** and **predictability**
- Manufacturing innovation to **reduce COGS**
- Deep **expertise in new disease** areas

Alnylam R&D: Spring-Loaded for Growth

Priority Focus Areas

- Rapidly gain approval of vutrisiran in ATTR-CM around the world
- Deliver on mid-stage pipeline, which includes multiple blockbuster opportunities
  - Three Ph3 study starts in 2025
- Invest in platform and new targets to drive the next wave of innovation
- Scale our capabilities with continued emphasis on bold clinical development and flawless execution

2025 R&D Day Agenda

TIME	TOPIC		PRESENTER
9:00 – 9:10a ET	**Welcoming Remarks**		**Yvonne Greenstreet, M.D.,** Chief Executive Officer
9:10 – 9:25a ET	**Spring-loaded for Growth**		**Pushkal Garg, M.D.,** Chief Medical Officer
9:25 – 9:50a ET	**TTR Amyloidosis – Market Leadership With Rapid Knockdown**		**John Vest**, M.D., SVP, ATTR Development Lead
9:50 – 10:05a ET	**Cardiovascular – Zilebesiran: Continuous Control of Hypertension**		**Simon Fox, Ph.D.,** VP, Program Lead, Zilebesiran
10:05 – 10:50a ET	**Neuroscience**	**Mivelsiran: A Differentiated Approach for Alzheimer's Disease and Cerebral Amyloid Angiopathy** **Overview of Huntington's Disease Unmet Need** **ALN-HTT02: Hope for Huntington's Disease Patients**	**Julia Shirvan, M.D., Ph.D.,** Snr. Dir., Mivelsiran Clinical Lead **Professor Sarah Tabrizi, M.D., Ph.D.** FMedSci FRS, UCL **Kevin Sloan, Ph.D.,** VP, Program Lead, Early CNS Programs
10:50 – 11:00a ET	*Intermission*		
11:00 – 11:30a ET	**Q&A**		**Pushkal Garg, M.D.,** Chief Medical Officer *(moderator)*
11:30 – 11:45a ET	**Durable Leadership in RNAi Therapeutics**		**Kevin Fitzgerald, Ph.D.,** Chief Scientific Officer
11:45a – 12:00p ET	**Metabolic – Next Wave of Innovation**		**Sandeep Menon, M.D., Ph.D.,** Chief Development Officer
12:00 – 12:15p ET	**Next Wave of RNAi Therapeutics to Fuel a Robust Clinical Pipeline**		**Paul Nioi, Ph.D.,** SVP, Research **Anna Borodovsky, Ph.D.,** VP, Research
12:15 – 12:30p ET	**Platform Innovation**		**Vasant Jadhav, Ph.D.,** Chief Technology Officer
12:30 – 12:55p ET	**Q&A**		**Kevin Fitzgerald, Ph.D.,** Chief Scientific Officer *(moderator)*
12:55 – 1:00p ET	**Closing Remarks**		**Pushkal Garg, M.D.,** Chief Medical Officer

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Leadership Here Today

Yvonne Greenstreet, M.D.
Chief Executive Officer

Pushkal Garg, M.D.
Chief Medical Officer

Jeff Poulton
Chief Financial Officer

Tolga Tanguler
Chief Commercial Officer

Christine Lindenboom
Chief Corporate Communications Officer

Kevin Fitzgerald, Ph.D.
Chief Scientific Officer

Sandeep Menon, M.D., Ph.D.
Chief Development Officer

Vasant Jadhav, Ph.D.
Chief Technology Officer

John Vest, M.D.
Senior Vice President, ATTR Development Lead

Simon Fox, Ph.D.
Vice President, Zilebesiran Program Lead

Julia Shirvan, M.D., Ph.D.
Senior Director, Mivelsiran Clinical Lead

Kevin Sloan, Ph.D.
Vice President, Early Neuroscience Programs

Paul Nioi, Ph.D.
Senior Vice President, Research

Anna Borodovsky, Ph.D.
Vice President, Research

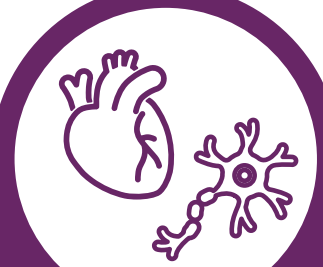
Alnylam Innovates For Patients

ATTR Amyloidosis – Market Leadership With Rapid Knockdown

John Vest, M.D.
SVP, ATTR Development Lead

Key Near- to Midterm Growth Drivers

Potential For Three Blockbuster Franchises



ATTR Amyloidosis

Cardiovascular

Neuroscience

Alnylam

ATTR Amyloidosis

Rare, Progressively Debilitating, and Fatal Disease

Description

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

Predominantly manifests as cardiomyopathy and/or polyneuropathy

Hereditary ATTR (hATTR) Amyloidosis

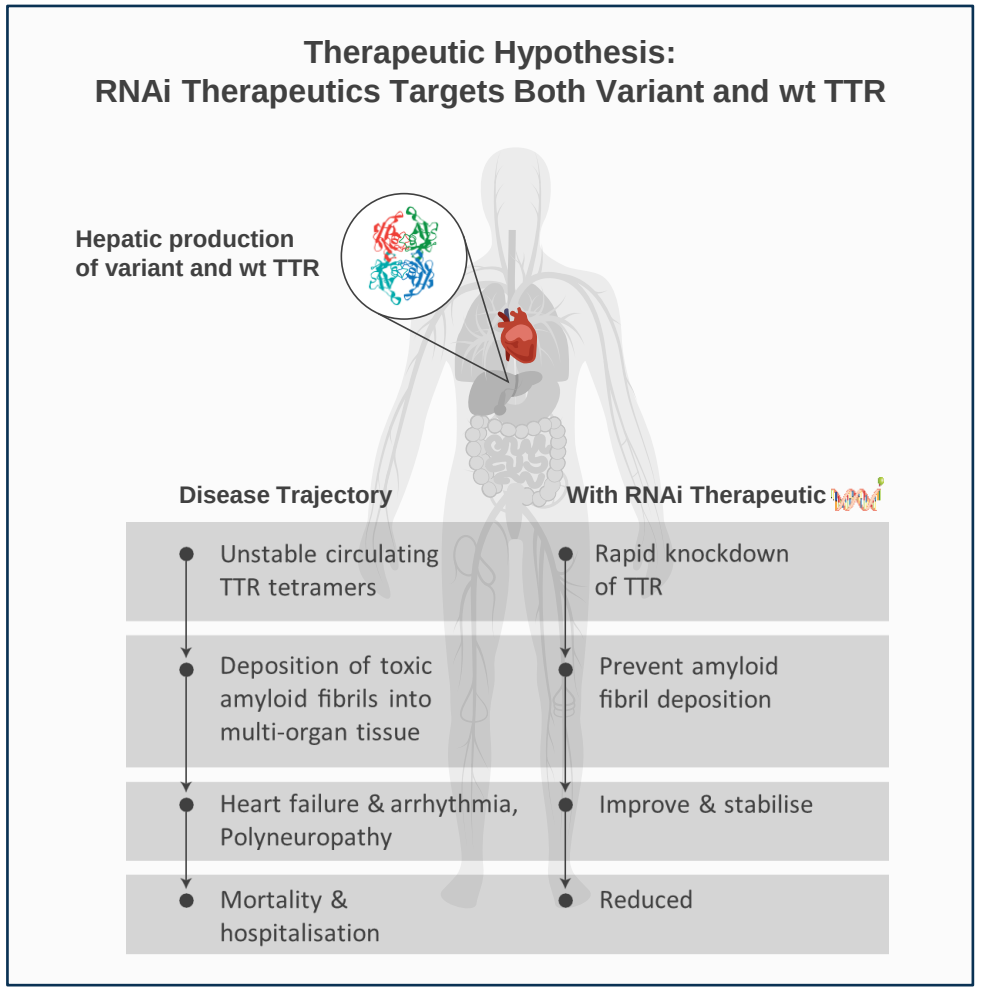
~50,000

patients worldwide[2]

Wild-Type ATTR (wtATTR) Amyloidosis

>300,000

patients worldwide[3]



1. Coelho T, et al. N Engl J Med. 2013;369(9):819-829. 2. Ando, et al. Orphanet J Rare Dis, 2013; Ruberg, et al. Circulation, 2012 (includes hATTR amyloidosis patients with polyneuropathy and cardiomyopathy); Gertz, et al. Am J Manag Care. 2017;23:S107-S112. 3. Information based on Alnylam modeling data

Alnylam

Building a Durable ATTR Franchise

Potential to Establish RNAi Therapeutics as First Line SOC with ONPATTRO and AMVUTTRA

onpattro (patisiran) lipid complex injection 10 mg/5 mL

An Approved RNAi Therapeutic for Treatment of Polyneuropathy of hATTR Amyloidosis[1]

- Based on APOLLO data, commercially available in >30 countries for hATTR amyloidosis with polyneuropathy
- Positive results from APOLLO-B[3]
- IV administration, 1x every 3 weeks

amvuttra (vutrisiran) injection 25 mg/0.5 mL

An Approved RNAi Therapeutic for Treatment of Polyneuropathy of hATTR Amyloidosis[2]

- Based on HELIOS-A data, approved in US, EU, UK, JP, and BR
- Positive HELIOS-B data in ATTR amyloidosis with CM[4]
- Subcutaneous administration, once quarterly

Nucresiran (ALN-TTRsc04)

An Investigational RNAi Therapeutic for Potential Treatment of ATTR Amyloidosis

- Phase 1 study ongoing
- Potential for >90% serum TTR reduction with biannual dosing
- No third-party royalties; exclusivity expected beyond 2040

1. ONPATTRO is approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU, Switzerland and Brazil for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy; see Full Prescribing Information; 2. AMVUTTRA is approved in the U.S. for the treatment of the PN of hATTR amyloidosis in adults, in the EU for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy; in Japan for transthyretin (TTR) type familial amyloidosis with polyneuropathy and in Brazil for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adults see Full Prescribing Information; 3. Patisiran has not been approved by the FDA or EMA for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population; 4. Vutrisiran has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population

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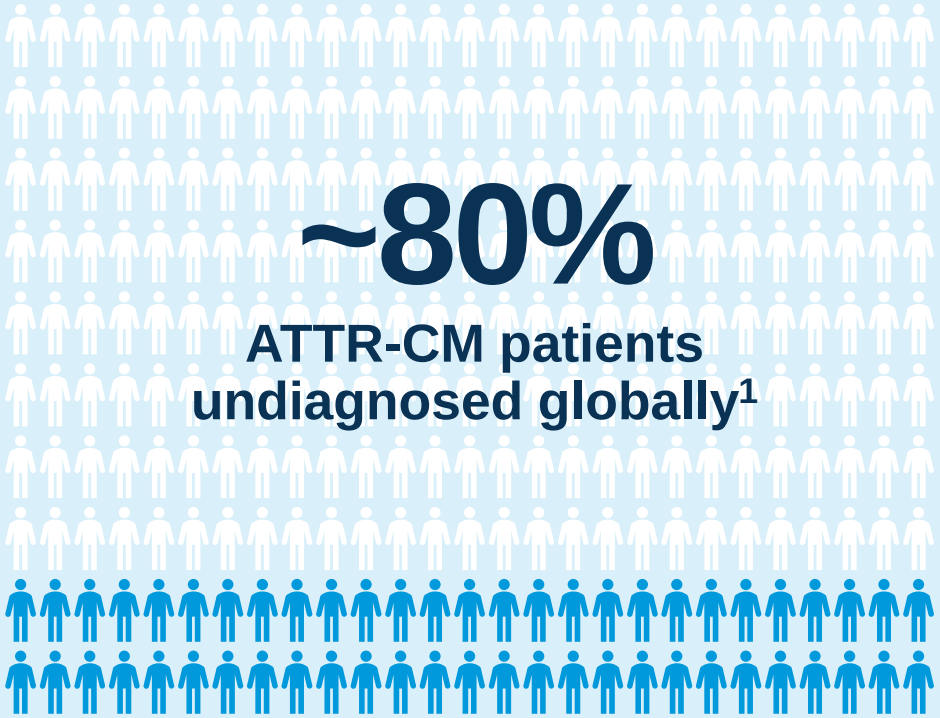
Opportunity for Significant Impact in ATTR-CM

Significant Unmet Patient Need in ATTR-CM

>300K patients globally[1]



Building on Our Leadership in hATTR-PN

Grew hATTR-PN Category
>5x
Growth since 2019

Expanded Prescriber Base
2x
Growth in HCP prescriber base since 2021

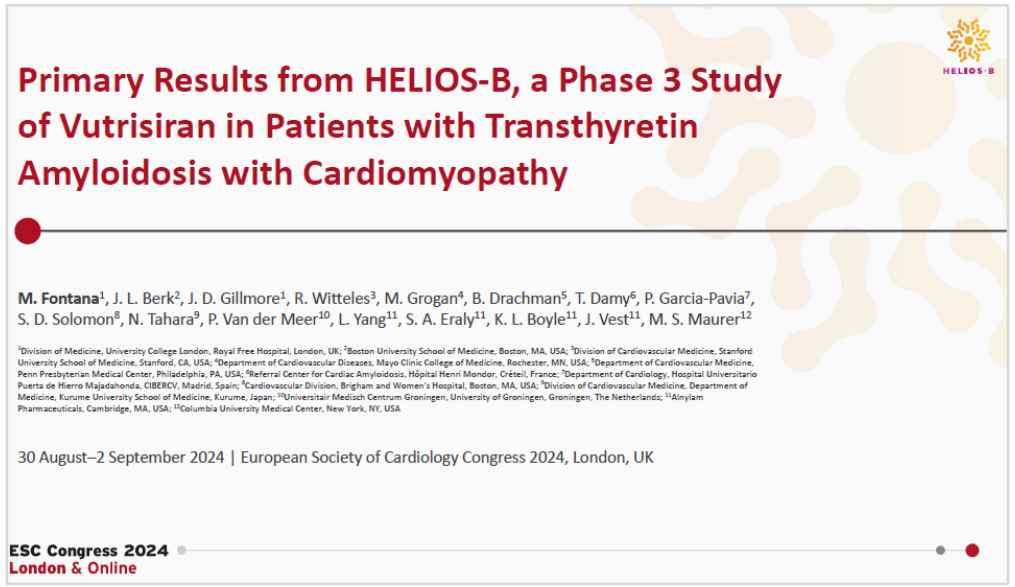
Established Leadership
>80%
Estimated share of the hATTR-PN category in markets with competition

1. *Information based on Alnylam modeling data*

Readout of the Landmark HELIOS-B Study

Transformational Profile Expected to Drive a Robust and Growing Market

ESC Congress 2024 London



The NEW ENGLAND JOURNAL of MEDICINE

"This finding has the potential to establish a new standard of care"
Giampaolo Merlini, M.D. (NEJM Editorial)

Medical writing assistance was provided by Christopher Bulman, PhD, of Adelphi Communications Ltd, UK, and funded by Alnylam Pharmaceuticals in accordance with Good Publication Practice Guidelines. This study was funded by Alnylam Pharmaceuticals. If you are seeking additional scientific information related to Alnylam therapeutics, US HCPs may visit the Alnylam US Medical Affairs website at RNAiScience.com. Non-US HCPs should contact medinfo@alnylam.com

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HELIOS-B Enrolled Population Reflective of Today's Patient

Milder Patients on Substantial Background Therapy; Underscores Magnitude of Treatment Effect and Relevance to Evolving Patient Landscape

Milder Patients[1]

Less advanced baseline

- Baseline NT-proBNP lower than previous phase 3 studies
- Majority NYHA Class II
- Majority NAC stage I

Use of Substantial Background Medications[1]

~50%

of patients were on tafamidis at baseline or during the DB period

~30%

of patients started SGLT2 inhibitors during the DB period

~80%

on diuretics at baseline and ~50% of patients had intensification or initiation of diuretics after first dose

1. M. Fontana et al, NEJM September 2024

HELIOS-B

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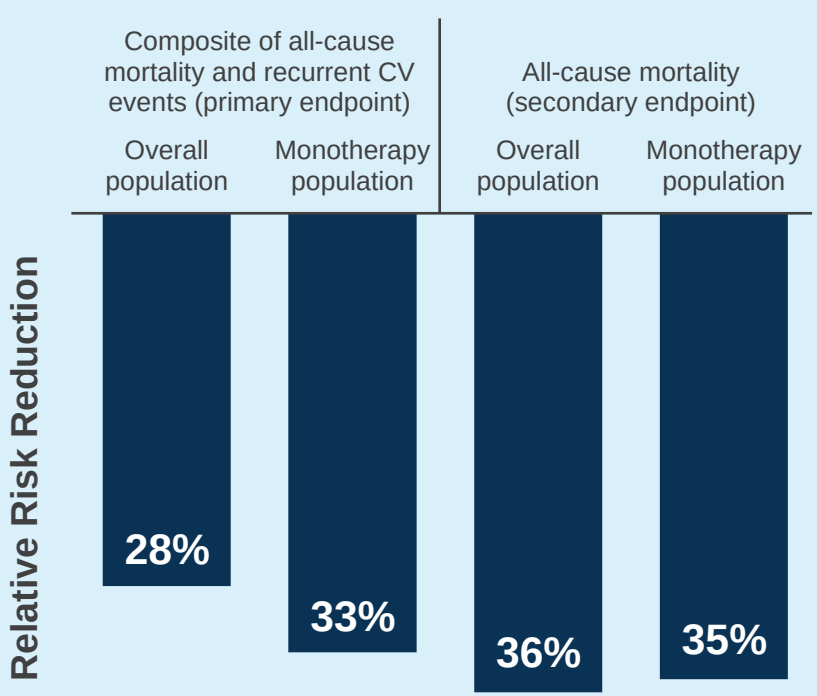
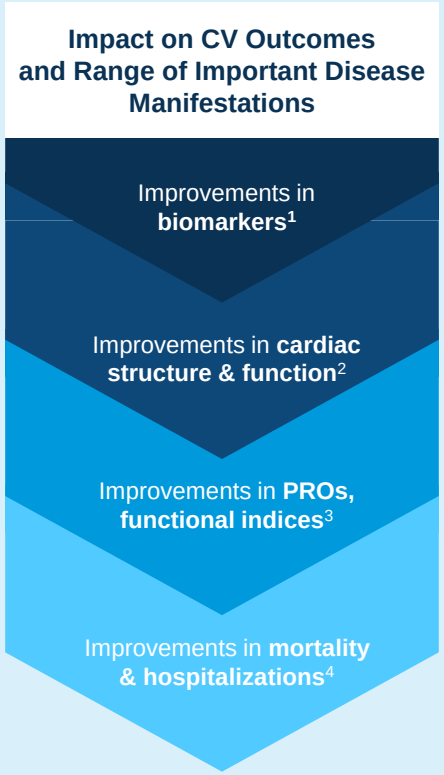
Vutrisiran Therapeutic Profile Supports First-Line Potential

HELIOS-B Study Demonstrated Impact of Rapid Knockdown in Population Representative of Today's ATTR-CM Patients





Key Observations

- Substantial effect despite extensive background therapy
- Disease modifying
- Works rapidly
- Evidence of stability over time
- Data support treating early; outsized benefit in milder disease
- Acceptable safety and tolerability profile, as previously established

HELIOS-B study, M. Fontana et al, NEJM September 2024; 1. 32% RRR for both NT-proBNP and Tropinin I at Month 30; 2. Improvement vs placebo in LV wall thickness, LV ejection fraction, and parameters of diastolic function at month 30; 3. At 30 months, 6-minute walk test: least-squares (LS) mean difference, 26.5 m; 95% CI, 13.4 to 39.6; P<0.001); KCCQ-OS score: LS mean difference, 5.8 points; 95% CI, 2.4 to 9.2; P<0.001); improvement or no change in NYHA class (LS mean difference, 8.7 percentage points; 95% CI, 1.3 to 16.1; P=0.02); 4. 28% reduction in time to first CV event or all-cause mortality in overall population, 36% reduction in pre-specified secondary endpoint of all-cause mortality in overall population; † Internal data; Vutrisiran has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population

HELIOS-B

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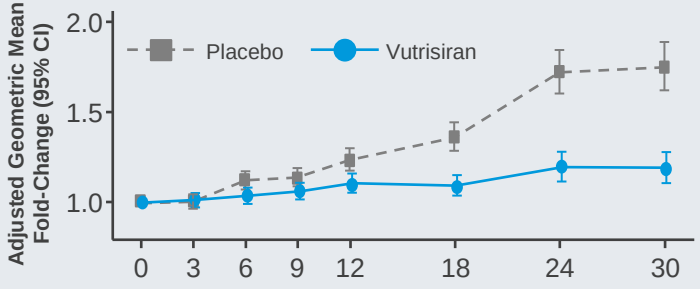
Favorable Impact on Multiple Measures of Disease Progression

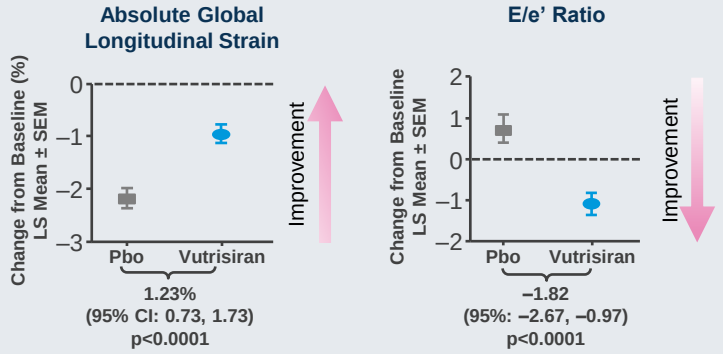
OVERALL POPULATION

Evidence for Disease Modifying Potential

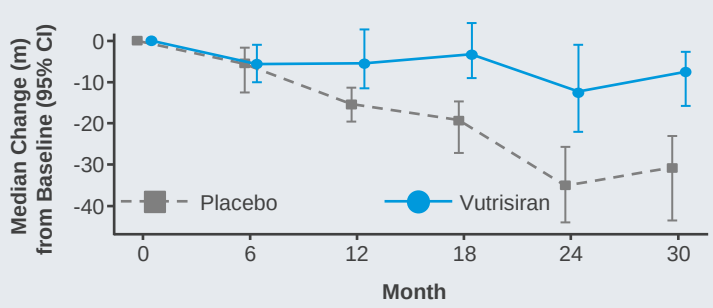
NT-proBNP



Systolic & Diastolic Function



6-MWT



- Observed clinical benefits cascade in a biologically rational manner
- Effects on well established biomarkers of cardiac health seen early
- Improvements compared to placebo on cardiac structure, as well as systolic and diastolic function; all important elements of underlying pathophysiology
- Preservation of functional status over 30 months

LS mean accounts for missing data due to death or HT/LVAD, unable to walk due to disease progression (only for 6-MWT) that were imputed from resampling of worst 10%. Median representation is based on observed data only, no imputations due to death/unable to walk due to disease progression. Abbreviations: 6-MWT, 6-minute walk test; CI, confidence interval; HT, heart transplant; LS, least squares; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; LVAD, left ventricular assist device; NYHA, New York Heart Association; SEM, standard error of the mean.

HELIOS-B

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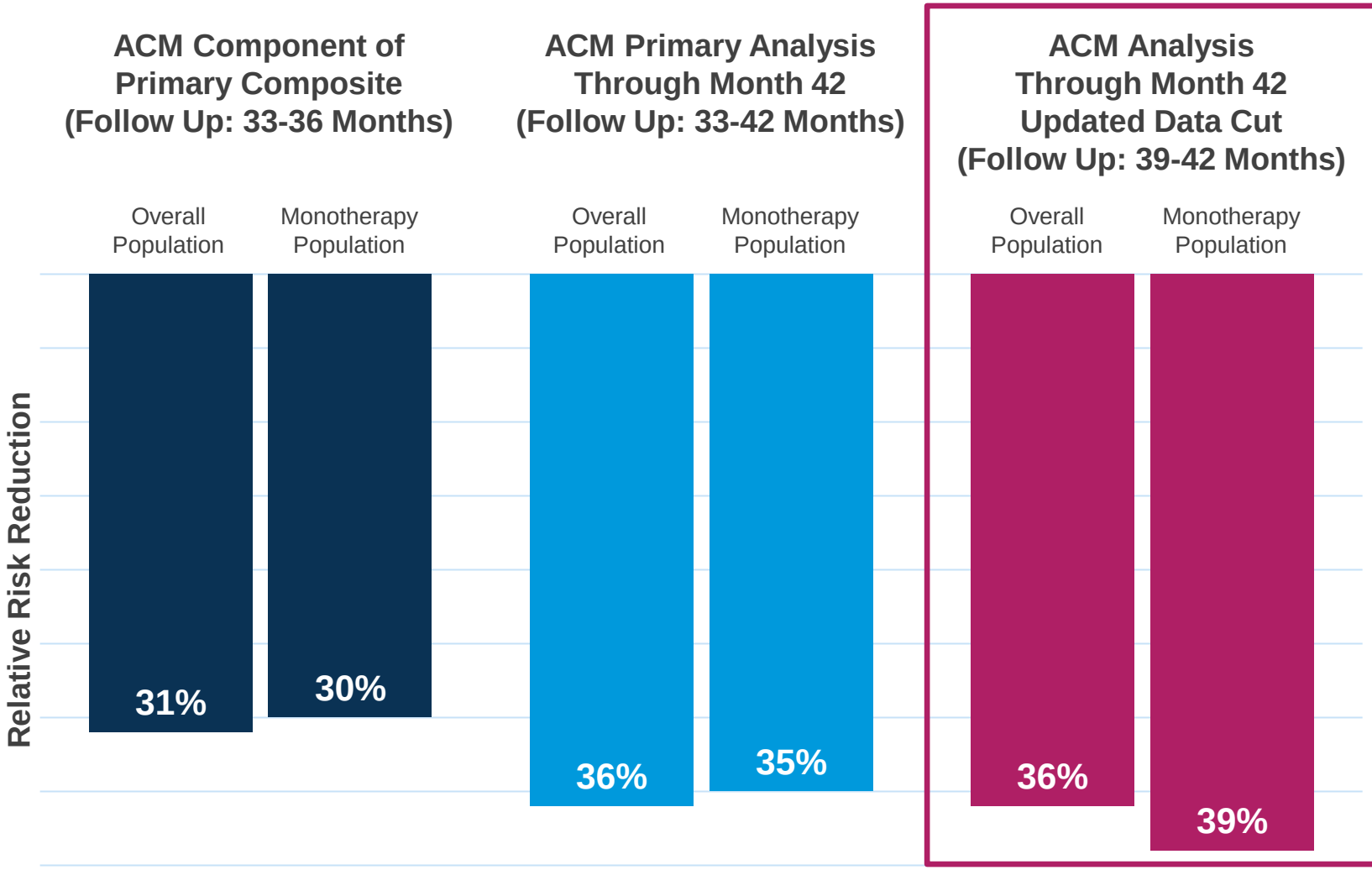
Updated Data Cut Corroborates Primary Analysis of Mortality

Consistent results across analyses of all-cause mortality



- **Analysis with near complete data for ACM through month 42**
- **>99% ascertainment of vital status**
- **Further details in planned publication**

At the primary analysis of the primary composite endpoint, the component analysis of all-cause mortality included data from the DB period (33–36 months), while the analysis of all-cause mortality as a secondary endpoint incorporated data through 42 months, including up to 6 months of OLE data for patients who crossed over. An updated mortality analysis was conducted based on the Nov 2024 cutoff date which included nearly complete ACM data through 42 months.

HELIOS-B

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Additional Data to be Presented at ACC 2025 Further Support Vutrisiran's Compelling Profile

- The Relationship Between Cardiac Structure, Function, and Clinical Outcomes and the Impact of Vutrisiran from the HELIOS-B Trial
- Maintenance or Improvement of Functional Capacity, Health Status, and Quality of Life with Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy: Data from the HELIOS-B Study
- Impact of Baseline Heart Failure Severity on Efficacy of Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy in the HELIOS-B Trial: A Subgroup Analysis
- Real-World Persistency on Tafamidis: An Analysis of US Insurance Claims Data

Vutrisiran's Compelling Profile

- ✓ Reduced hospitalizations
- ✓ Saved lives
- ✓ Helped people to feel and function better
- ✓ Disease modifying
- ✓ Benefit demonstrated across both major disease manifestations (CM and PN)
- ✓ Infrequent quarterly dosing
- ✓ Encouraging safety profile

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Vutrisiran Regulatory Filings Submitted in U.S., EU, Japan, Brazil

HELIOS·B

U.S. PDUFA Date March 23, 2025

PRIORITY

Additional global regulatory submissions ongoing

Note: Vutrisiran is an investigational therapeutic in development for ATTR-CM, and efficacy and safety in this patient population has not been established or approved by any health authority

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Nucresiran Continues Alnylam's Innovation for Patients

Poised to Drive Category Leadership in ATTR Amyloidosis Through the 2040s

onpattro (patisiran) lipid complex injection 10 mg/5 mL

An Approved RNAi Therapeutic for Treatment of Polyneuropathy of hATTR Amyloidosis[1]

- Based on APOLLO data, commercially available in >30 countries for hATTR amyloidosis with polyneuropathy
- Positive results from APOLLO-B[3]
- IV administration, 1x every 3 weeks

amvuttra (vutrisiran) injection 25 mg/0.5 mL

An Approved RNAi Therapeutic for Treatment of Polyneuropathy of hATTR Amyloidosis[2]

- Based on HELIOS-A data, approved in US, EU, UK, JP, and BR
- Positive HELIOS-B data in ATTR amyloidosis with CM[4]
- Subcutaneous administration, once quarterly

Nucresiran (ALN-TTRsc04)

An Investigational RNAi Therapeutic for Potential Treatment of ATTR Amyloidosis

- Phase 1 study ongoing
- Potential for >90% serum TTR reduction with biannual dosing
- No third-party royalties; exclusivity expected beyond 2040

1. ONPATTRO is approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU, Switzerland and Brazil for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy; see Full Prescribing Information; 2. AMVUTTRA is approved in the U.S. for the treatment of the PN of hATTR amyloidosis in adults, in the EU for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy; in Japan for transthyretin (TTR) type familial amyloidosis with polyneuropathy and in Brazil for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adults see Full Prescribing Information; 3. Patisiran has not been approved by the FDA or EMA for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population; 4. Vutrisiran has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population

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Elevating Alnylam's ATTR Leadership with Nucresiran

Next Generation Profile with Potential to Improve Patient Outcomes

Deeper and Faster TTR Knockdown with Low Interpatient Variability
>90% reduction maintained over 6 months

Infrequent Dosing
twice annually

Innovative Development Program Anticipating Future Category Dynamics

Robust Data Set to Inform HCPs and Access Decision Making
ATTR Cardiomyopathy outcomes study

Accelerating Speed to Market
hATTR Polyneuropathy potential fast to market

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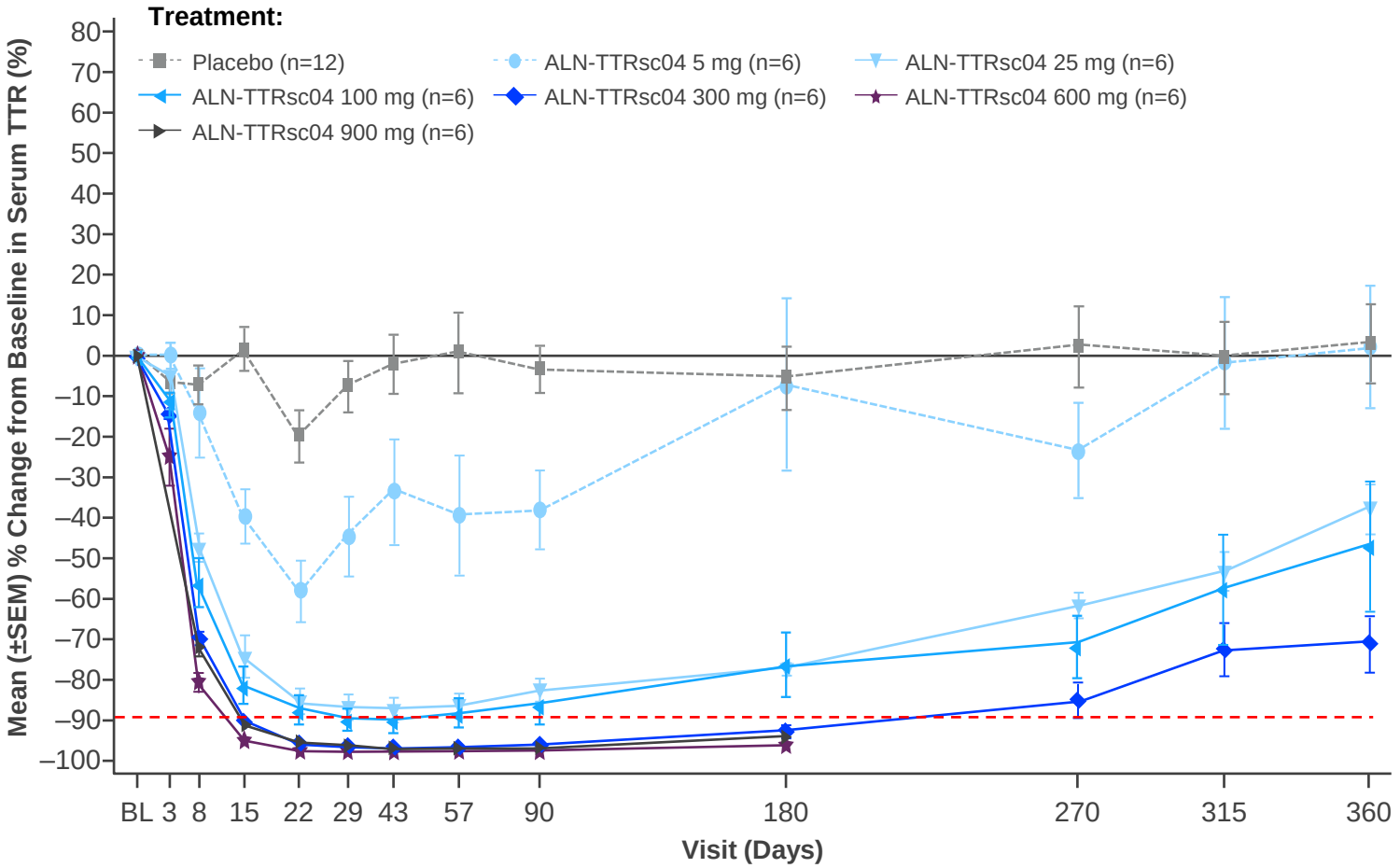
Rapid, Deep and Sustained TTR Knockdown with Nucresiran

Potential for Best-in-Class Profile



- **Rapid** knockdown in serum TTR at Day 15; mean reductions of 90.3% (300 mg), 95.0% (600 mg)
- **Deep** knockdown of TTR by Day 29; mean reductions of 96.5% (300 mg), 97.8% (600 mg)
- **Sustained** knockdown of TTR through Day 180; mean reductions of 92.6% (300 mg), 96.0% (600 mg)
- **Low variability** of TTR knockdown on Day 29 (% TTR reduction range): 96.0–96.7% (300 mg), 96.6–98.6% (600 mg)

Abbreviations: *BL, baseline; SEM, standard error of the mean; TTR, transthyretin*

Mauer et al., AHA 2024

Ongoing, Phase 1, randomized, double-blind, placebo-controlled, single ascending dose study of ALN-TTRsc04 (NCT05661916). NCT05661916 Available from: https://clinicaltrials.gov/study/NCT05661916.

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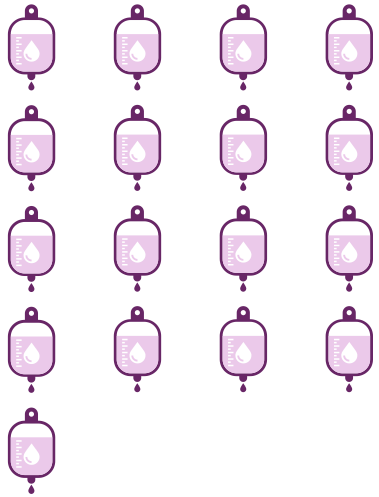
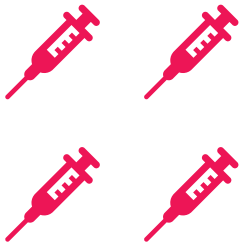
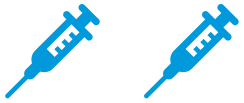
Driving Innovation for Clinical Impact and Patient Experience

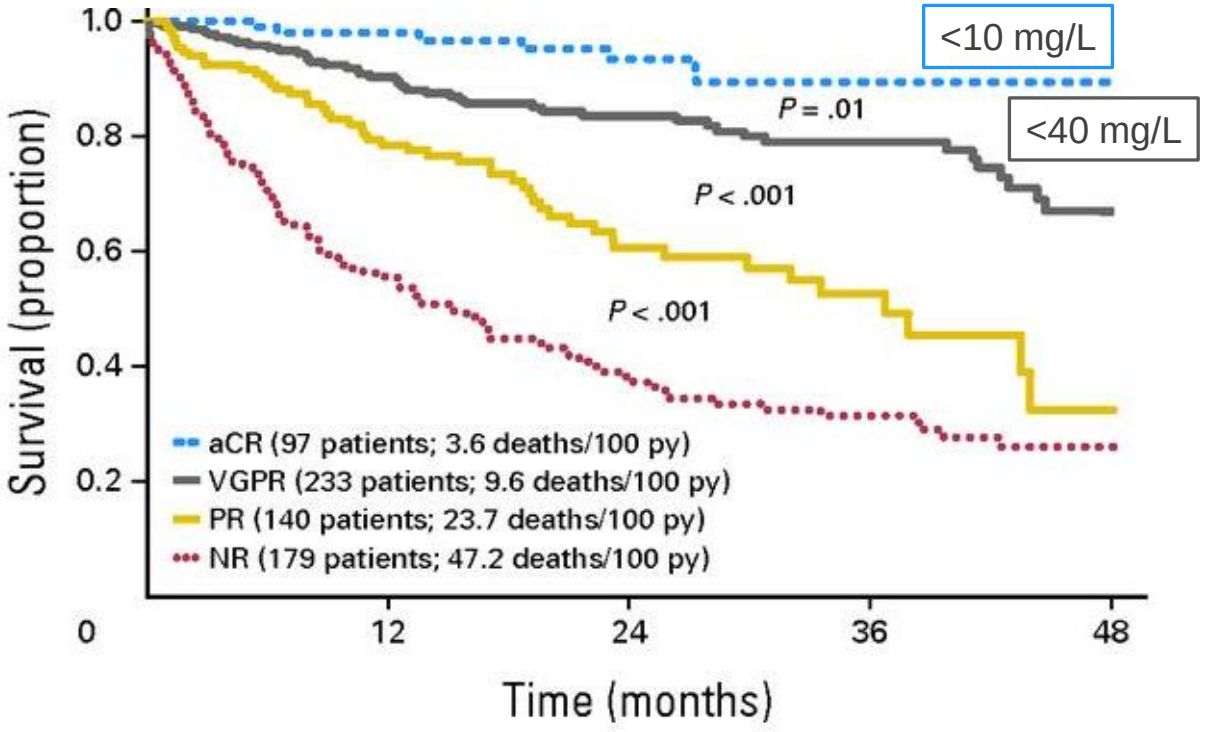
	Patisiran	Vutrisiran	Nucresiran
TTR Knockdown Profile	~ 85% TTR KD	~ 85% TTR KD	~ 95% TTR KD
			
Route of Administration	IV Infusion	SC Injection	SC Injection
Frequency of Administration	Every 3 weeks (~17x/year)	Every 3 months (4x/year)	Biannual (2x/year)

AL and AA Amyloidosis: Maximal Knockdown → Best Outcomes

Proving the Therapeutic Hypothesis Required Decades of Clinical Experience

AL Amyloidosis

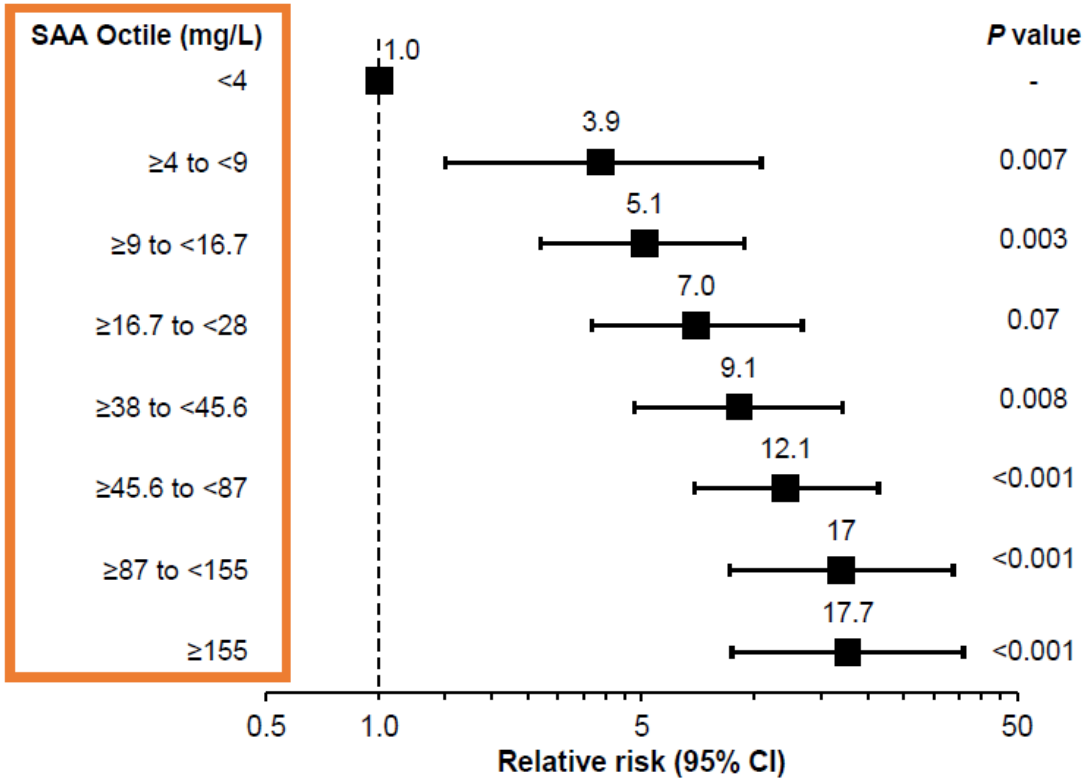
Survival Probability by Response to Therapy[1]



aCR, amyloid complete response. VGPR, very good partial response. PR, partial response. NR, no response.
Palladini 2012

AA Amyloidosis

Unadjusted relative risk of death associated with the most recent median annual SAA concentration during follow-up[2]



1. Palladini. J Clin Oncol 2012;30:4541-9; 2. Lachmann. N Engl J Med 2007; 356:2361-71.

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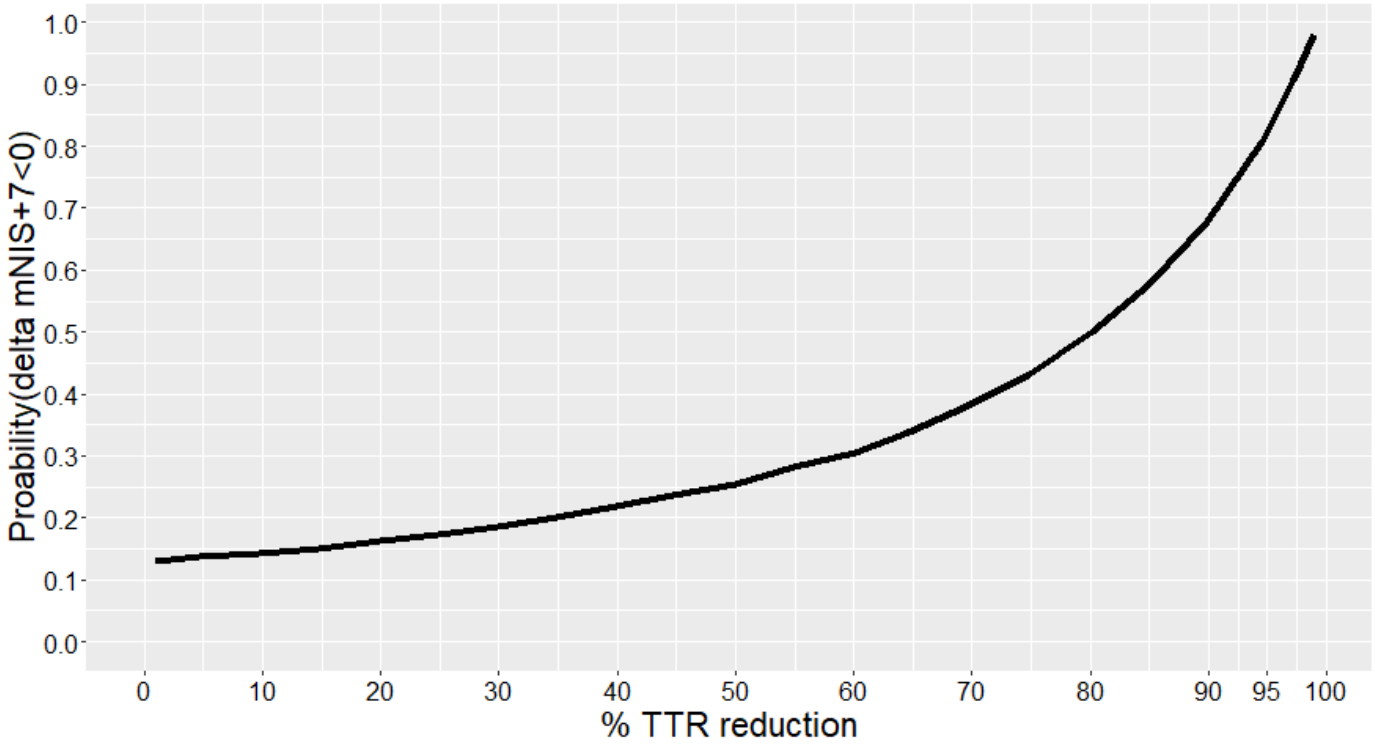
Modeling from APOLLO Supports Hypothesis that Greater Serum TTR Knockdown Leads to Improved Clinical Outcomes in ATTR Amyloidosis

Predicted % of Patients with mNIS+7 Improvement at 18 Months by TTR Reduction Based on APOLLO Modelling



- Modelling using APOLLO Phase 3 data shows **greater TTR reduction leads to higher probability of improvement in clinical outcomes**
- By ensuring almost **complete TTR reduction, the probability of successful clinical outcomes is improved** for individual patients
- Continued innovation with therapies that have the potential to offer even **higher levels of TTR knockdown** could therefore potentially **improve ATTR amyloidosis outcomes**

APOLLO Phase 3 Data; Internal Alnylam modeling

Key Considerations for Nucresiran ATTR CM Phase 3 Program

Evolving patient landscape and market dynamics inform phase 3 design and highlight tailwinds to optimize for success

Outcomes benefit will drive durable market-leading profile in a competitive environment	• Critical to HCPs and payors
Combination therapy	• Increased use of silencers in combination with stabilizer post tafamidis loss of exclusivity in ~2028 • Data package to inform nucresiran as monotherapy or in combination with stabilizer; HELIOS-B data strongly support opportunity
Patients will be identified earlier and with milder disease	• Dynamic will enrich nucresiran phase 3 population for patients with greatest opportunity for benefit based on HELIOS-B subgroup data and other previous phase 3 studies

Nucresiran TRITON-CM ATTR-CM CLINICAL STUDY Phase 3 Study

Randomized, Double-Blind Event Driven Outcomes Study in ATTR Amyloidosis Patients with Cardiomyopathy

Patient Population (~1200)

- ATTR: wild-type or any TTR variant
- Confirmed cardiomyopathy and medical history of symptomatic HF
- NYHA Class ≤III
- Background stabilizer therapy permissible

Select Exclusion Criteria

- NYHA Class IV HF
- PND Score ≥III at the screening visit
- Prior or current TTR lowering treatment

RANDOMIZATION[2]

Nucresiran SC q6M 300 mg

or

Placebo SC q6M

Primary Endpoints

- Composite of all-cause mortality and CV events (event driven)

Nucresiran SC q6M 300 mg

Abbreviations: 6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; BL, baseline; CV, cardiovascular; DB, double-blind; HF, heart failure; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire – Overall Summary; NYHA, New York Heart Association; OLE, open label extension; PND, polyneuropathy disability; q3M, every 3 months; SC, subcutaneous; TTR, transthyretin. References: Clinicaltrials.gov identifier: NCT04153149

1. NT-proBNP levels of >300 pg/mL and <8500 pg/mL (or >600 pg/mL and <8500 pg/mL for patients with atrial fibrillation). 2. Randomisation was stratified according to the use of tafamidis at baseline (yes versus no), ATTR disease type (hATTR or wtATTR), and NYHA class and age at baseline (NYHA class I or II and age <75 years versus all others). 3. Assessed in the overall population and monotherapy population as separate endpoints.

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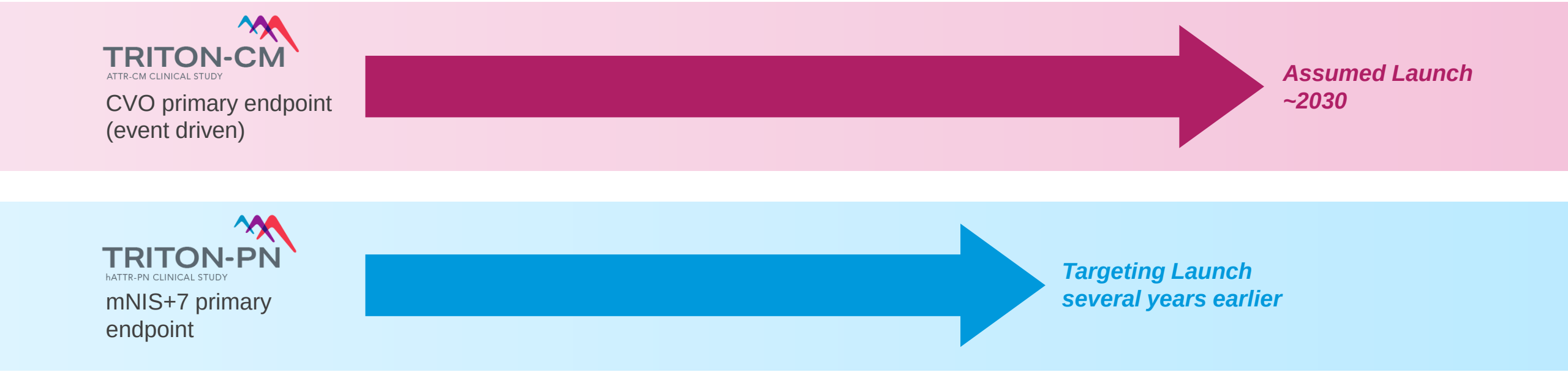
Nucresiran TRITON-PN hATTR-PN CLINICAL STUDY Ph3 Study in hATTR Polyneuropathy

Potential to Launch in hATTR-PN Ahead of ATTR-CM



- Target Phase 3 start late 2025
- Exploring efficient designs; history of innovative designs with vutrisiran FPI to top line in ~2 years
- Aligning potential study design with global regulators

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Investing to Continue Advancing ATTR Science

Continuous ATTR Evidence Generation

For vutrisiran…

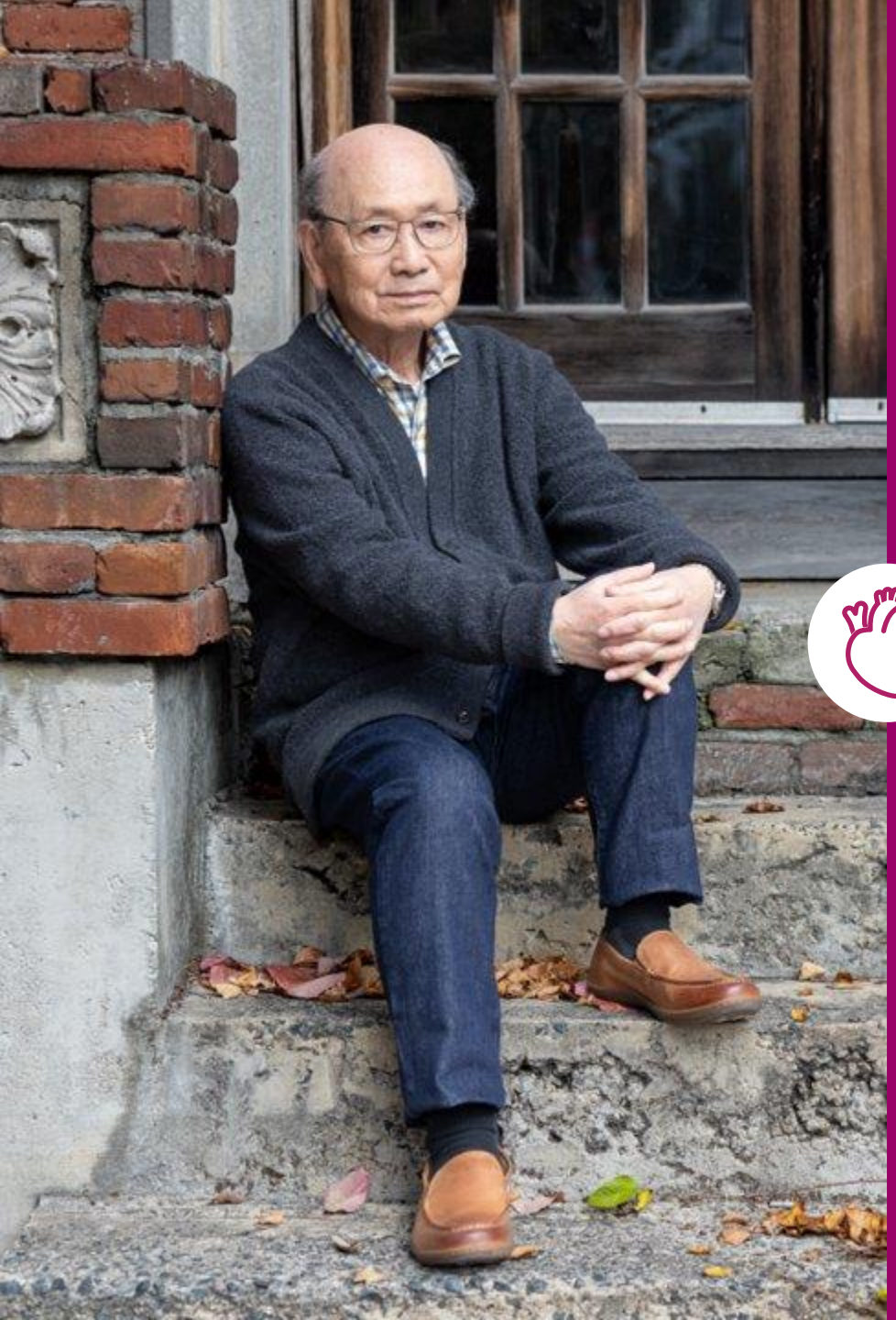
- 16 RWE studies
- 16 IIS / research collaborations
- HELIOS-B post hoc analyses

New ATTR Studies

- 3rd generation silencer program (nucresiran)

Clinical & Patient Community Support

- ATTR-relevant sponsorships & charitable contributions
- Fellowship programs support
- Global hATTR genetic testing
- Compassionate use & extended drug provision



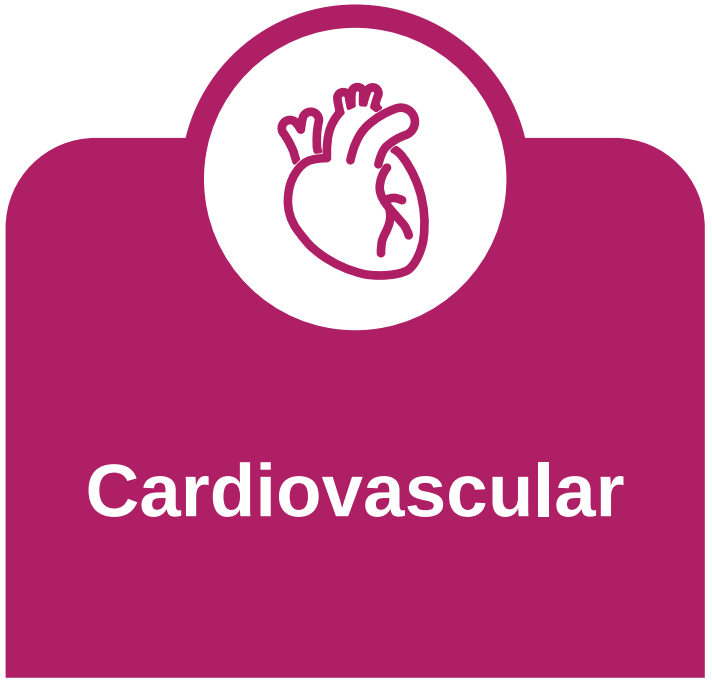
Cardiovascular – Zilebesiran: Continuous Control of Hypertension

Simon Fox, Ph.D.

Vice President, Zilebesiran Program Lead

Key Near-to Midterm Growth Drivers

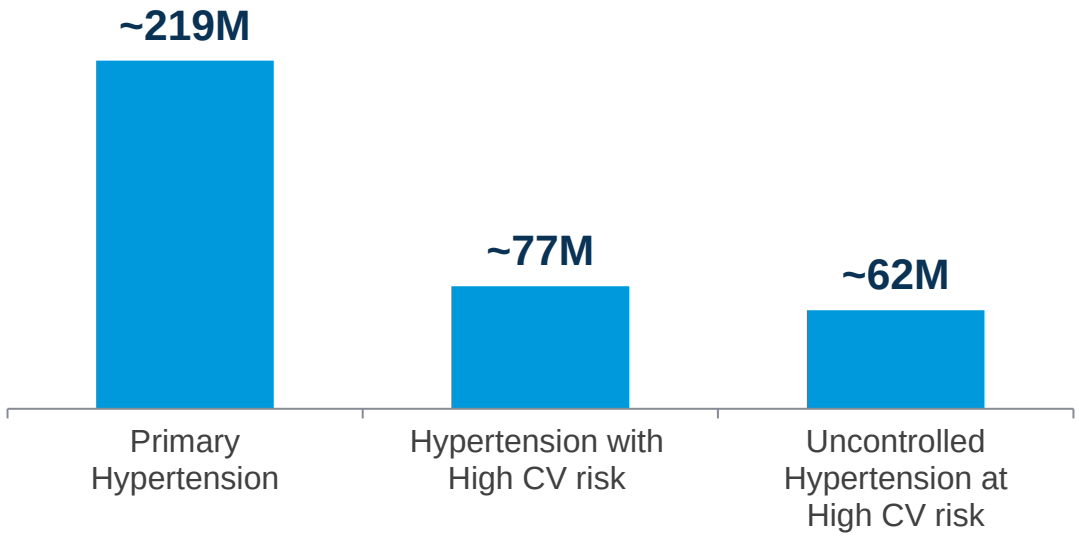
Potential For Three Blockbuster Franchises



Uncontrolled Hypertension is a Global Health Crisis

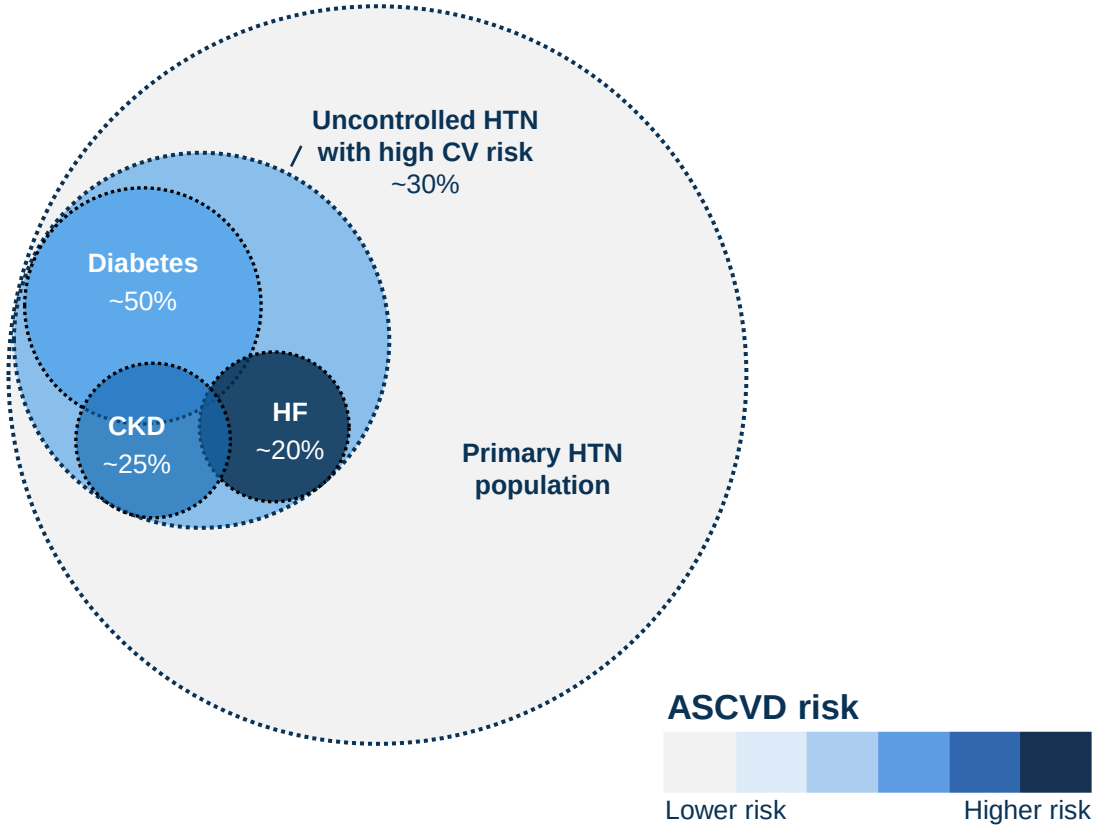
High Unmet Need with Many Patients Having Uncontrolled Hypertension and High CV Risk

Number of Patients (7 Major Markets)



	Risk Reduction per 5 mm Hg Decrease in SBP[1]
Major CV Events	10%
IHD	8%
Stroke	13%
HF	13%
CV Mortality	5%
All Cause Mortality	2%

Uncontrolled HTN with High CV Risk[2, 3]



1. Rahimi K, et al. Lancet 2021; 37: 1625–36. 2. Proportions derived from an analysis of a large US administrative claims and EMR database and 3. Muntner et al. Hypertension, 2022 (based BP ≥140/90); Comorbidities are not mutually exclusive. High CV risk patients defined as those with history of ASCVD or having a predicted 10-year ASCVD risk of 20% or more (https://tools.acc.org/ascvd-risk-estimator-plus/).

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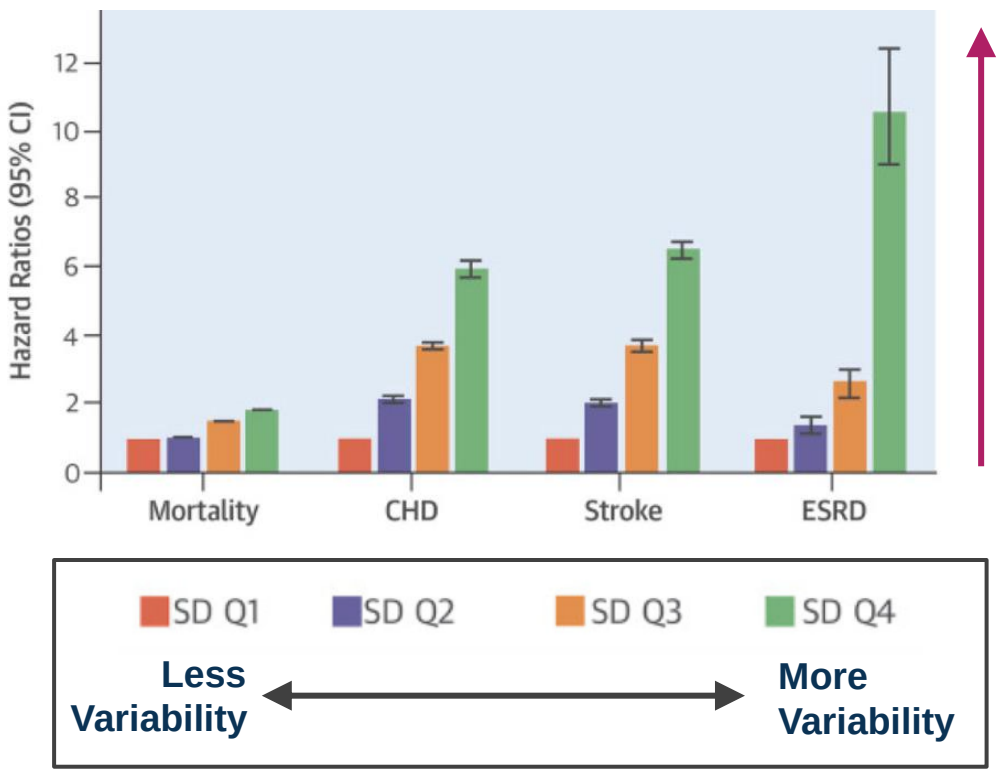
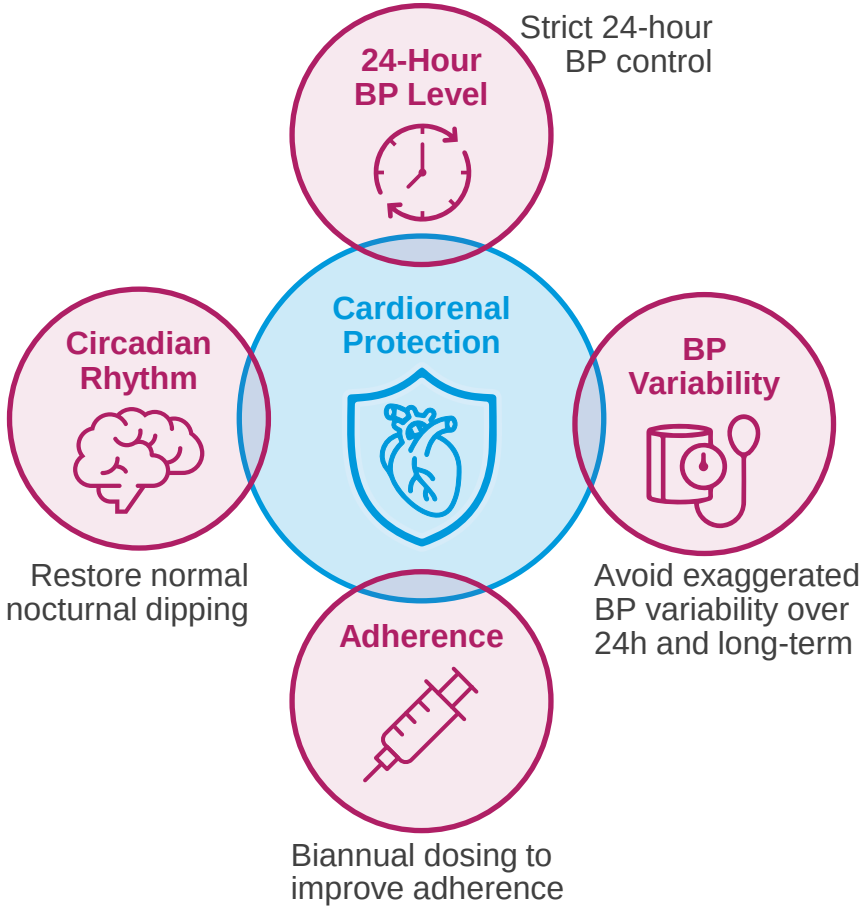
Targeting Continuous Control of Blood Pressure to Improve Outcomes

Excessive SBP variability Increases Cardiovascular and Renal Risk[1]



Zilebesiran: Targeting Continuous Control of BP to Reduce Cardiovascular and Renal Risk[2]



BP, blood pressure; SBP, systolic blood pressure; CV Risk, cardiovascular risk, CHD, coronary heart disease; ESRD, end stage renal disease;
**SD quartiles(<10.3, 10.3 to 12.7, 12.7 to 15.6, and ≥15.6 mm Hg) with all-cause mortality, incident coronary heart disease (CHD), stroke, and ESRD was examined using Cox models*
1. Gosmanova et al. J Am Coll Cardiol. 2016; 68(13) : 1375-1386. 2. Adapted from Kario K. Prog Cardiovasc Dis. 2016;9:262–81

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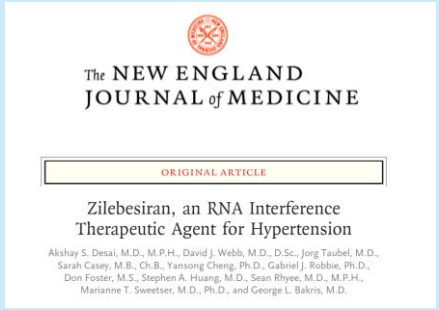
Comprehensive Clinical Development Plan

Exploring Power of Continuous Control of Blood Pressure to Improve Cardiovascular Outcomes

Phase 1

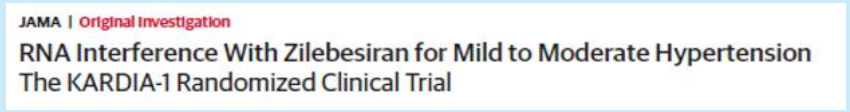
Zilebesiran safety, tolerability, and PK/PD in patients with mild-to-moderate hypertension[1]



Phase 2

KARDIA-1

Zilebesiran monotherapy in pts with mild-to-mod HTN[2]



KARDIA-2

Zilebesiran in combination with single antihypertensive in patients with mild-to-moderate hypertension[3]

Results Presented ACC April 7th, 2024

KARDIA-3

Zilebesiran in combination with ≥2 antihypertensives in high CV risk patients with uncontrolled hypertension

Enrollment Complete YE 2024, data to be presented 2H 2025

Phase 3

Cardiovascular Outcomes Trial (CVOT)

Study in patients with uncontrolled hypertension with established CVD or at high risk of CVD (≥20% ASCVD risk) evaluating composite MACE endpoint

Initiate 2H 2025

Launch with label to reduce cardiovascular morbidity and mortality

Expected ~2030

The safety and efficacy of zilebesiran have not been established or evaluated by the FDA, EMA or any other health authority. Launch assumes positive clinical trial results and regulatory approval. MACE, major adverse cardiovascular event; 1. Desai AS, et al. N Engl J Med. 2023;389:228-238; 2. Bakris GL, et al. JAMA. 2024;331(9):740–749; 3 Bakris et al. ACC Scientific Sessions 2024

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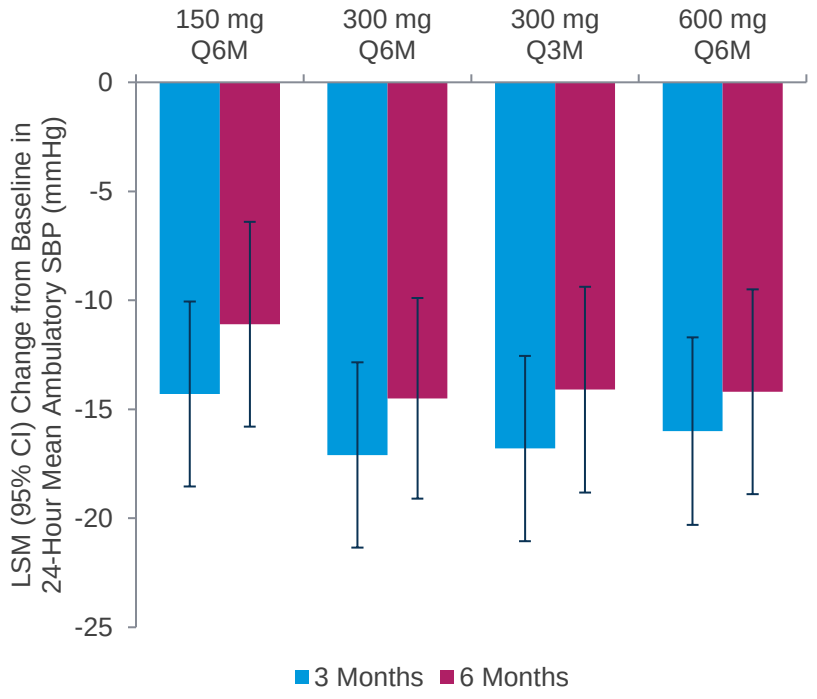
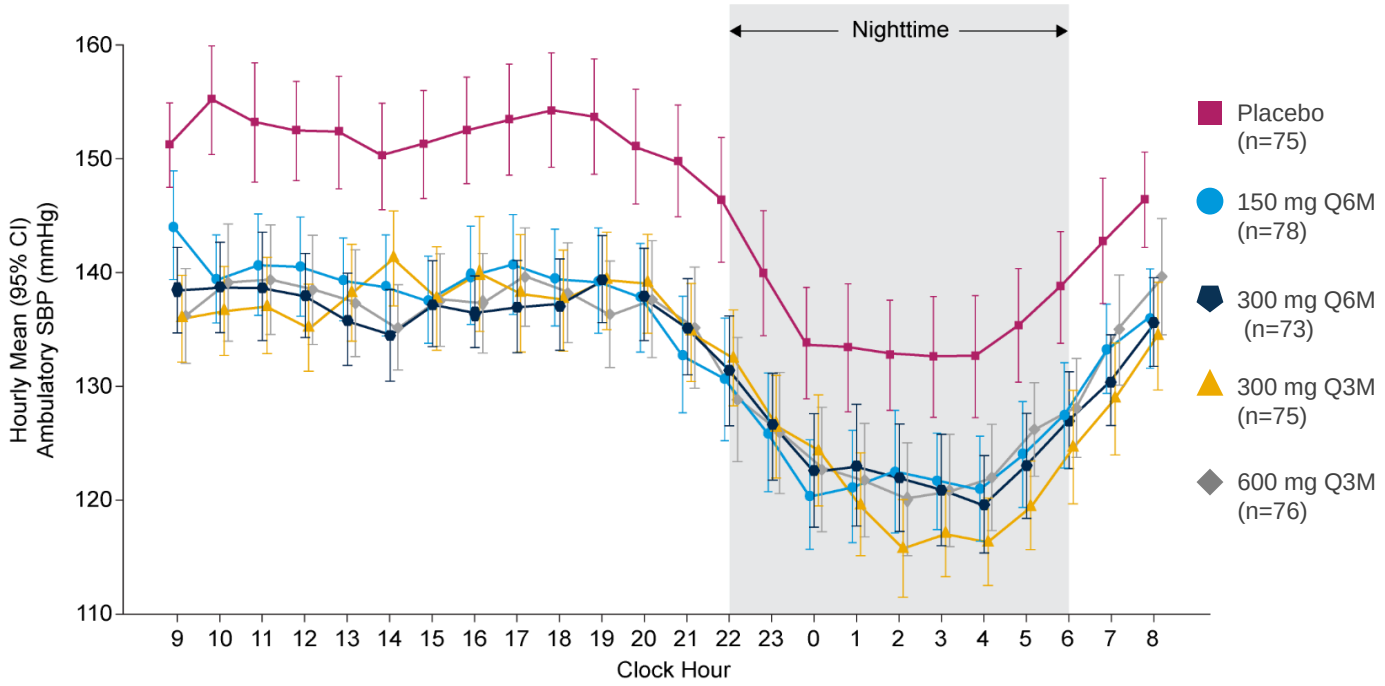
KARDIA 1 Zilebesiran Monotherapy

Continuous Control of Blood Pressure Out to Six Months with Single Doses of Zilebesiran

Robust 24-hour Mean SBP Reduction[1]



24-hour BP Control Maintained Out to Month 6[2]



- Generally well tolerated
- Low incidence of AEs of ISR, hyperkalemia, and hypotension, which were mild or moderate in severity and transient; most did not require therapeutic intervention

p<0.0001; Blood pressure assessments were censored if taken while patients were receiving or within 2 weeks after stopping any rescue medication. Data points are staggered for visualization; Zilebesiran is an investigational RNAi therapeutic for the treatment of hypertension; 1. Bakris et al. AHA Scientific Sessions 2023; [a] Adjusted 95% CIs and p values for the Month 3 primary analysis are based on Dunnett's test; BL, baseline; CI, confidence interval; LSM, least-squares mean; LSMD, LSM difference; Q3M, every 3 months; Q6M, every 6 months; SBP, systolic blood pressure; AEs, adverse events; ISR, injection site reaction. 2. Bakris GL, et al. JAMA. 2024;331(9):740–749

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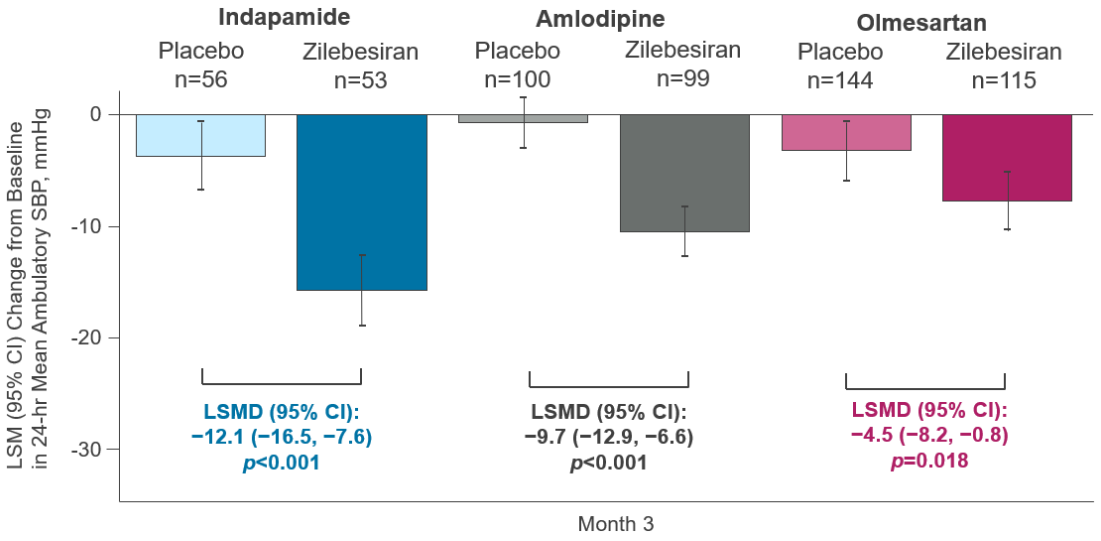
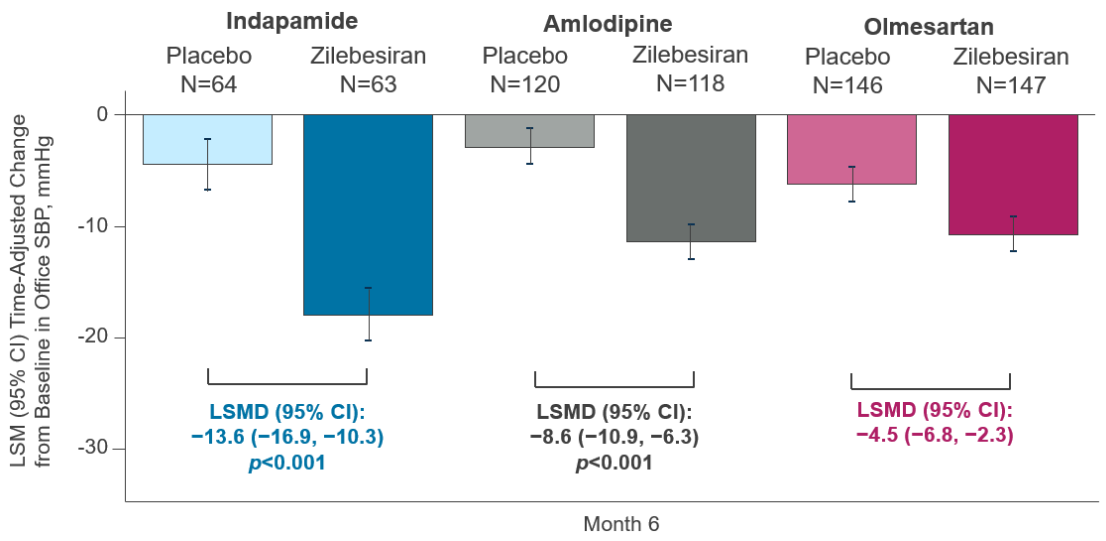
KARDIA$_2$ Zilebesiran in Combination with Standard of Care

Continuous Control of Blood Pressure When Single Doses of Zilebesiran Added to Standard of Care

Primary Endpoint: 24-hr Mean Ambulatory SBP Reduction at Month 3[1]



Secondary Endpoint: Time adjusted Office SBP Reduction at Month 6[1]



- Zilebesiran was generally well tolerated
- Increased rate of mild hyperkalemia, hypotension, and eGFR decline >30% in those treated with zilebesiran vs placebo
  - Most AEs were non-serious, transient, and resolved without intervention

Blood pressure assessed while patients were receiving or within 2 weeks of stopping any rescue medication is censored.

1. Bakris GL et al. ACC Scientific Sessions, April 6-8th 2024.

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KARDIA-3 Phase 2 Combination Study in High CV Risk

Randomized, Double-Blind Study in High CV Risk Patients with Uncontrolled Hypertension

Study Population

Cohort A: eGFR ≥ 45 (N~270)

Cohort B: eGFR 30 – 44 (N~60-120)

Key Inclusion Criteria

- Adult patients with high CV risk, ASCVD or CKD
- Automated office SBP (AOSBP) ≥140 & ≤170 mmHg
- On stable doses of 2+ antihypertensive agents; ACEi/ARB allowed at appropriate therapeutic dose

Screening (45 d)

Maintain stable background antihypertensive regimen

COHORT A
eGFR ≥ 45
(n=90/arm)

- Zilebesiran 600 mg q6M
- Zilebesiran 300 mg q6M
- Placebo

COHORT B
eGFR 30 – 44
(n=15-30/arm)

- Zilebesiran 600 mg q6M
- Zilebesiran 300 mg q6M
- Zilebesiran 150 mg q6M
- Placebo

Treatment Period (6 months)

- Continue background antihypertensive regimen
- aHTN intensification allowed only after M3

Outcomes and Endpoints

Primary Endpoint

- Change at Month 3 in seated office SBP

Secondary Endpoint

- Change at Month 3 and Month 6 in 24 hour mean SBP and DBP, assessed by ABPM
- Change at Month 3 in seated office DBP
- Change at Month 6 in seated office SBP and DBP
- Change in serum AGT

Enrollment Complete
Data presentation 2H 2025

6-month DB treatment period will be followed by a 12-month safety follow up

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KARDIA-3 Phase 2 Combination Study in High CV Risk

Randomized, Double-Blind Study in High CV Risk Patients with Uncontrolled Hypertension

Informing Phase 3 CVOT

- Dose selection
- Inclusion & exclusion criteria
- Power & sample size

6-month DB treatment period will be followed by a 12-month safety follow up

Zilebesiran Phase 3 Cardiovascular Outcomes Trial

Large, Global, Multi-Center, Event Driven Trial with Up to 11,000 Patients

Global Footprint

- Large Global Multi-Center Trial
- >30 Countries
- Up to 11,000 patients

Patient Population

- ≥2 background antihypertensives
- Established CVD or patients at high risk for CVD

Event Driven Trial

- MACE-4 (non-fatal MI, non-fatal stroke, CV death, hospitalization for HF or urgent HF visits)
- Minimum follow-up 2y (duration: ~4.5y)

Strategic Partnerships

Roche

Duke Clinical Research Institute

PPD

Phase 3 CVOT to initiate in 2H 2025

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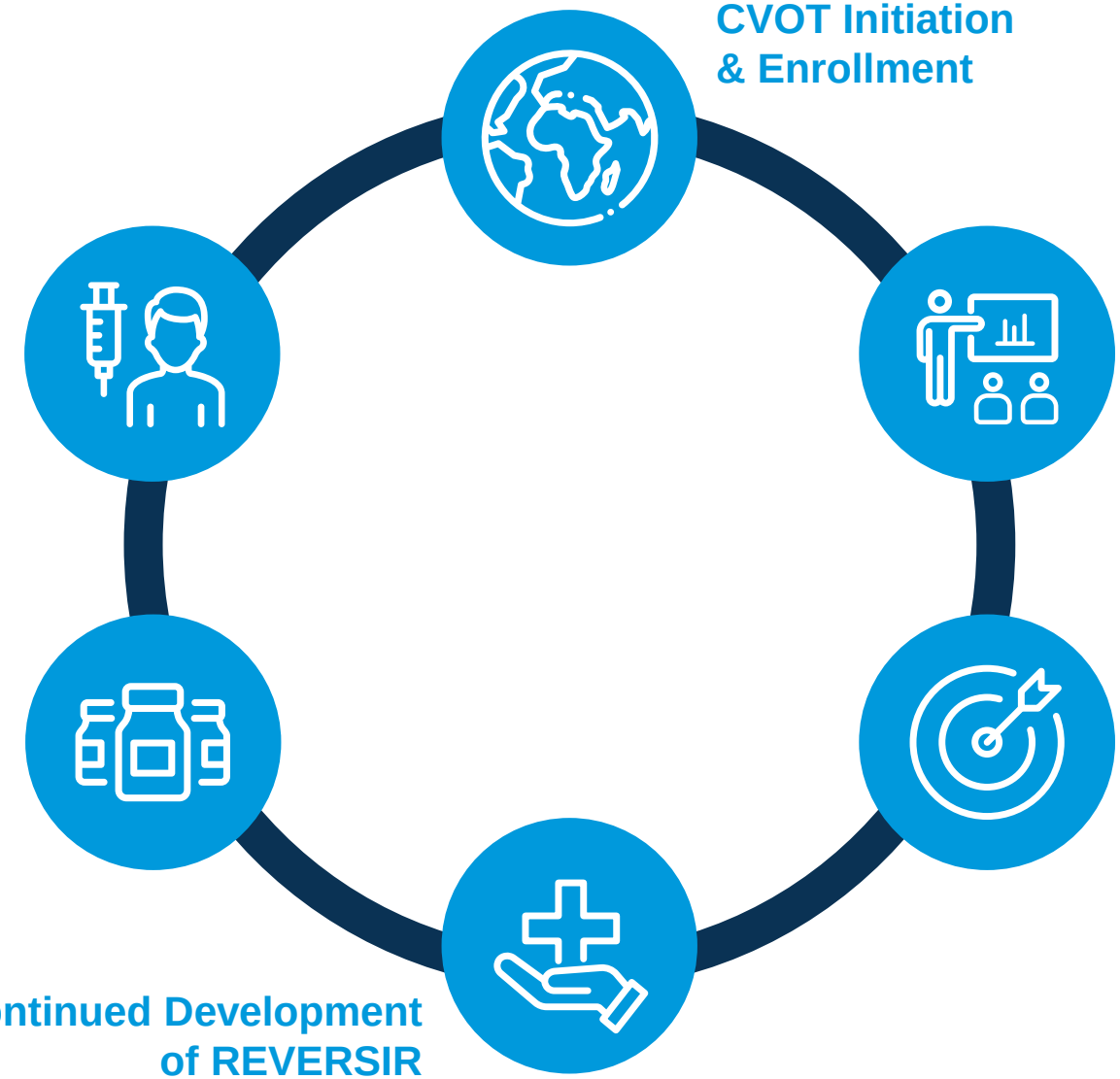
Comprehensive Strategy to Maximize Potential of Zilebesiran



Zilebesiran: Transforming Hypertension Management

Generating Cardiovascular Outcomes Data Will Optimize the Value of Zilebesiran

Zilebesiran Potential Value Proposition

Cardiovascular Outcomes
Clinically significant MACE reduction

Continuous Control of BP
Clinically meaningful BP reduction

Infrequent Dosing
Biannual dosing to optimize adherence

Safety
Generally well tolerated with the ability to combine with other antihypertensives

Payers
Favorable guideline positioning & demonstrates value to healthcare systems

HCPs
Enables rapid uptake & differentiation

Patients
Drives confidence & preference

Zilebesiran is an investigational therapeutic in development for hypertension and improving cardiovascular outcomes. The safety and efficacy of zilebesiran have not been established or approved by the FDA, EMA or any other health authority. The safety and efficacy of zilebesiran are currently being evaluated by these regulatory authorities. This information is intended to provide an overview of the potential clinical profile of zilebesiran for the treatment of hypertension, assuming positive results in ongoing and planned clinical trials.

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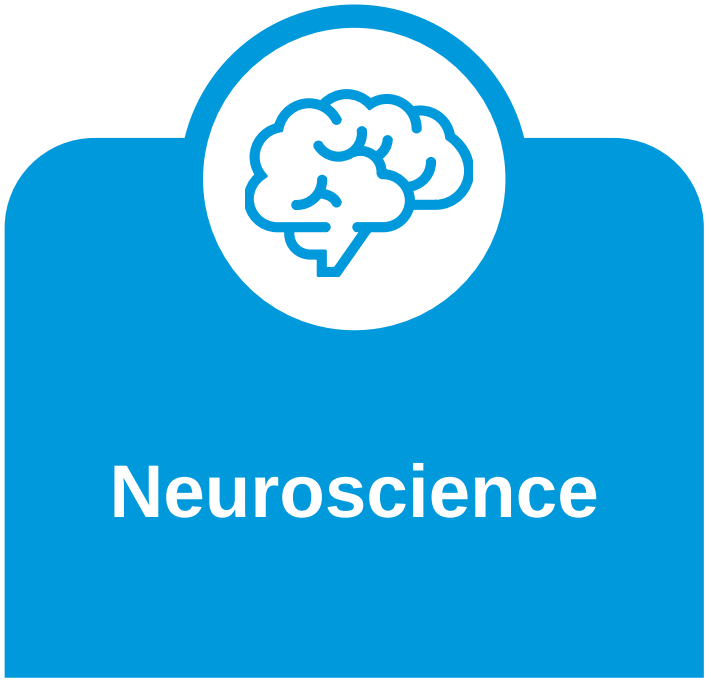
Neuroscience – Mivelsiran: A Differentiated Approach for Alzheimer's Disease and Cerebral Amyloid Angiopathy

Julia Shirvan, M.D., Ph.D.
Senior Director, Mivelsiran Clinical Lead

Key Near- to Midterm Growth Drivers

Potential For Three Blockbuster Franchises



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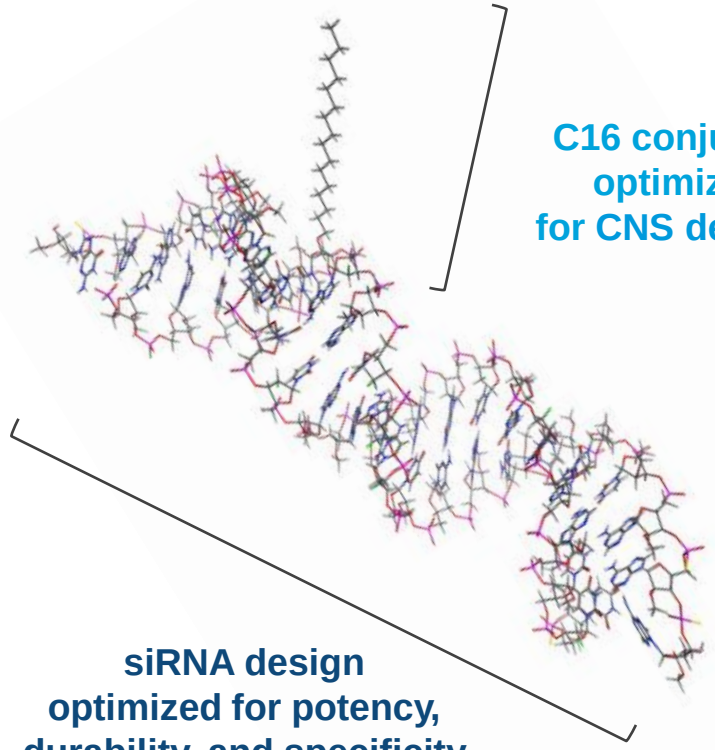
Alnylam Leads Field in Targeting CNS with RNAi

Severe Neurologic Disease is Focus of C-16 Delivery Platform

Neuroscience Pipeline

Asset	Indication	Phase	Partnership Status
Mivelsiran	AD	1	Alnylam, proprietary
	CAA	2	
ALN-HTT02	Huntington's Disease	1	Alnylam-led, Regeneron-partnered
ALN-SOD	SOD1-ALS	1	Regeneron-led, Alnylam-partnered

- Other programs rapidly approaching clinic
- Guided by R&D strategic principles
  - Prioritizes high conviction targets
  - Best-in-class opportunities: potency, durability, safety

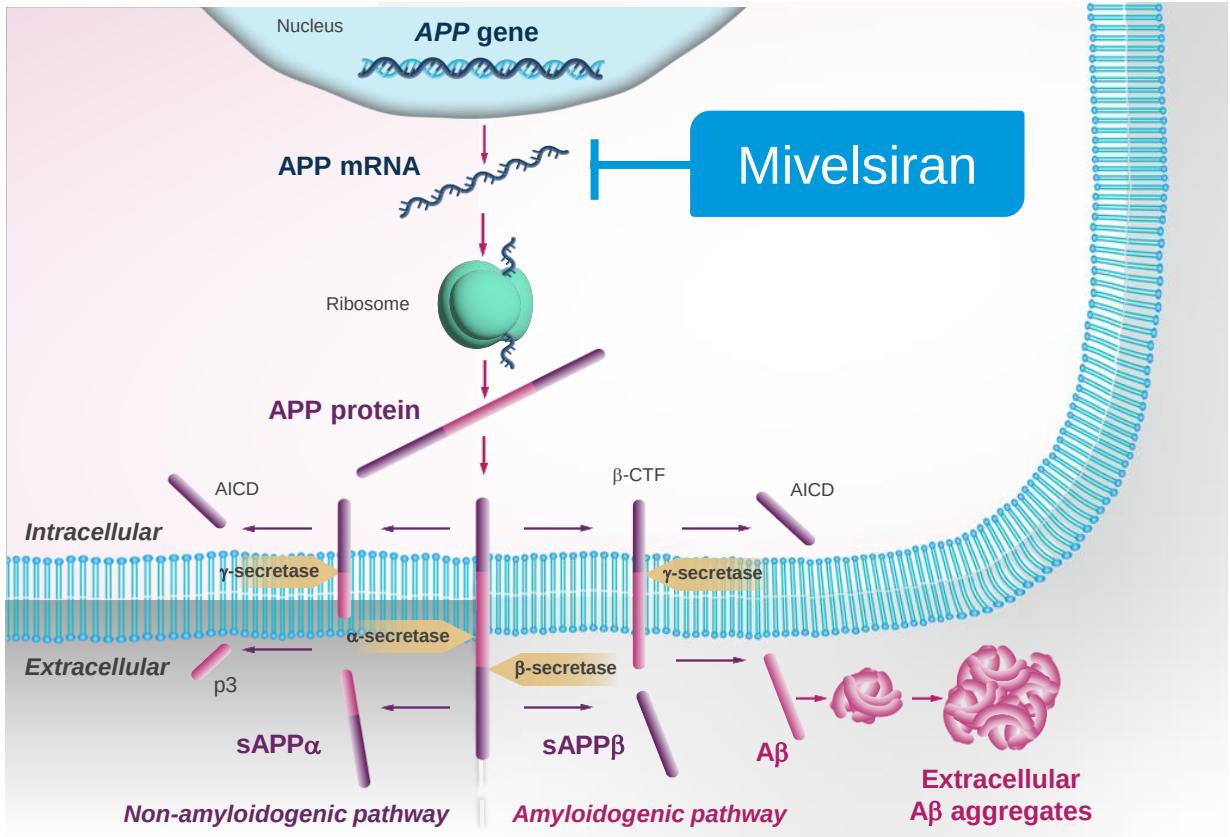


CNS, Central Nervous System; AD, Alzheimer's Disease; CAA, Cerebral Amyloid Angiopathy; SOD1, Superoxide dismutase 1; ALS, Amyotrophic lateral sclerosis

Mivelsiran is Designed to Reduce Amyloid Production

Investigational RNAi Therapeutic Targets Amyloid Precursor Protein (APP)

- Upstream mechanism reduces amyloid production at its source
  - Amyloid-beta precursor protein (APP) mRNA encodes APP
  - APP is precursor to all Aβ peptides
    - Intracellular and extracellular Aβ
- Lowering substrate for amyloid accumulation may enable natural clearance of Aβ



Aβ, amyloid-beta; AICD, activation-induced cell death; APP, amyloid-beta precursor protein; β-CTF, β-C-terminal fragment; CAA, cerebral amyloid angiopathy; sAPP, soluble amyloid precursor protein

Amyloid Pathology Contributes to Severe Neurologic Diseases

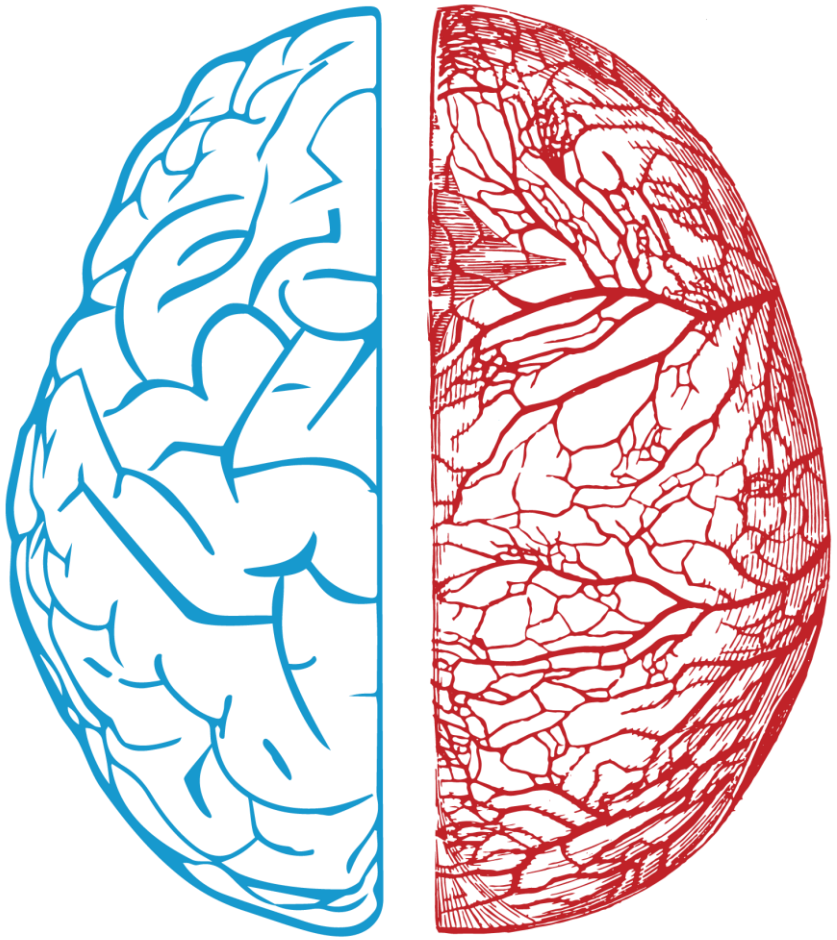
Mivelsiran May Provide Benefit for AD and CAA

Alzheimer's Disease[1-3]

Aβ accumulates in cortex, leading to neurologic decline

Leading cause of dementia, disability, and death

High unmet need for therapies with improved efficacy and safety



Cerebral Amyloid Angiopathy[4-6]

Aβ accumulates in small vessels, leading to cerebral bleeds

Major cause of intracerebral hemorrhage (ICH), the most severe form of stroke

No disease-modifying treatments to reduce risk of ICH

Aβ, amyloid beta; EOAD, Early-onset Alzheimer's disease; CAA, cerebral amyloid angiopathy; ICH, intracerebral hemorrhage; RNAi, RNA interference.

1. ClinicalTrials.gov. NCT05231785. Last updated October 3, 2024. Accessed October 24, 2024. https://clinicaltrials.gov/study/NCT05231785. 2. Scheltens P, et al. Lancet. 2021;397(10284):1577-1590. 3. Alzheimer's Association Report. Alzheimers Dement. 2023;19(4):1598-1695. 4. Jäkel L, et al. Alzheimers Dement. 2022;18(1):10-28. 5. ClinicalTrials.gov. NCT06393712. Last updated October 15, 2024. Accessed October 24, 2024. https://clinicaltrials.gov/study/NCT06393712. 6. Kozberg MG, et al. Int J Stroke. 2021;16(4):356-369.

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Phase 1 Study for Mivelsiran in Early-Onset Alzheimer's Disease (EOAD)

Enhanced Design of Phase 1 Study in EOAD for Mivelsiran

Recent Amendment Increased Duration and Scope of Open-label, Multidose Part B

Study Population

- Mild cognitive impairment or mild dementia with onset before age 65
- MMSE >20
- CDR® global score of 0.5 or 1.0
- Confirmed AD via CSF biomarkers or Aβ-PET

Endpoints

Primary endpoint

- Safety and tolerability

Secondary endpoints

- PK: Mivelsiran CSF and plasma profile
- PD: Change from baseline in CSF sAPPα and sAPPβ

Exploratory endpoints

- Biomarkers of disease progression
  - Part B: Change from baseline in amyloid PET, CSF biomarkers, and CDR-SB at 18M and 36M

Dose Cohorts	N	R (Mivelsiran or Pbo)	Single Ascending Dose (SAD, Part A)	Multiple Ascending Dose (MAD, Part B)
25 mg	6	2:1	→	
35 mg	8	3:1	→	
50 mg	8	3:1	→	
75 mg	6	2:1	Pooled analysis →	
75 mg	8	3:1	Pooled analysis →	
100 mg	9	3:1	→	
Additional SAD cohorts	Forthcoming		⇒	
50mg MAD	10	NA		⟶
Additional MAD cohorts	Forthcoming			⇒
Observation period			Up to 12 months	Up to 42 months

Aβ, amyloid beta; EOAD, Early-onset Alzheimer's disease; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; Pbo, placebo; PET, positron emission tomography; PD, pharmacodynamics; PK, pharmacokinetics; R, randomization; sAPP, soluble amyloid precursor protein; M, months.

Note: The Phase 1 study is subject to a partial clinical hold by the FDA. The FDA has confirmed that multiple-dosing may proceed at doses up to 180 mg given every six months, which covers all dose regimens planned to be explored in Part B. The partial clinical hold remains for higher or more frequent dosing regimens

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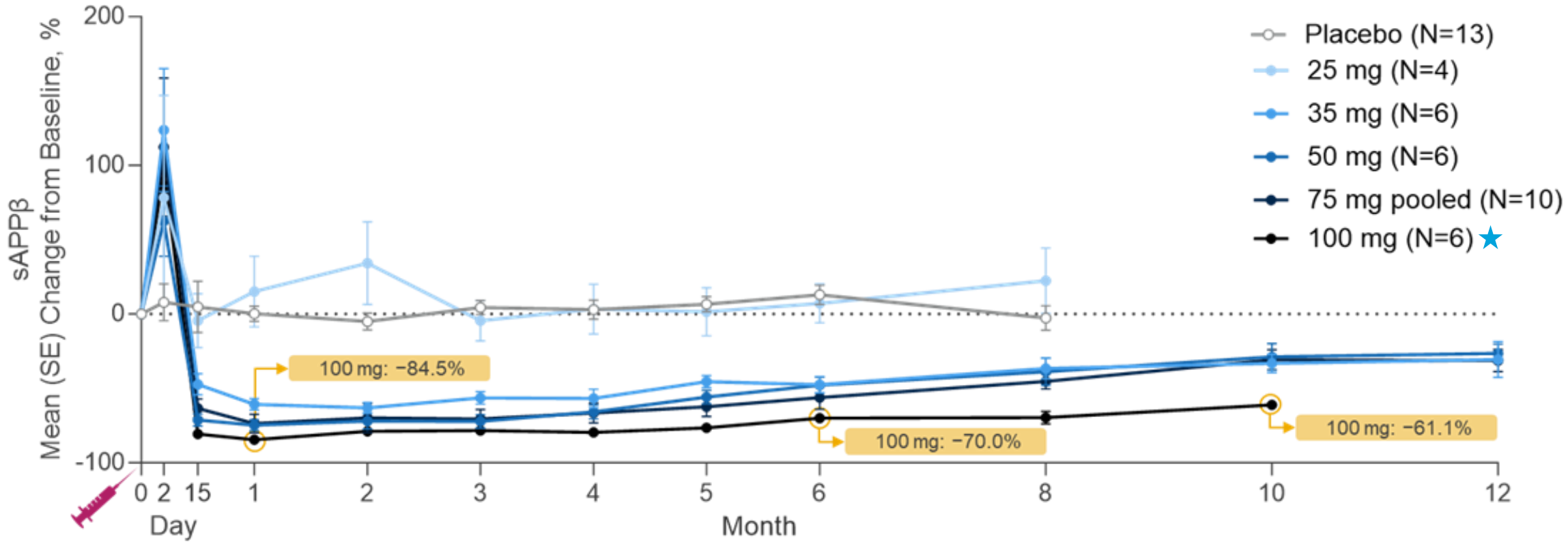
Potent, Durable, Dose-Dependent Reduction of APP in CSF

Robust Target Engagement Supports Infrequent Dosing and Lower Lifetime Drug Exposure

Figure 1. Change from Baseline in CSF sAPPβ Levels for Single Ascending Dose Cohorts



Data shown as of November 20, 2024. Time points with n<3 patients are not plotted. Placebo: n=13, except Day 2 (n=12), Day 15, Months 1–3 and 6 (n=11), Month 4 (n=10), Month 5 (n=9), and Month 8 (n=3); mivelsiran 25 mg: n=4, except Month 8 (n=3); mivelsiran 35 mg: n=6, except Month 8–10 (n=5) and Month 12 (n=4); mivelsiran 50 mg: n= 6, except Months 2 and 4–12 (n=5); mivelsiran 75 mg: n=10, except Day 2 (n=9) and Month 10–12 (n=8); mivelsiran 100 mg: n=6, except Months 2, 4, and 8–10 (n=5).

CSF, cerebrospinal fluid; sAPPβ, soluble amyloid-beta precursor protein beta; SE, standard error.

★ *New data* *Study drug administration*

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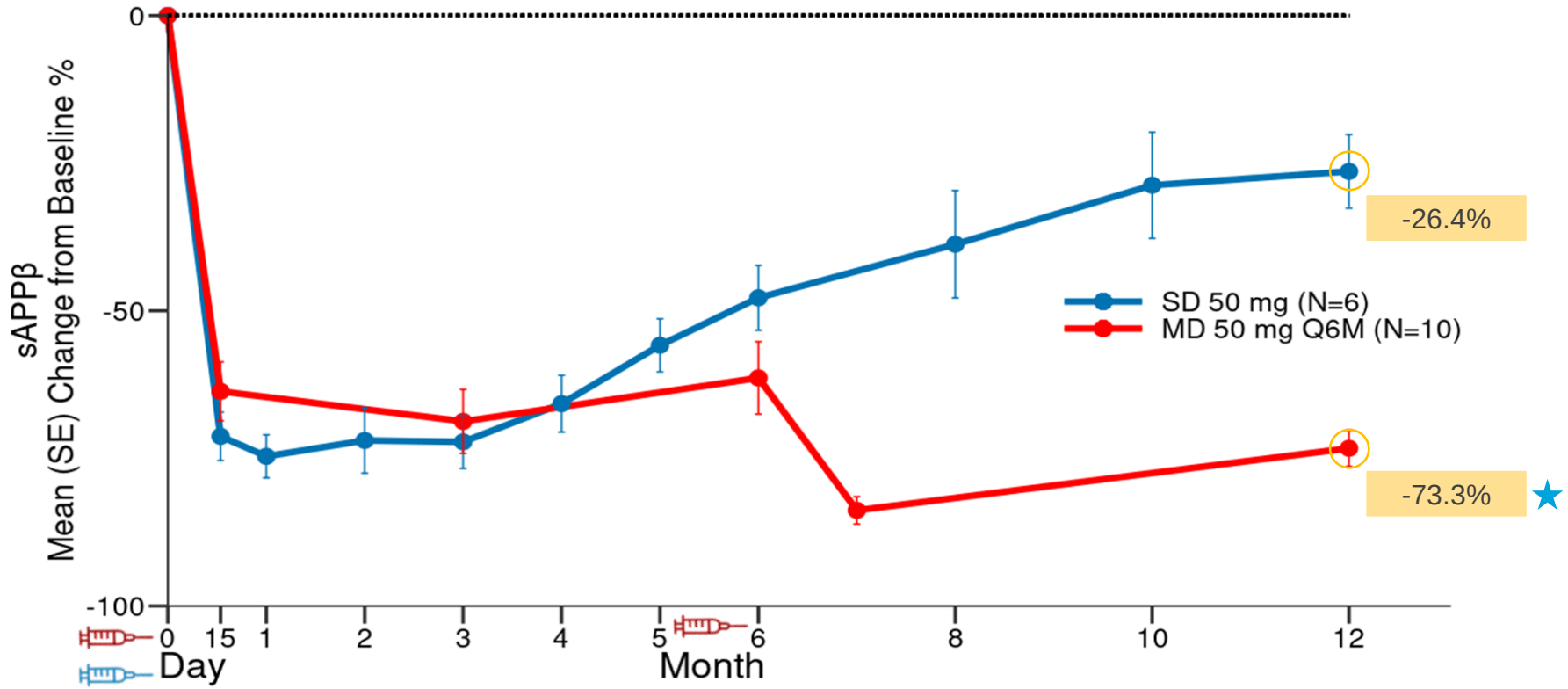
Second Doses Further Reduce APP in CSF

Multidose Data Support Best-in-Class Opportunity for RNAi in Clinical Pharmacology

Figure 1. Change from Baseline in CSF sAPPβ Levels for Single Ascending Dose Cohorts



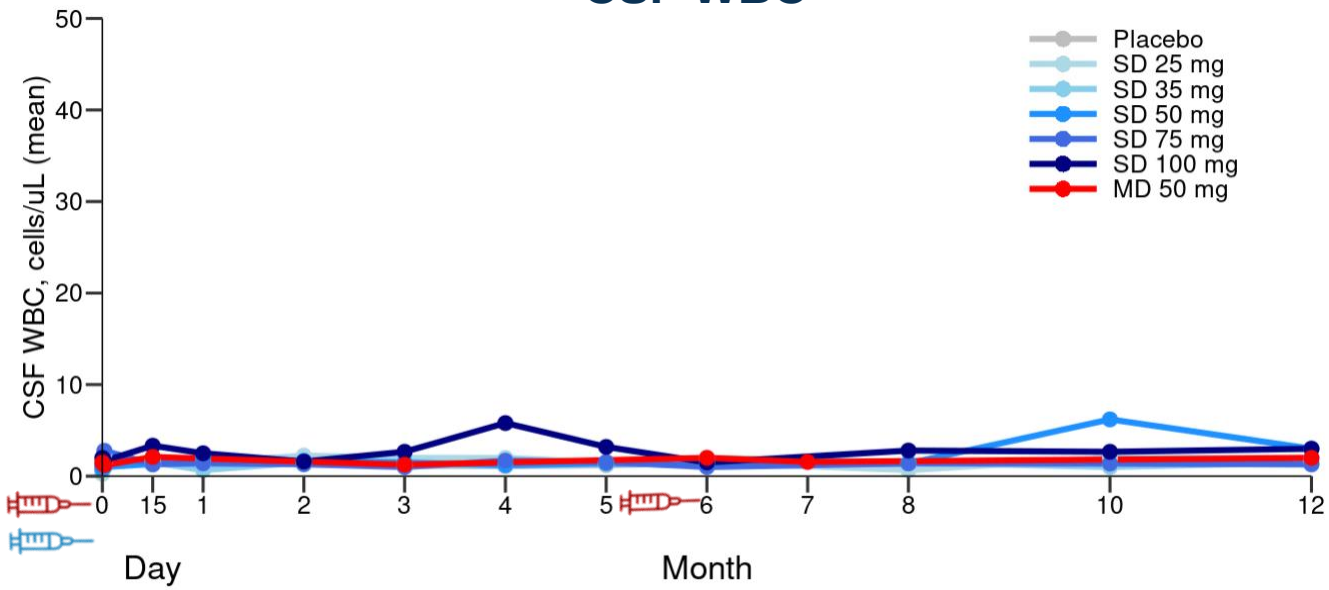
Data shown as of November 20, 2024. Single dose data decreases to n=5 at Month 6. Multidose data decreases to n=9 at Month 7 and n=7 at Month 12.
SD, single dose; MD, multidose; CSF, cerebrospinal fluid; sAPPβ, soluble amyloid-beta precursor protein beta; SE, standard error.; M, month

★ *New data* *SD Study drug administration* *MD Study drug administration*

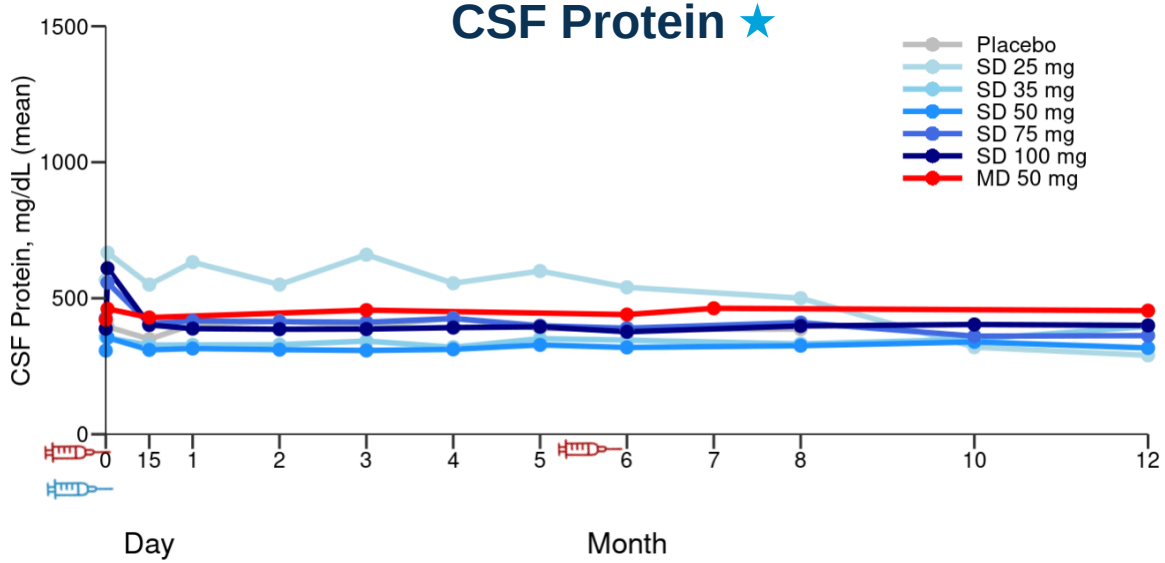
Favorable Safety Profile Supports Best-in-Class Opportunity

No immune response observed after single (SD) or multiple doses (MD)

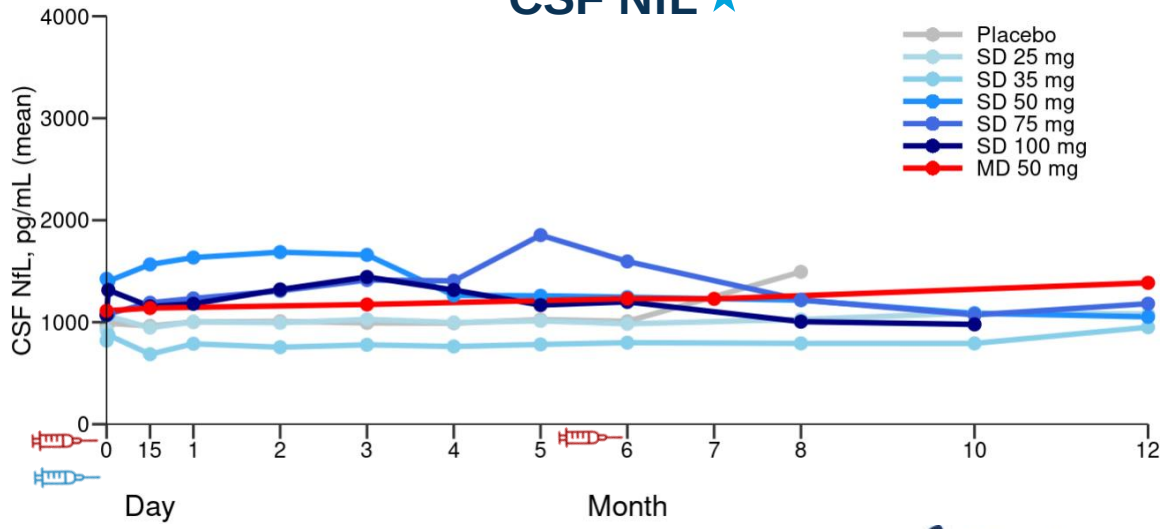
CSF WBC ★



CSF Protein ★



CSF NfL ★



SD, single dose; MD, multidose; CSF, cerebrospinal fluid; WBC, White Blood Cells; NfL, Neurofilament Light chains

Data shown as of November 20, 2024. Means are given by cohort through Month 12 visits; WBC values for 3 patients in MD 50mg and 1 SD 100mg patient were excluded due to confirmed laboratory errors

★ *New data* *SD Study drug administration* *MD Study drug administration*

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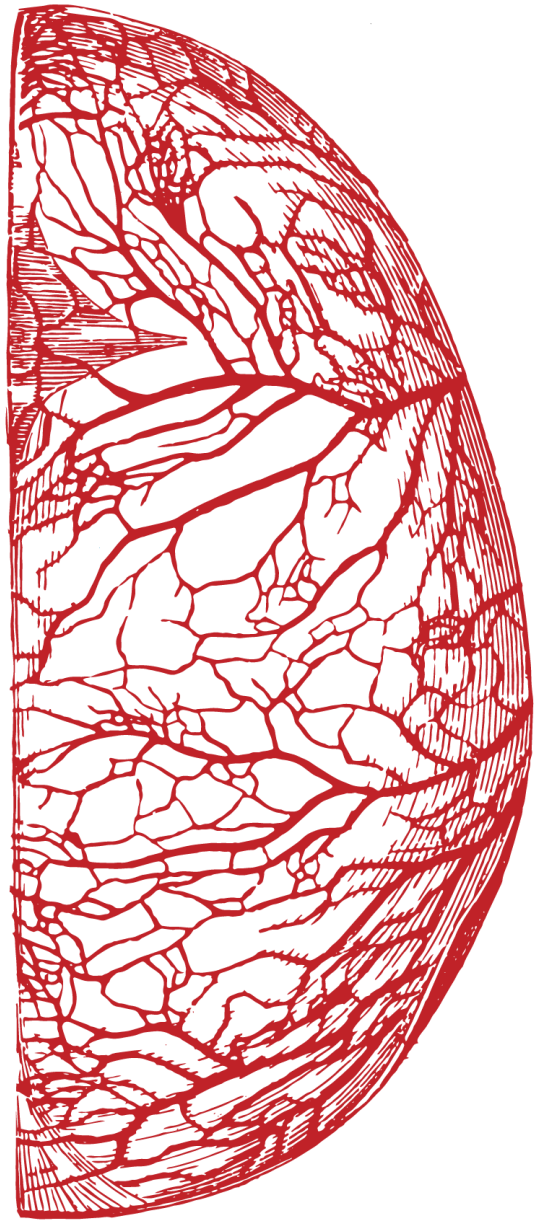
Next Steps in AD Development

Follow the Mechanism to Clearest Path to Proof of Concept

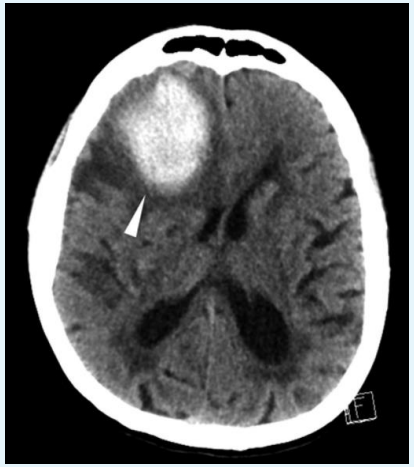
- R&D guiding principles direct work towards goal of Phase 2 study in late 2025
  - Compelling human genetics
  - Best-in-class opportunities
- Considerations in selection of AD population
  - Genetic or sporadic
  - Symptomatic or pre-symptomatic
  - Early or late disease stages
- Enhanced Phase 1 EOAD study data will inform decisions

cAPPricorn-1: Mivelsiran's Phase 2 Study in Cerebral Amyloid Angiopathy (CAA)



CAA is a Severe, Progressive Cerebrovascular Disease

CAA Often Manifests Together with AD



ICH: Life-threatening clinical sequelae of CAA

2nd most common cause of ICH[1,2] (after hypertension)

3x more likely to recur than other causes of ICH[3]

major driver of disability and mortality

CAA and Cognition

- CAA and AD are frequently comorbid in patients
- Microhemorrhage and vascular disease independently contribute to cognitive decline and dementia[4]
- Advanced CAA pathology is independently associated with faster cognitive decline[4]

Aβ, amyloid beta; AD, Alzheimer's disease; APP, amyloid precursor protein; CAA, cerebral amyloid angiopathy; ICH, intracerebral hemorrhage.

1. Koemans EA, et al. Lancet Neurol. 2023;22:632-42. 2. Kozberg MG, et al. Int J Stroke. 2021;16(4):356-69. 3. Charidimou A, et al. Neurology. 2017;89:820-29. 4. Boyle PA, et al. Neurology. 2015 Dec 1; 85(22): 1930–1936.

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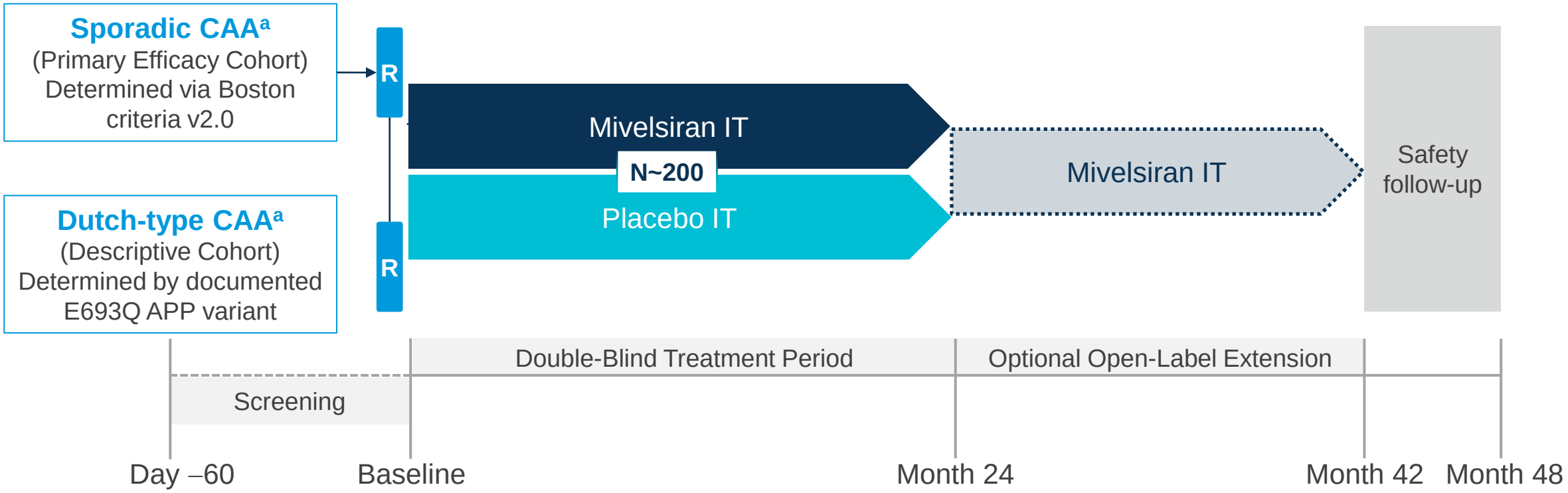
cAPPricorn-1 is Enrolling in North America, Europe, and Australia

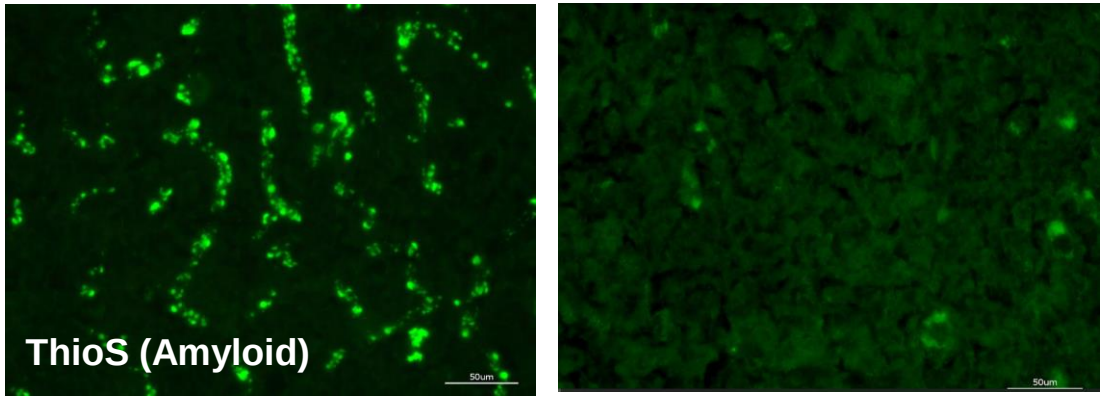
Endpoints Include Hemorrhagic and Non-hemorrhagic Manifestations of CAA



NCT06393712. aSporadic and Dutch-type CAA cohorts will be analyzed separately.
APP, amyloid-beta precursor protein; CAA, cerebral amyloid angiopathy; IT, intrathecal; R, randomization.

APP Lowering Reduced Amyloid Deposition in Preclinical Models

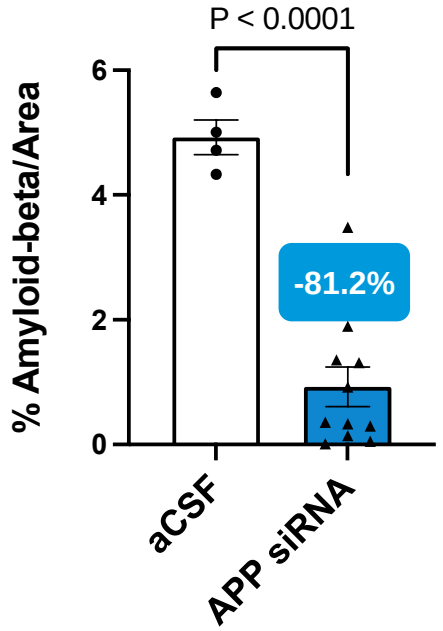
Amyloid deposits in vessels
6 months post-dose



aCSF Control

APP-lowering siRNA

Vascular area occupied by amyloid
6 months post-dose

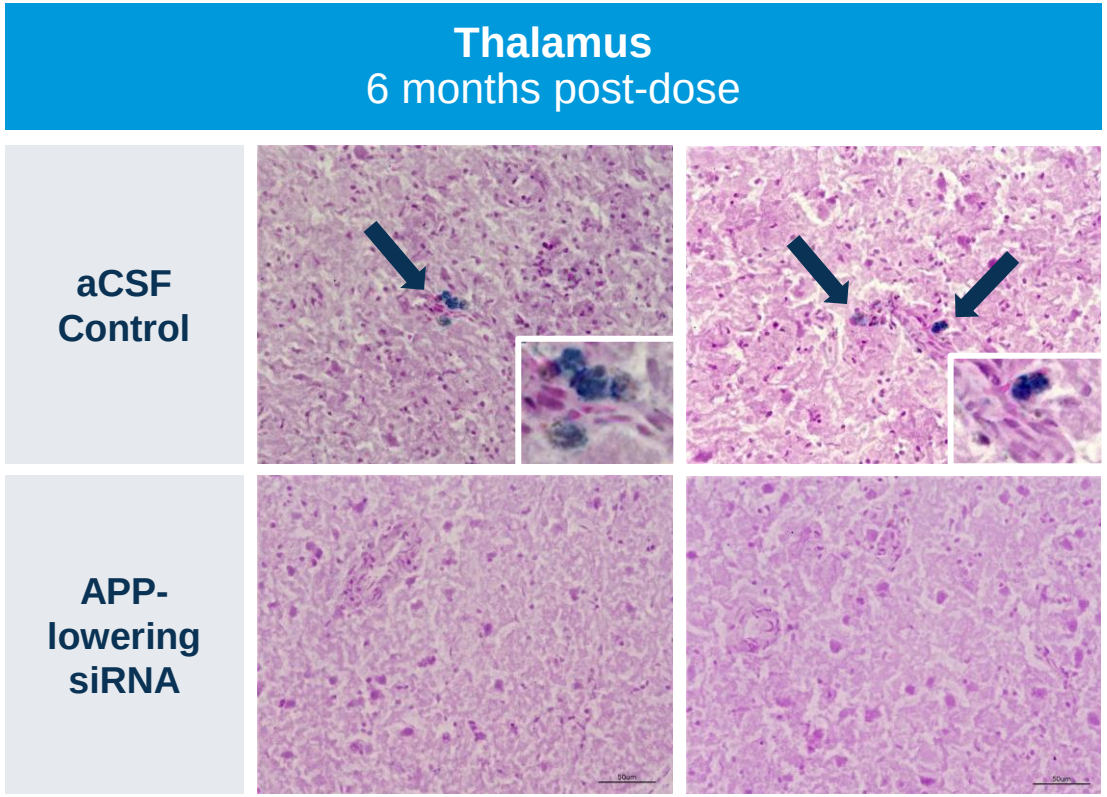


rTg-DI transgenic rats had a significant **reduction in Aβ accumulation in the Hippocampus vasculature** compared with controls

a. Staining greater than background was quantified

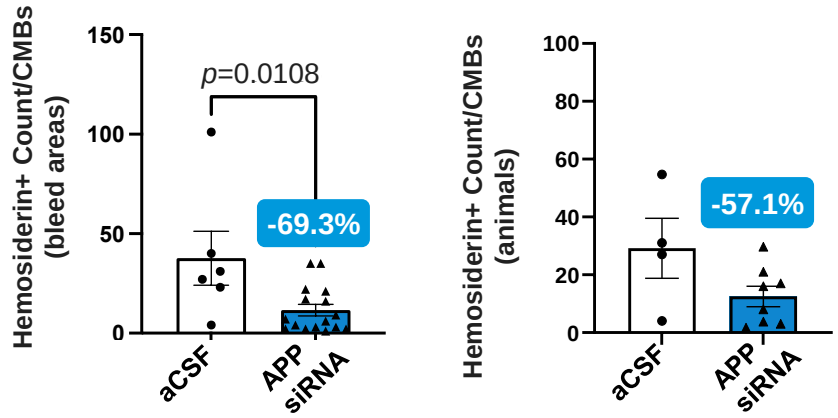
Aβ, amyloid-beta; aCSF, artificial cerebrospinal fluid; APP, amyloid-beta precursor protein; ns, not significant; siRNA, small interfering RNA; ThioS, Thioflavin S.

APP Lowering Reduced the Number and Size of CMBs in Preclinical Models

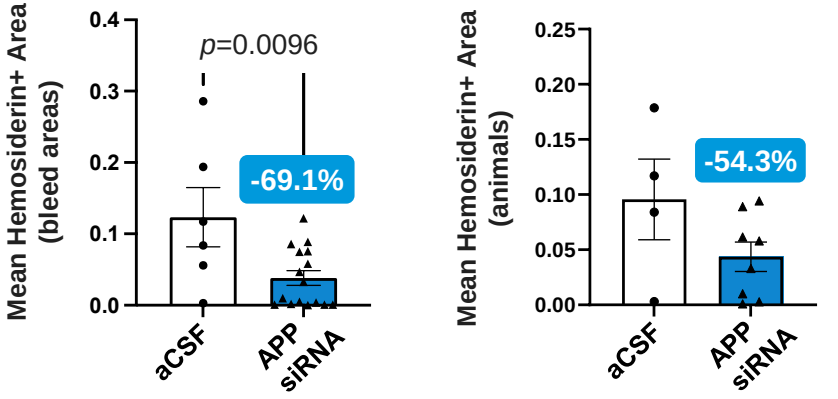


Microhemorrhages (blue) shown with arrows

Cerebral microbleed occurrence[a]



Cerebral microbleed size[a]



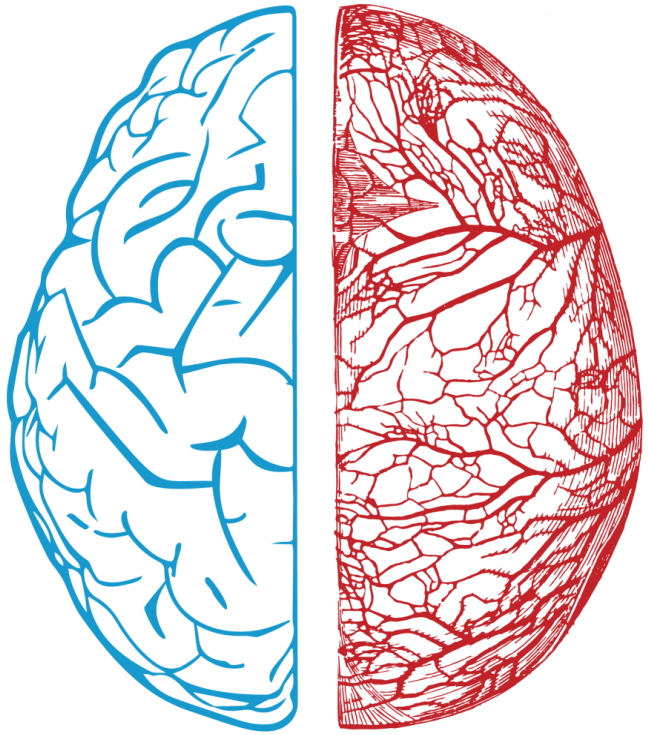
rTg-DI transgenic rats had a **reduction in number of CMBs[b] and mean CMB size** 6 months post-dose compared with controls

a. Left panel: each dot plotted represents an individual bleed area. Right panel: each dot plotted represents a single animal. [b]Number of CMBs per cluster
aCSF, artificial cerebrospinal fluid; APP, amyloid-beta precursor protein; CMB, cerebral microbleed; siRNA, small interfering RNA.

Mivelsiran Leads a Transformative Gene-Targeting CNS Platform

Interim Phase 1 Results Support Potential of RNAi in CNS

- Mivelsiran studies ongoing for 2 severe neurologic diseases: AD and CAA
- Phase 1 EOAD interim data support best-in-class opportunity in clinical pharmacology and safety
  - Robust APP reduction
  - Infrequent dosing
  - Well tolerated
- CNS programs advance based on R&D guiding principles
  - Multiple IND-enabling programs
  - Additional clinical programs: Huntington's Disease and SOD1-ALS



CNS, Central Nervous System; AD, Alzheimer's Disease; CAA, Cerebral Amyloid Angiopathy; EOAD, Early-onset Alzheimer's Disease; SOD1, Superoxide dismutase 1; ALS, Amyotrophic lateral sclerosis

Neuroscience – ALN-HTT02: Hope for Huntington’s Disease Patients

Kevin Sloan, Ph.D.
Vice President, Early Neuroscience Programs

Huntington's Disease

- **Progressive & fatal monogenic neurodegenerative disease** caused by a CAG repeat expansion in the Huntingtin (HTT) gene
  - Autosomal dominant; >100K symptomatic individuals; many more presymptomatic or undiagnosed
  - Physical and mental abilities deteriorate during prime working years; like having ALS, Parkinson's and Alzheimer's combined
- **No disease-modifying therapies exist;** HTT-lowering is the primary therapeutic strategy being pursued in the field
  - Hampered by technical & platform limitations
- **Key question:** Can HTT-lowering provide clinical benefit, while remaining well-tolerated?

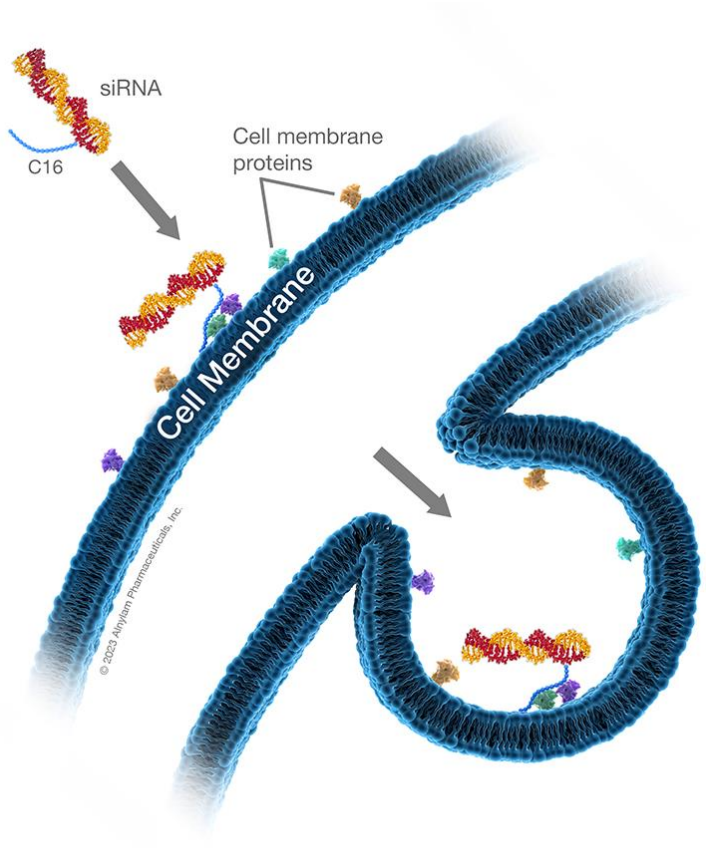
Charles Sabine & John Sabine
(patient/advocate & patient)

Nancy Wexler & patient
(patient & HD research pioneer)

ALN-HTT02 Program

Leverages Same C16-siRNA Delivery Platform as Mivelsiran

- **Vision:** ALN-HTT02 will slow or halt disease progression to improve quality of life for patients
  - Best-in-class disease modifying therapeutic
- **Differentiation vs. other HTT-lowering approaches:**
  - Inclusive exon 1 targeting strategy
  - Potential to fully explore deep & widespread HTT-lowering
  - Safety & durability of C16-siRNA delivery platform
- **Opportunity:** Aspiration to move from Ph1b directly into a Ph2/3 registrational study
  - Potential for accelerated approval



Note: ALN-HTT02 is an investigational therapeutic in development for Huntington's Disease. The safety and efficacy of ALN-HTT02 have not been established or approved by the FDA, EMA or any other health authority. Safety and efficacy of ALN-HTT02 are currently being evaluated by these regulatory authorities.

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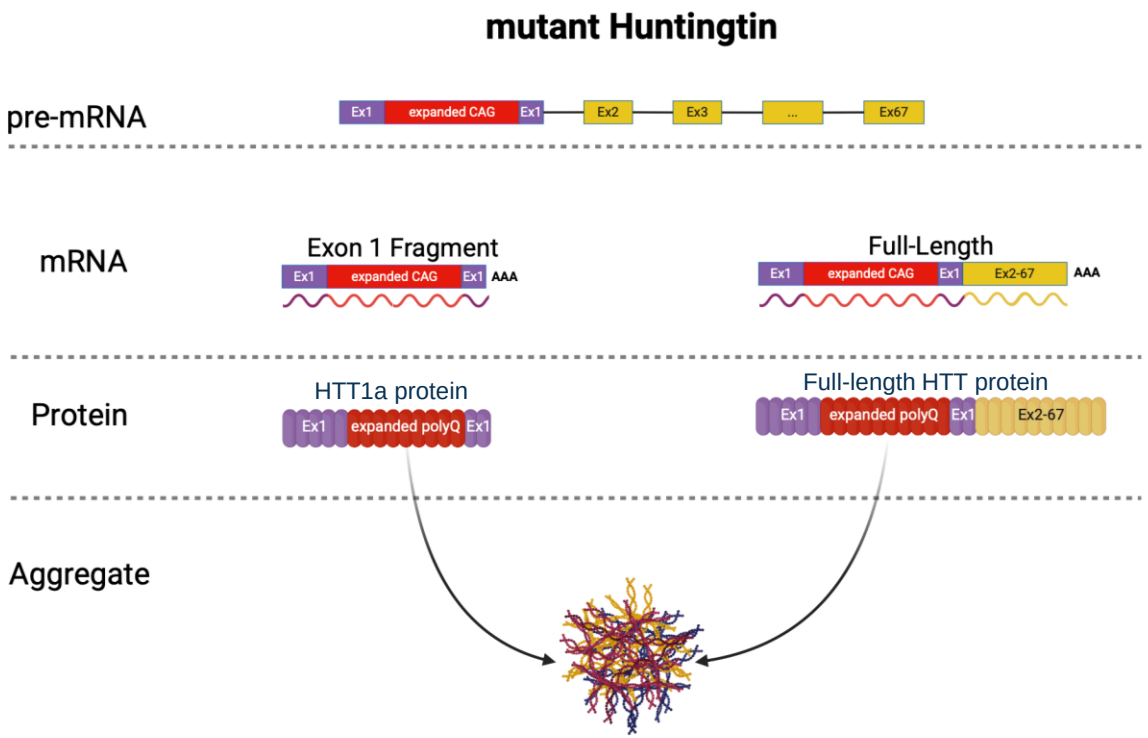
HTT is a Genetically Validated Target for Huntington's Disease[1]



- **Huntington's disease (HD) is progressive and fatal, driven by mutant huntingtin (HTT)[1,3]**
  - Toxic, broadly disruptive gain of function
  - CAG repeat expansion; somatic instability
  - HTT1a expression; protein aggregation
  - Widespread neurodegeneration
- **Both full-length mutant HTT and shorter HTT1a (exon 1) splice isoform likely contribute to disease pathology[2]**
- **HTT-lowering may alter the course of HD progression[1,4]**
  - Safety and extent of achievable clinical benefit have yet to be elucidated

CAG, cytosine-adenine-guanine; HD, Huntington's disease; HTT, huntingtin.

1. Tabrizi SJ, et al. Lancet Neurol. 2022;21(7):645-658. 2. Sampaio C. Parkinsonism Relat Disord. 2024;122:106049. 3. Bates GP, et al. Nat Rev Dis Primers. 2015;1:15005. 4. Ferguson MW, et al. J Cent Nerv Syst Dis. 2022;14:11795735221092517.

The Case for Targeting Exon 1

HTT1a Isoform Links CAG Repeat Expansion to Disease Pathology

CAG repeat expansion
(somatic instability)

- **Somatic instability leads to expansion of CAG repeats over time**[1]
  - Longer repeats correlate with increasing transcriptional dysregulation in human brain[1]

Expression of HTT1a
(aberrant splicing)

- **Expanded CAG repeats drive aberrant splicing, yielding expression of a shorter HTT1a (exon 1)** transcript and protein[2,3,4]
  - Longer repeats correlate with increasing expression of HTT1a[5]

Protein aggregation
Dysregulated gene expression

- **HTT1a protein is aggregation prone and highly toxic** in mouse models[6]

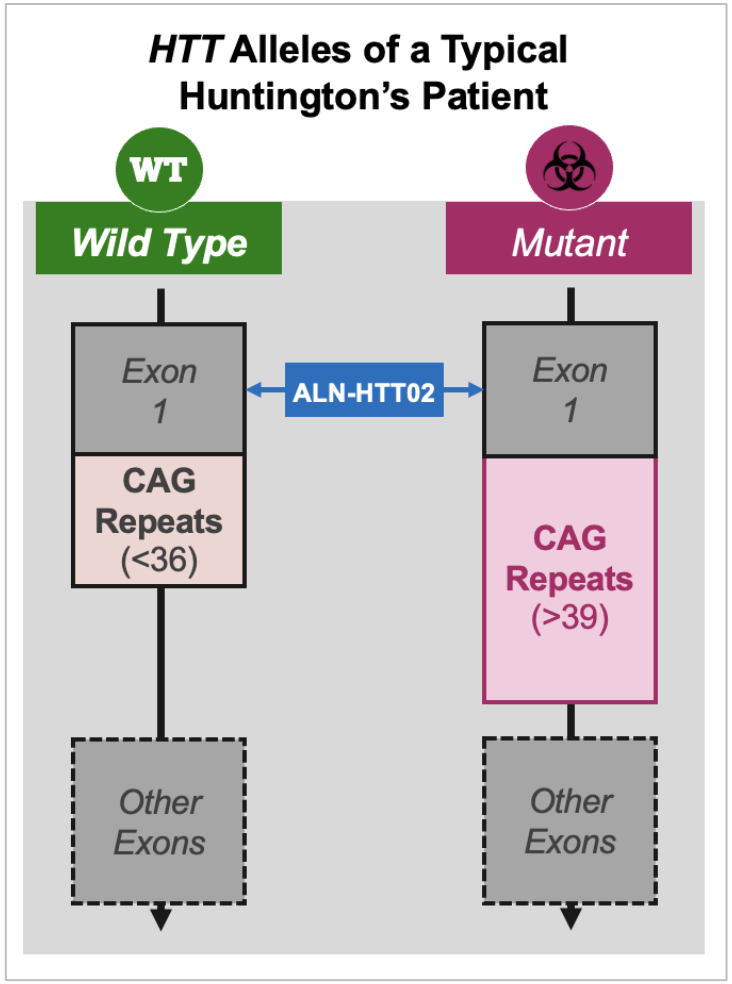
Neurodegeneration & brain atrophy

- **HTT-lowering approaches that include HTT1a prevent protein aggregation & transcriptional dysregulation** in mouse models[7,8]
  - Approaches that lower only full-length HTT are less effective[7,8]

[1]Handsaker, Cell 2025 https://doi.org/10.1016/j.cell.2024.11.038; [2]Sathasivam, PNAS 2013 https://doi.org/10.1073/pnas.1221891110; [3]Hoschek, Molec Med 2015 https://doi.org/10.1186/s10020-024-00801-2; [4]Sapp, bioRxiv 2024 https://doi.org/10.1101/2024.12.31.630891; [5]Landles, Brain Com 2024 https://doi.org/10.1093/braincomms/fcae410; [6]Neueder, Sci Rep 2017 https://doi.org/10.1038/s41598-017-01510-z; [7]Bates G, et al. Oral presentation at the Hereditary Disease Foundation (HDF) Symposium, August 7-10, 2024, Cambridge, MA; [8]Carroll J, Oral presentation at the Hereditary Disease Foundation (HDF) Symposium, August 7-10, 2024, Cambridge, MA

Alnylam

ALN-HTT02 is an Investigational RNAi Therapeutic Targeting Exon 1 of HTT



Therapeutic Hypothesis

- ALN-HTT02 targets a conserved mRNA sequence within exon 1
- Designed to reduce expression of all HTT protein species
  - Including shorter HTT1a fragments implicated in disease pathology
- By reducing all forms of mutant HTT, ALN-HTT02 has the potential to limit toxic gain of function activities and alter the course of HD progression

CAG, cytosine-adenine-guanine; CNS, central nervous system; HD, Huntington's disease; HTT, huntingtin; mHTT, mutant huntingtin; mRNA, messenger RNA; siRNA, small interfering RNA; wtHTT, wild-type huntingtin.

Biological mechanisms and therapeutics in Huntington's disease

Professor Sarah J Tabrizi MD PhD FMedSci FRS
Director UCL Huntington's disease Centre
UCL Institute of Neurology,
National Hospital for Neurology and Neurosurgery,
Queen Square, London

Alnylam R&D Investor Day
25th Feb 2025

UCL

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Huntington's Disease

- Universally fatal, usually in mid-adult life
- Monogenic, fully penetrant
- No effective treatments

Polyglutamine

- Mutant huntingtin protein (mHTT)
- New mechanisms of pathogenesis

Juvenile HD

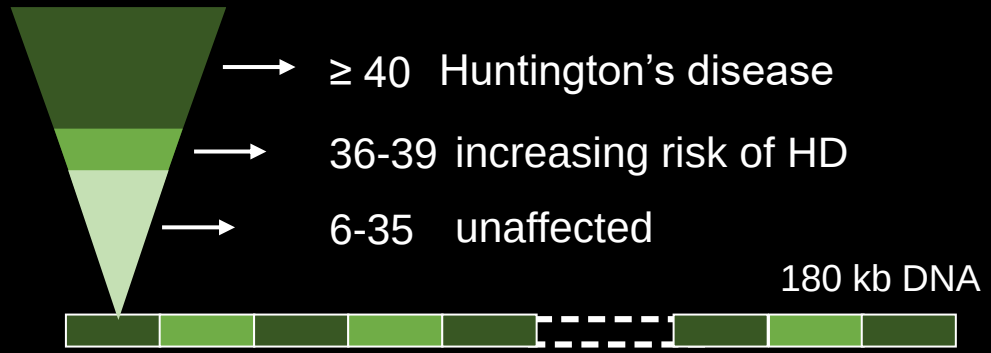
Huntington's disease – a huge unmet need

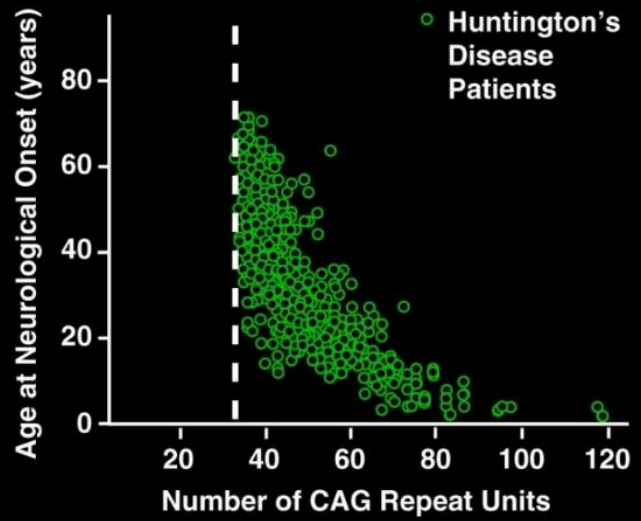
- Common 'rare' disorder – Ibanez et al Nature Medicine 2024 – 1 in 4109 worldwide, much more common than previously thought
- Orphan disease designation
- Critical Path RSC in HD helps facilitate discussions with regulators early
- Huge health economic burden - costs 100s millions of dollars worldwide

The molecular basis of Huntington's disease – rate driver

Step 1

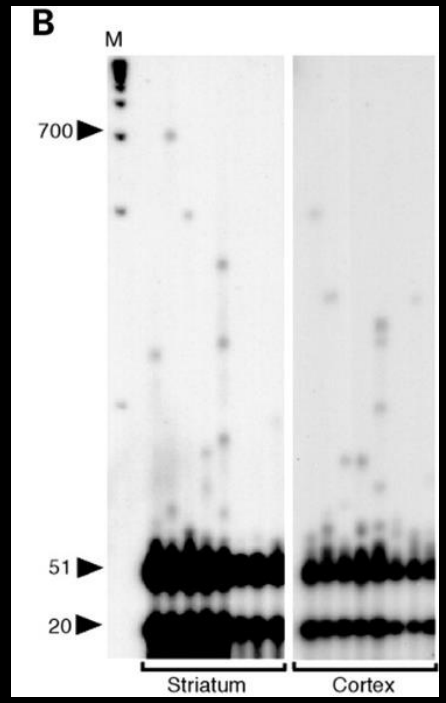
CAG CAG CAG….





Somatic CAG repeat expansion

Expansions to repeats of several 100 CAGs occur in brain regions



Genetic modifiers in DNA damage repair pathways act on somatic CAG expansion

Somatic CAG repeat expansion drives the age at disease onset and rate of disease progression for Huntington's disease

The molecular basis of Huntington's disease

Step 2: HTT Exon 1 and N-terminal proteolytic fragments (toxicity driver)

CAG CAG CAG….

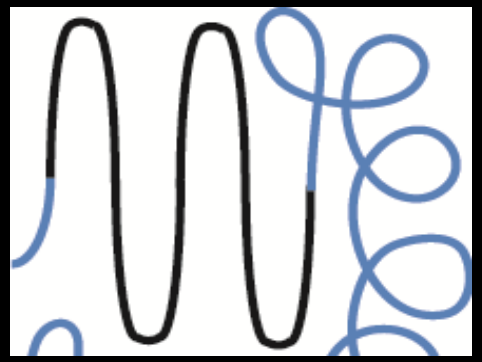
HTT gene

1 2 3 66 67

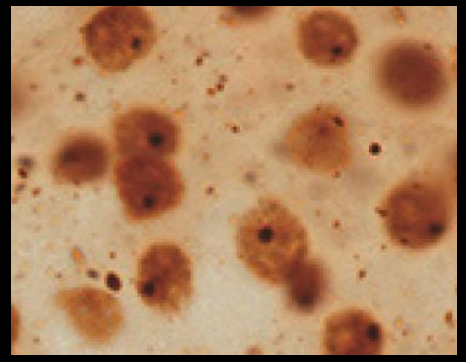
Increasing CAG repeat somatic expansion -

1 *HTT1a* mRNA

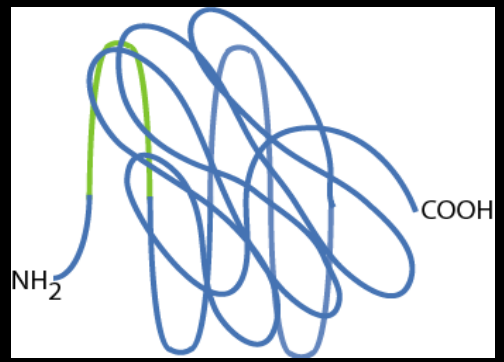
1 67 *HTT* mRNA



HTT1a/ Exon1 protein



Cells with aggregated HTT

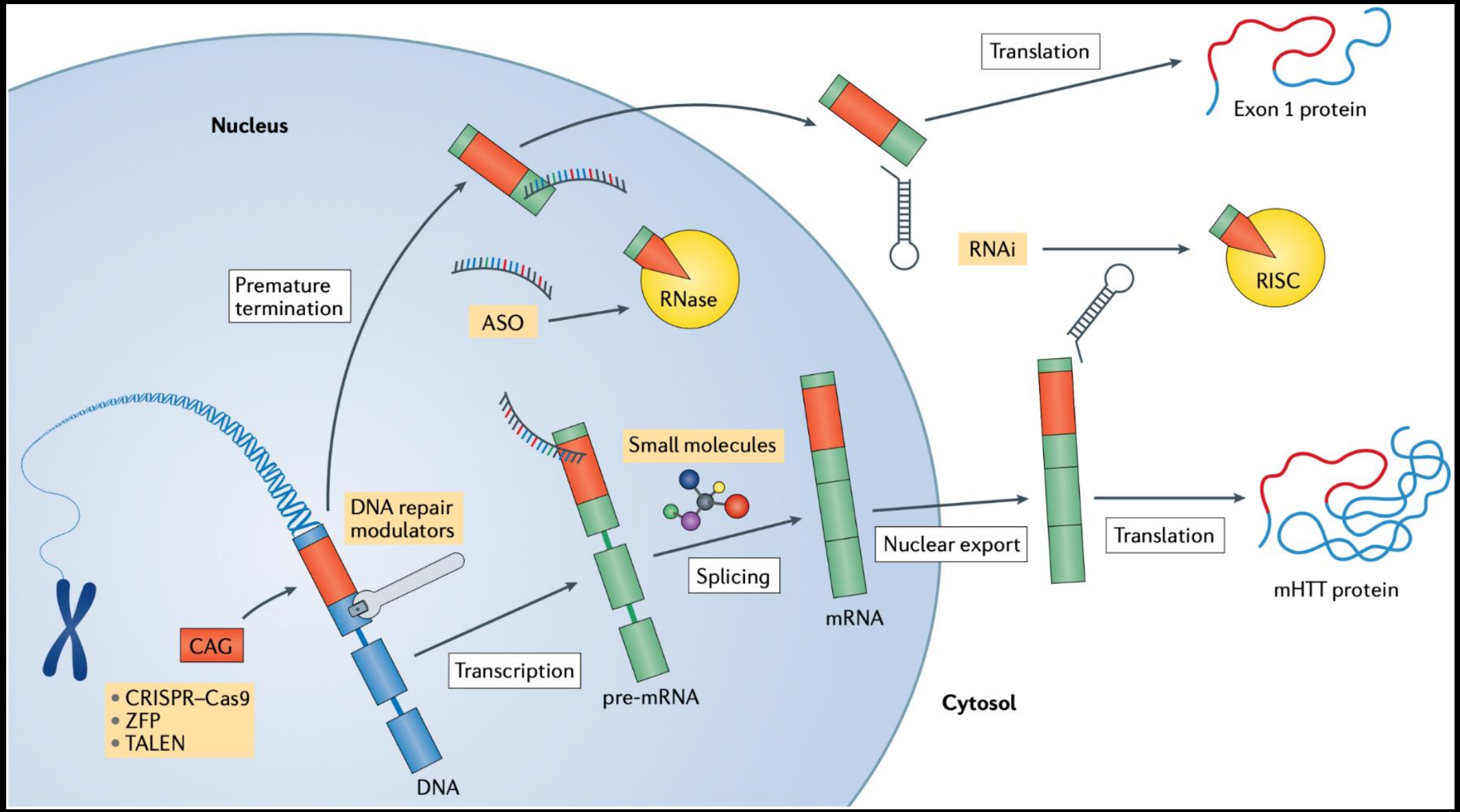


HTT protein

Proteolytic fragments

Edited from Gill Bates

Overview of potential DM therapies in development



Tabrizi, Flower, Ross and Wild Nature Reviews Neurology 2020

HTT lowering as a therapeutic for Huntington’s disease

RNA interference improves motor and neuropathological abnormalities in a Huntington's disease mouse model

Scott Q. Harper*†, Patrick D. Staber*†, Xiaohua He*†, Steven L. Eliason*†, Inês H. Martins*†, Qinwen Mao*†, Linda Yang‡, Robert M. Kotin‡, Henry L. Paulson*§, and Beverly L. Davidson*†§¶‖

Intrastriatal rAAV-Mediated Delivery of Anti-huntingtin shRNAs Induces Partial Reversal of Disease Progression in R6/1 Huntington's Disease Transgenic Mice

Edgardo Rodriguez-Lebron,[1,*] Eileen M. Denovan-Wright,[2] Kevin Nash,[3] Alfred S. Lewin,[3] and Ronald J. Mandel[1,†]

Silencing Mutant Huntingtin by Adeno-Associated Virus-Mediated RNA Interference Ameliorates Disease Manifestations in the YAC128 Mouse Model of Huntington's Disease

Lisa M. Stanek, Sergio P. Sardi, Bryan Mastis, Amy R. Richards, Christopher M. Treleaven, Tatyana Taksir, Kuma Misra, Seng H. Cheng, and Lamya S. Shihabuddin

Therapeutic silencing of mutant huntingtin with siRNA attenuates striatal and cortical neuropathology and behavioral deficits

M. DiFiglia*, M. Sena-Esteves*, K. Chase†, E. Sapp*, E. Pfister†, M. Sass†, J. Yoder*, P. Reeves*, R. K. Pandey‡, K. G. Rajeev‡, M. Manoharan‡, D. W. Y. Sah‡, P. D. Zamore§, and N. Aronin†¶

Nonallele-specific Silencing of Mutant and Wild-type Huntingtin Demonstrates Therapeutic Efficacy in Huntington's Disease Mice

Ryan L Boudreau[1], Jodi L McBride[1], Inês Martins[1], Shihao Shen[2], Yi Xing[1,3], Barrie J Carter[4] and Beverly L Davidson[1,5,6]

Sustained Therapeutic Reversal of Huntington's Disease by Transient Repression of Huntingtin Synthesis

Holly B. Kordasiewicz,[1] Lisa M. Stanek,[2] Edward V. Wancewicz,[3] Curt Mazur,[3] Melissa M. McAlonis,[1] Kimberly A. Pytel,[1] Jonathan W. Artates,[1] Andreas Weiss,[4] Seng H. Cheng,[2] Lamya S. Shihabuddin,[2] Gene Hung,[3] C. Frank Bennett,[3] and Don W. Cleveland[1,*]

Antisense Oligonucleotide-Mediated Correction of Transcriptional Dysregulation is Correlated with Behavioral Benefits in the YAC128 Mouse Model of Huntington's Disease

Lisa M. Stanek[a,*], Wendy Yang[a], Stuart Angus[a], Pablo S. Sardi[a], Michael R. Hayden[b], Gene H. Hung[c], C. Frank Bennett[c], Seng H. Cheng[a] and Lamya S. Shihabuddin[a]

Reversal of Neuropathology and Motor Dysfunction in a Conditional Model of Huntington's Disease

Ai Yamamoto,† José J. Lucas,†‡ and René Hen*

Intrajugular Vein Delivery of AAV9-RNAi Prevents Neuropathological Changes and Weight Loss in Huntington's Disease Mice

Brett D Dufour[1,2], Catherine A Smith[2], Randall L Clark[2], Timothy R Walker[2] and Jodi L McBride[1,2,3]

Neuronal targets for reducing mutant huntingtin expression to ameliorate disease in a mouse model of Huntington's disease

Nan Wang[1,2,9], Michelle Gray[1,2,8,9], Xiao-Hong Lu[1,2], Jeffrey P Cantle[1,2], Sandra M Holley[2,3], Erin Greiner[1,2,4], Xiaofeng Gu[1,2], Dyna Shirasaki[1,2,4], Carlos Cepeda[2,3], Yuqing Li[5], Hongwei Dong[6,8], Michael S Levine[2,3] & X William Yang[1,2,7]

CRISPR/Cas9-mediated gene editing ameliorates neurotoxicity in mouse model of Huntington's disease

Su Yang, … , Shihua Li, Xiao-Jiang Li

Targeting CAG repeat RNAs reduces Huntington's disease phenotype independently of huntingtin levels

Laura Rué, … , Xavier Estivill, Eulàlia Martí

Huntingtin suppression restores cognitive function in a mouse model of Huntington's disease

Amber L. Southwell[1]*, Holly B. Kordasiewicz[2], Douglas Langbehn[3], Niels H. Skotte[1†], Matthew P. Parsons[4‡], Erika B. Villanueva[1§], Nicholas S. Caron[1], Michael E. Østergaard[2], Lisa M. Anderson[1], Yuanyun Xie[1], Louisa Dal Cengio[1], Hailey Findlay-Black[1], Crystal N. Doty[1], Bethany Fitsimmons[2], Eric E. Swayze[2], Punit P. Seth[2], Lynn A. Raymond[4], C. Frank Bennett[2], Michael R. Hayden[1¶]

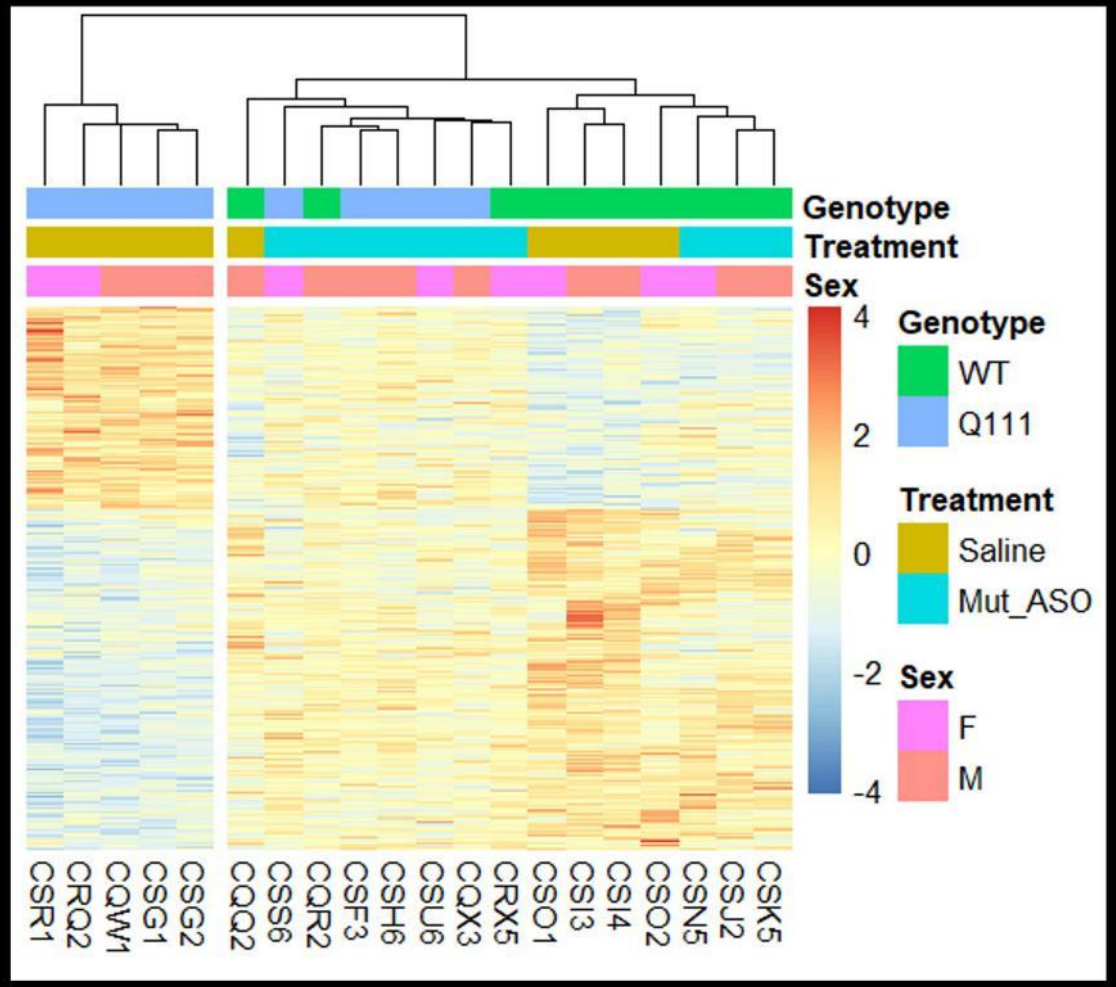
Allele-selective transcriptional repression of mutant *HTT* for the treatment of Huntington's disease

Bryan Zeitler[1*], Steven Froelich[1], Kimberly Marlen[1], David A Shivak[1], Qi Yu[1], Davis Li[1], Jocelynn R Pearl[1], Jeffrey C Miller[1], Lei Zhang[1], David E Paschon[1], Sarah J Hinkley[1], Irina Ankoudinova[1], Stephen Lam[1], Dmitry Guschin[1,8], Lexi Kopan[1], Jennifer M Cherone[1], Hoang-Oanh B Nguyen[1], Guijuan Qiao[1], Yasaman Ataei[1], Matthew C Mendel[1], Rainier Amora[1], Richard Surosky[1], Josee Laganiere[1,9], B Joseph Vu[1], Anand Narayanan[1], Yalda Sedaghat[2], Karsten Tillack[2], Christina Thiede[2], Annette Gärtner[2], Seung Kwak[3], Jonathan Bard[3], Ladislav Mrzljak[3], Larry Park[3], Taneli Heikkinen[4], Kimmo K Lehtimäki[4], Marie M Svedberg[5], Jenny Häggkvist[5], Lenke Tari[5], Miklós Tóth[5], Andrea Varrone[5], Christer Halldin[5], Andrea E Kudwa[6], Sylvie Ramboz[6], Michelle Day[7], Jyothisri Kondapalli[7], D James Surmeier[7], Fyodor D Urnov[1,10], Philip D Gregory[1], Edward J Rebar[1], Ignacio Muñoz-Sanjuán[3*] and H Steve Zhang[1,11]

Potent and sustained huntingtin lowering via AAV5 encoding miRNA preserves striatal volume and cognitive function in a humanized mouse model of Huntington disease

Nicholas S. Caron[1,2,3,†], Amber L. Southwell[1,2,3,4,†], Cynthia C. Brouwers[5], Louisa Dal Cengio[1], Yuanyun Xie[1,4], Hailey Findlay Black[1,2,3], Lisa M. Anderson[1], Seunghyun Ko[1], Xiang Zhu[4], Sander J. van Deventer[5], Melvin M. Evers[5], Pavlina Konstantinova[5] and Michael R. Hayden[1,2,3,*]

Why targeting toxic HTT Exon 1 is so important?

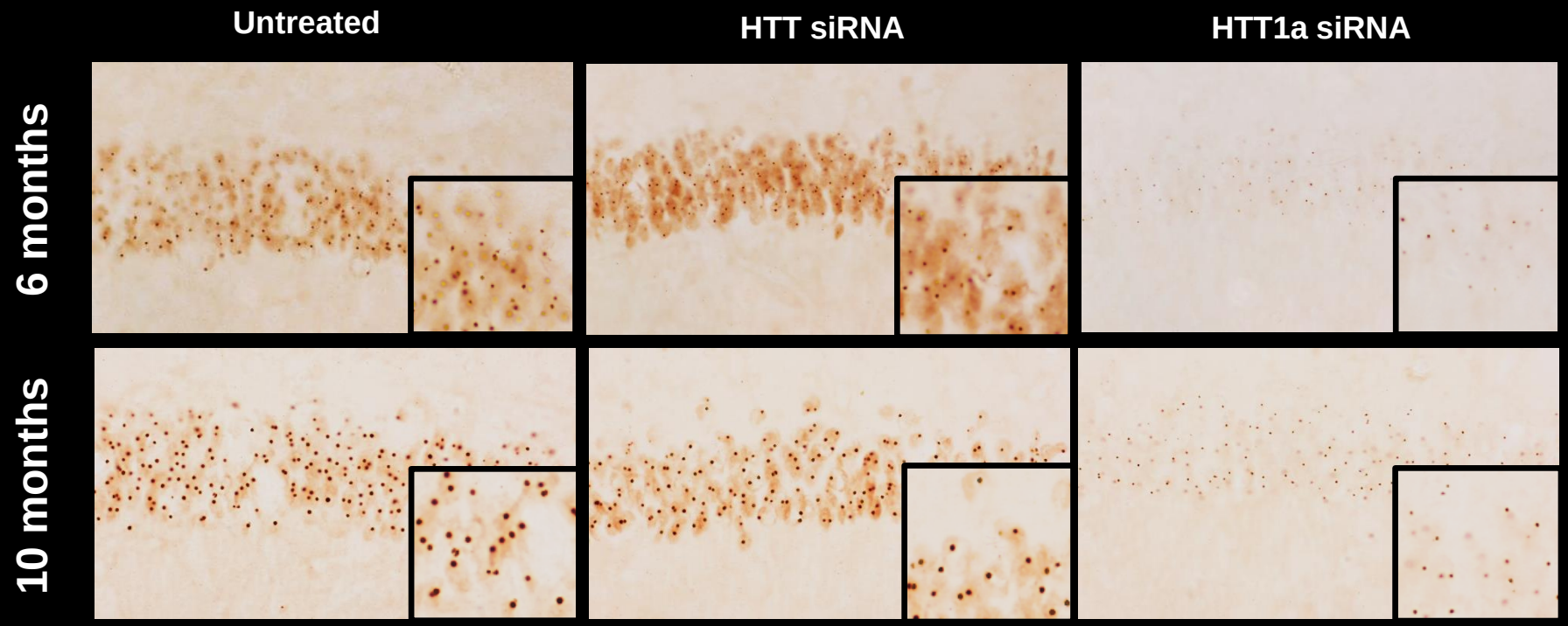


Unsupervised clustering of samples based on expression of HD DEGs splits mice into two distinct groups:

1. Saline-treated HttQ111/+ mice
2. Everything else

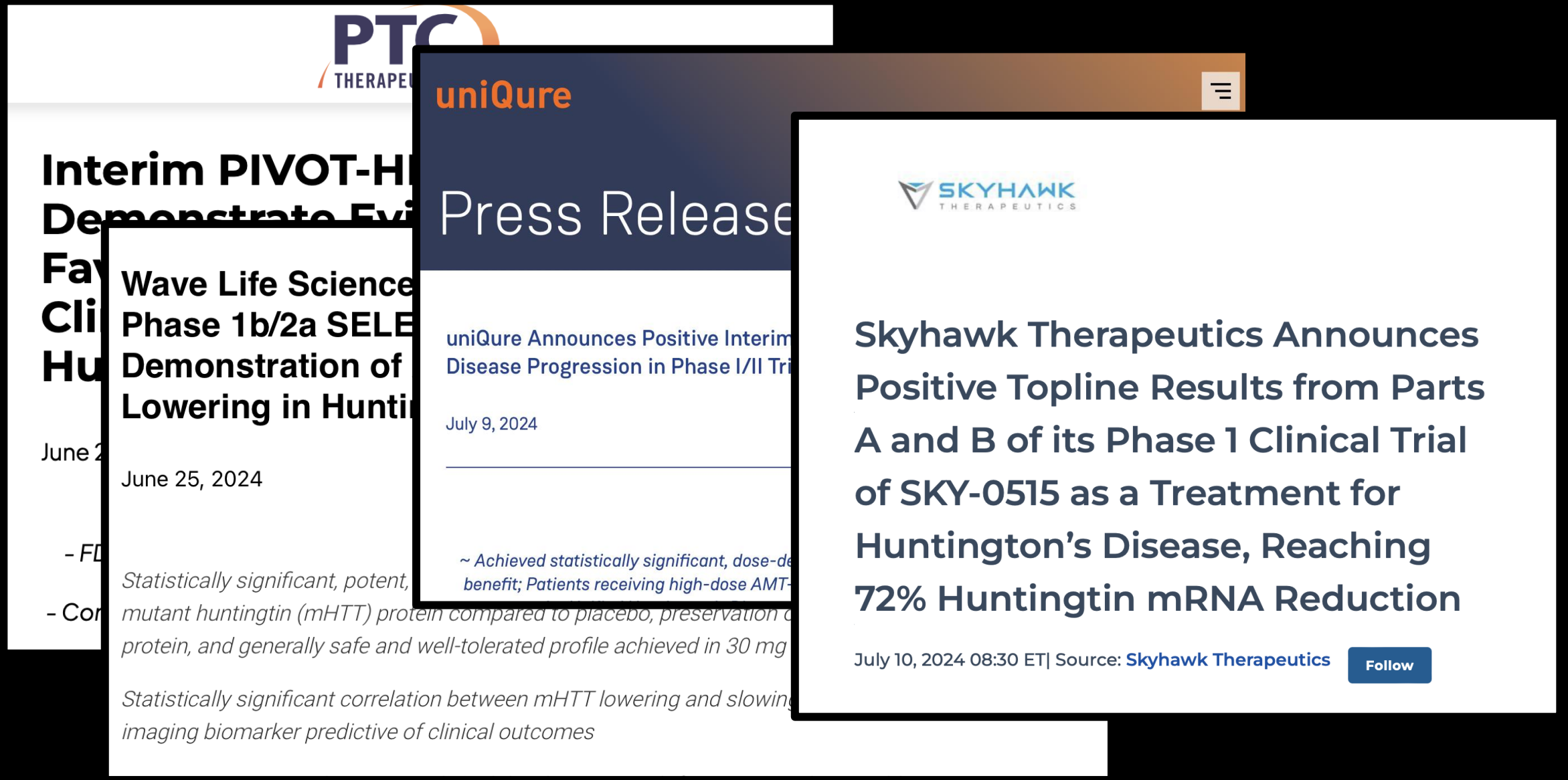
This is the best transcriptional rescue we've ever observed in an interventional study! Jeff Carroll HDF 2024

Why targeting toxic HTT Exon 1 is so important?



Gill Bates HDF 2024

- Collectively, targeting HTT1a has a more pronounced effect on HTT aggregation and transcriptional dysregulation than full-length HTT
- These data have important implications for HTT lowering strategies and strongly support strategies that also lower Exon1 HTT


Interim PIVOT-H
Wave Life Science
Phase 1b/2a SELE
Demonstration of
Lowering in Hunti
June 25, 2024
Statistically significant, potent,
mutant huntingtin (mHTT) protein compared to placebo, preservation
protein, and generally safe and well-tolerated profile achieved in 30 mg
Statistically significant correlation between mHTT lowering and slowing
imaging biomarker predictive of clinical outcomes
uniQure
Press Release
uniQure Announces Positive Interim
Disease Progression in Phase I/II Tri
July 9, 2024
~ Achieved statistically significant, dose-de
benefit; Patients receiving high-dose AMT-
SKYHAWK
THERAPEUTICS
Skyhawk Therapeutics Announces Positive Topline Results from Parts A and B of its Phase 1 Clinical Trial of SKY-0515 as a Treatment for Huntington's Disease, Reaching 72% Huntingtin mRNA Reduction
July 10, 2024 08:30 ET| Source: Skyhawk Therapeutics
Follow

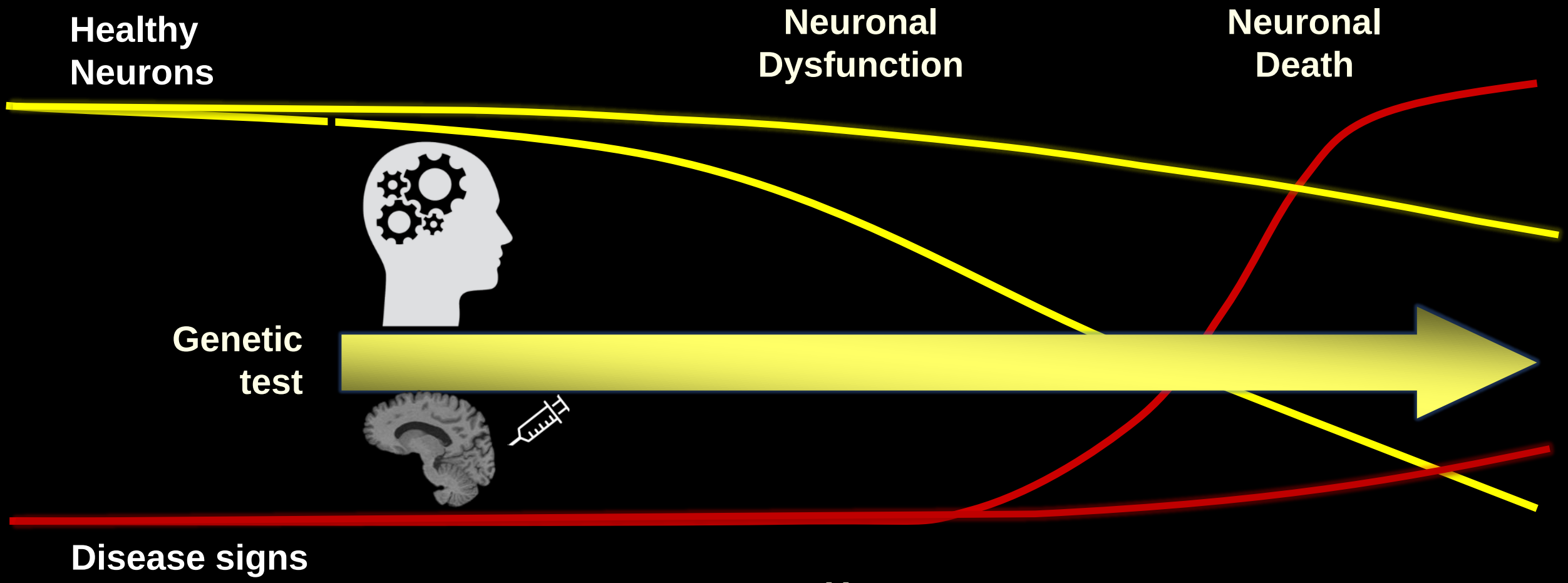
HTT lowering summary so far

Program	Exon 1	Allele Selective	Treatment duration	Trough mHTT	Peak NFL	Ventricles vs placebo
Tominersen	No	No	2 years	-55%	+30%	+300%
Wave 1&2	No	Yes	4 months	0%	0%	ND
Branaplam	No	No	4 months	-25%	+400%	+250%
PTC518	No	No	12 months	-43%	0%	ND
Wave 3	No	Yes	4 months	-35%	+60%	‘in line w nat hist’
Uniqure	Yes	No	24 months+	0%	+400% surgery related	‘Increase’
Alnylam	Yes	No	TBD	TBD	TBD	TBD

Importance of Alnylam Approach

- Exon 1 targeting – critical in my view
- Broad CNS distribution, including striatum and cortex
- Potential for infrequent dosing
- Potential (or emerging) safety profile of C16-siRNA platform

Hope for the future:
To treat PwHD BEFORE clinical symptoms



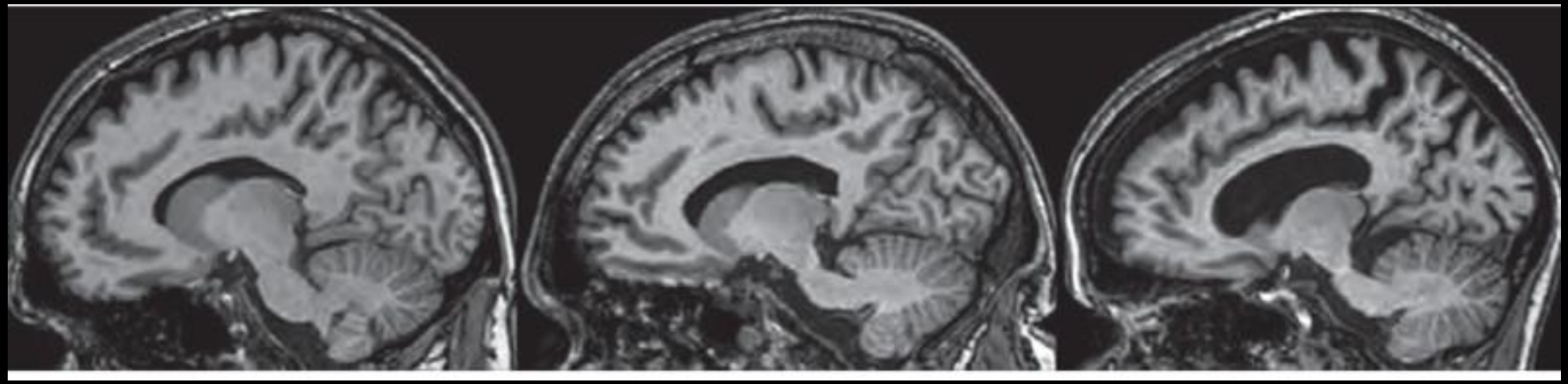
Scahill et al Lancet Neurology 2020

Challenge: clinical diagnosis is a *late event* in the course of the disease!

Control

PwHD
(years before clinical diagnosis)

PwHD
(clinically diagnosed)



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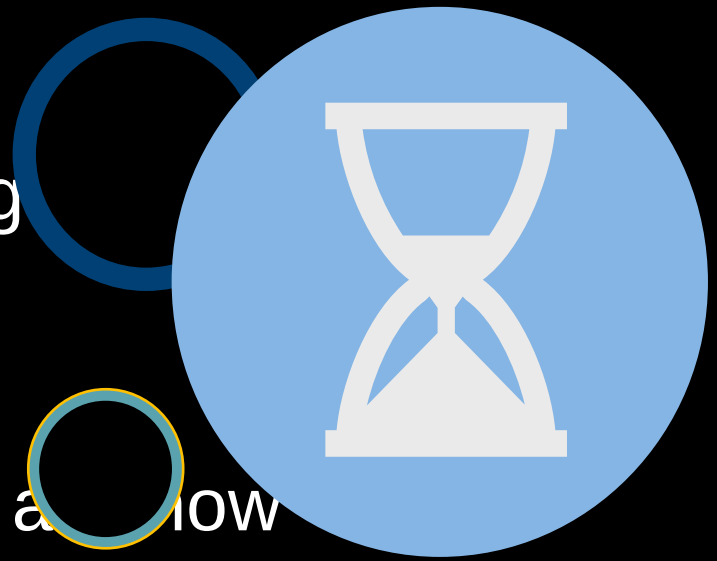
HUNTINGTON'S DISEASE CENTRE

Tabrizi, Sarah J et al. The Lancet. Neurology vol. 8,9 (2009): 791-801.

Challenge: clinical diagnosis is a *late event* in the course of the disease!

- HD cases early in the disease course are not identified, making preventative trials impossible
- Disease-related signs and symptoms occurring accounted for
- Current trial endpoints (TFC, cUHDRS, etc.) – a[illegible]low movement in later part of the disease



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What is the HD Integrated Staging System (HD-ISS)?

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HD biological research definition

- Huntington's disease is defined as the presence of a CAG expansion in exon 1 of the HTT gene of
  - ≥ 40 CAG; or
  - ≥ 36 CAG and the presence of a disease-specific biomarker or disease-specific clinical syndrome.

Because future research is needed to formally establish criteria to define HD in the CAG = 36-39 range, the following Staging criteria are outlined for individuals with CAG ≥ 40.

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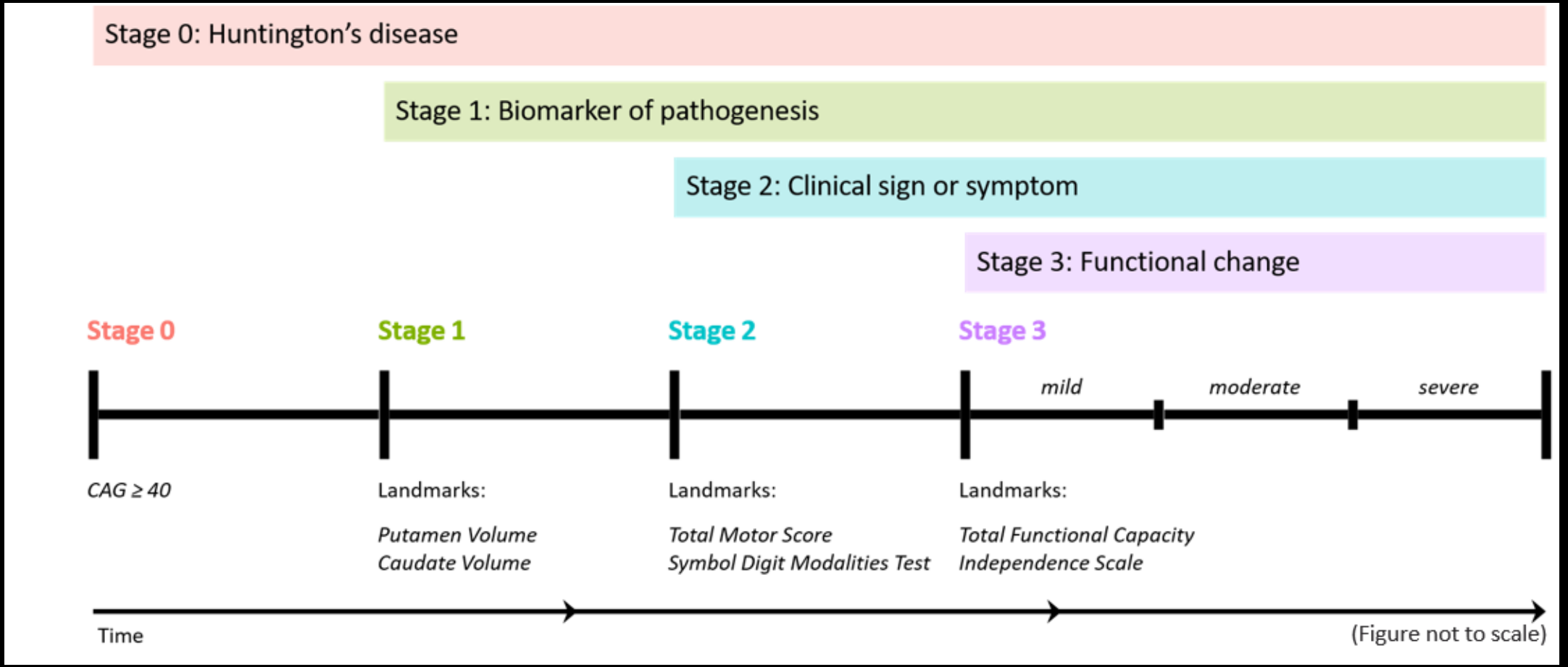
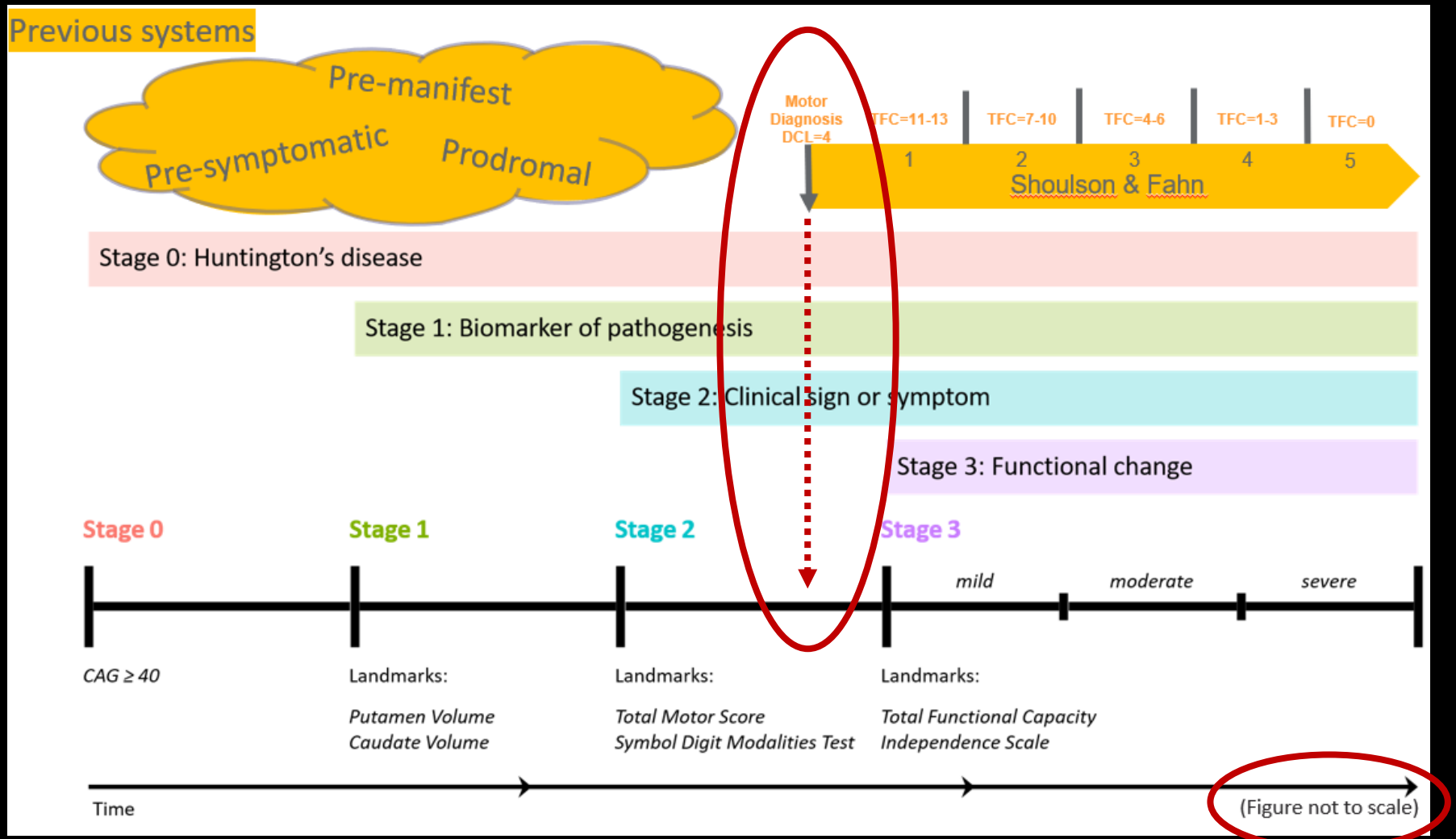
Tabrizi et. al., 2022, Lancet Neurology

HD-ISS represents the entire course of HD



Tabrizi et. al., 2022, Lancet Neurology

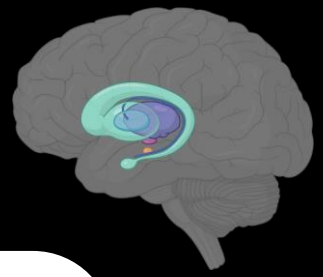
HD-ISS represents the entire course of HD

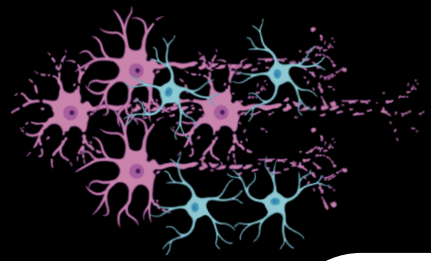


Tabrizi et. al., 2022, Lancet Neurology

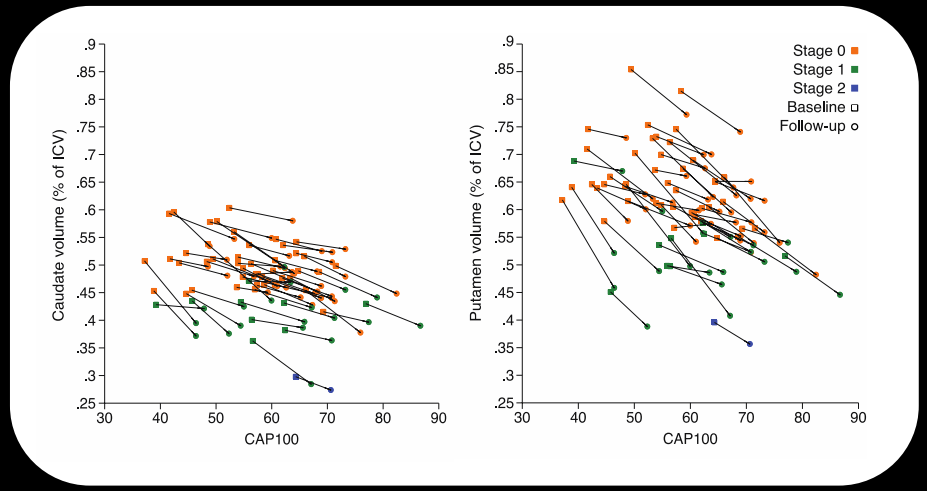
Biomarkers – Path to Earlier Stage Trials

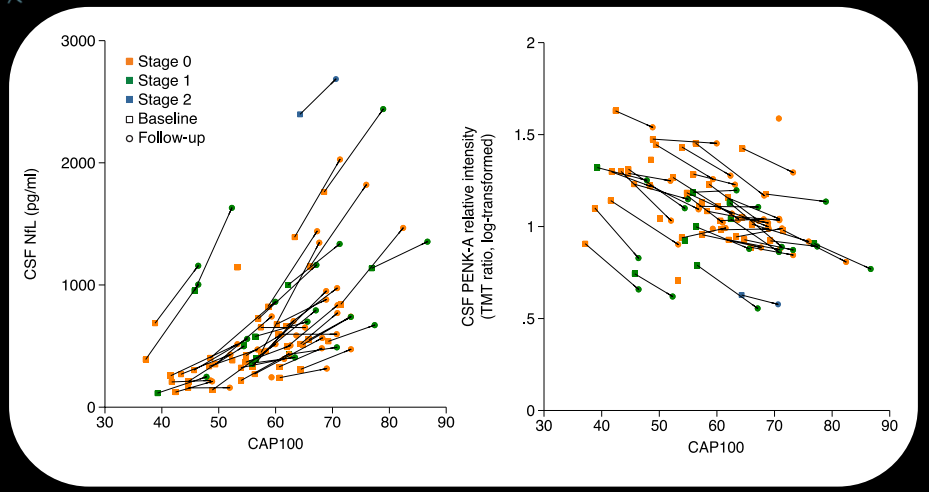
Change in caudate and putamen volume





Change in CSF NfL and PENK levels





HD-ISS

Stage 0

Stage 1

A 3-year clinical trial with a 50% treatment effect requires:

n=125 caudate atrophy

n=146 putamen atrophy

n=104 CSF NfL

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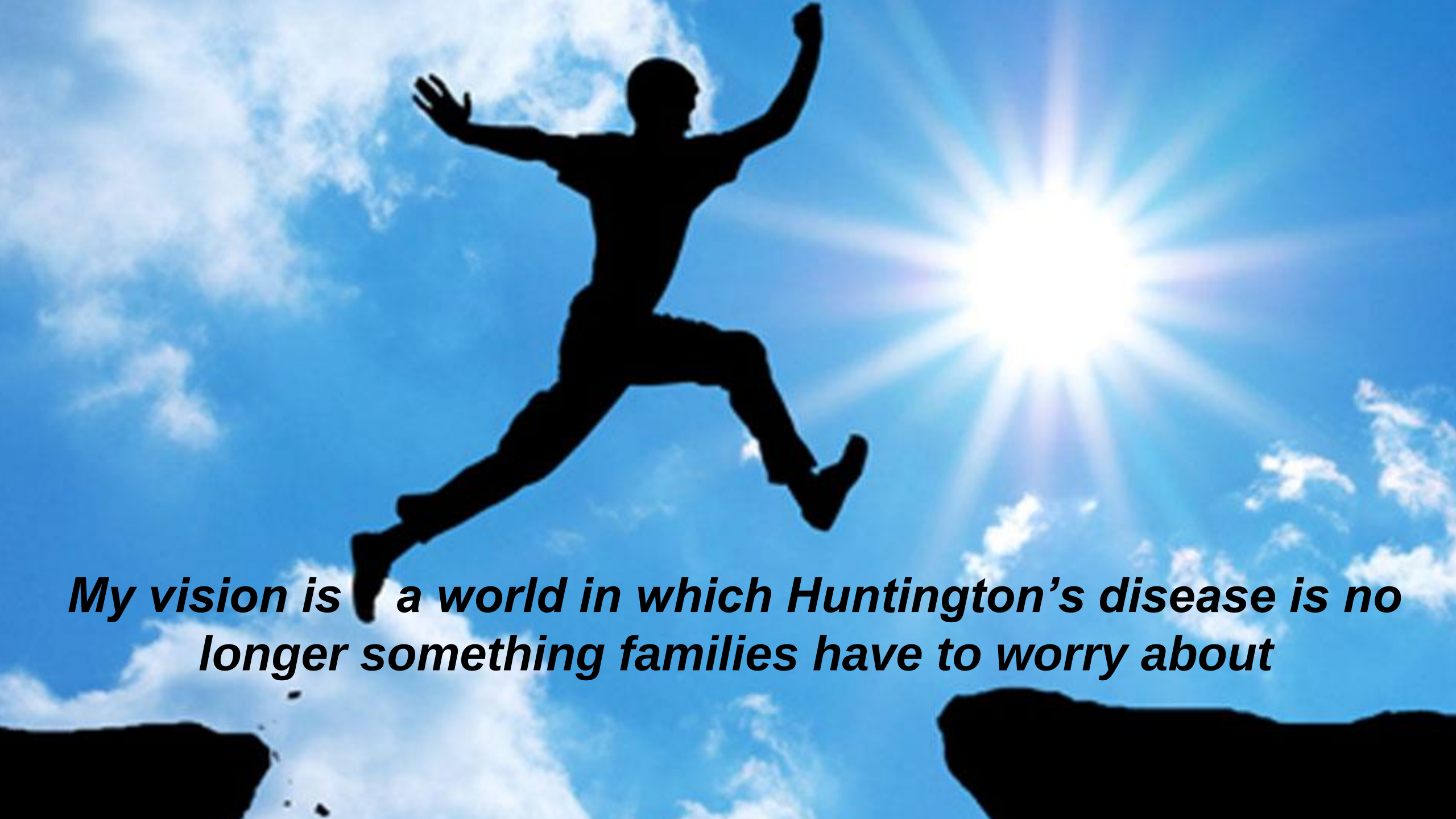
HUNTINGTON'S DISEASE CENTRE


My vision is a world in which Huntington’s disease is no longer something families have to worry about

Thank You!

Tabrizi Group

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Dr Rob Goold
Dr Emma Bunting
Dr Jasmine Donaldson
Dr Mike Flower
Dr Marwa Elmasri
Dr Joseph Hamilton
Dr Ekene Anakor
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Dr Brinda Prasad
Dr Michael Finley
Dr Ramee Lee
Dr Cristina Sampaio
Dr Emily Gantmann

HUNTINGTON'S DISEASE CENTRE

wellcome

NATA Nucleic Acid Therapy Accelerator

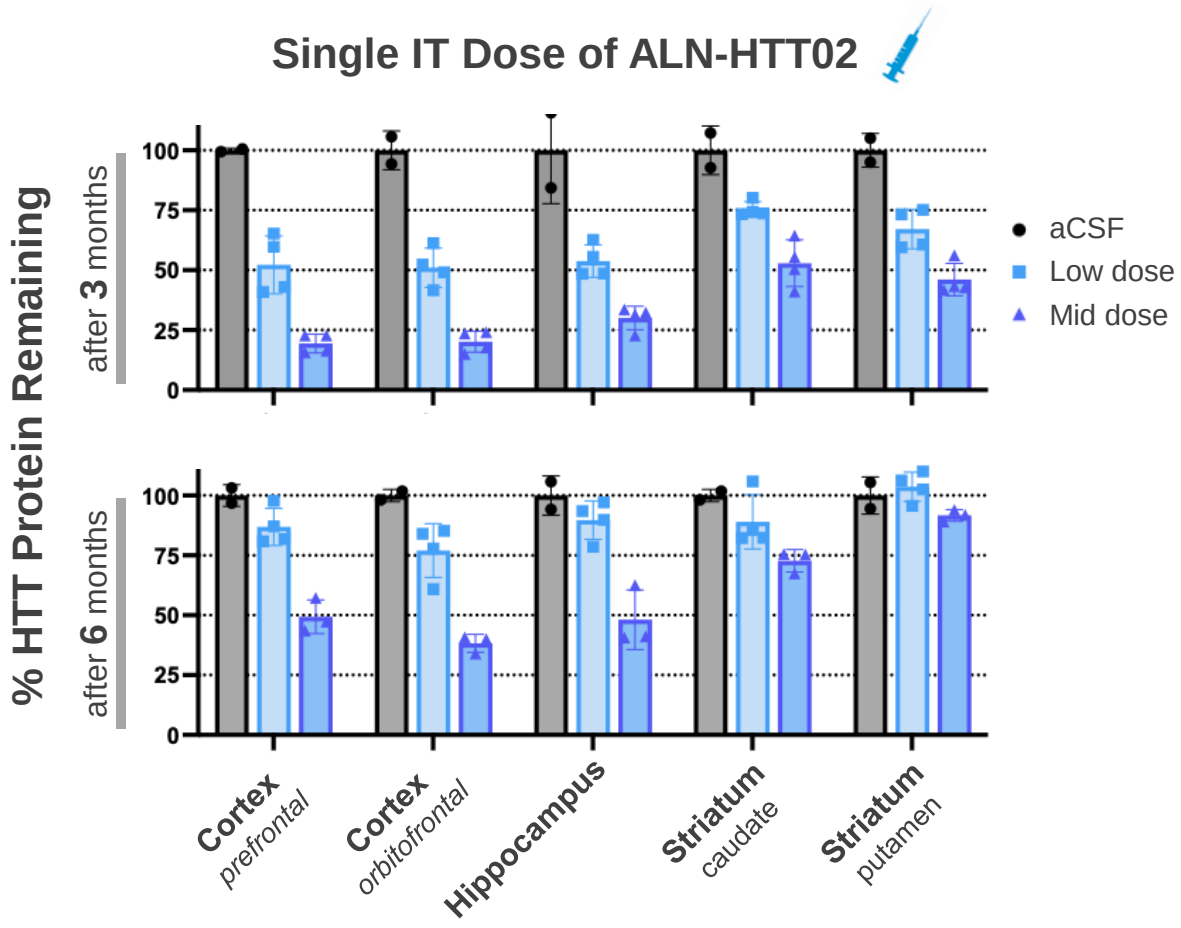
MRC Medical Research Council

UK Dementia Research Institute

CHDI FOUNDATION

ALN-HTT02 Demonstrates Broad CNS Distribution and Durable HTT-Lowering in NHP[1]

PK/PD Profile Consistent with Prior RNAi Experience in the CNS



Observations following a single dose of ALN-HTT02:

- **Widespread distribution** across CNS regions
- **Durable, dose-dependent** HTT-lowering, supporting infrequent dosing
- **Encouraging safety profile through 6 months**
  - No in-life neurological abnormalities
  - No elevations in CSF NfL
  - No elevations in CSF total protein

aCSF, artificial cerebrospinal fluid; CNS, central nervous system; CSF, cerebrospinal fluid; HTT, huntingtin; IT, intrathecal; NHP, non-human primates; NfL, neurofilament light chain; PD, pharmacodynamic; PK, pharmacokinetic; RNAi, RNA interference.

1. Sloan K, et al. Oral Presentation at the European Huntington's Disease Network and Enroll-HD 2024 Meeting. September 12-14, 2024. Strasbourg, France (recording available online at EHDN.org).

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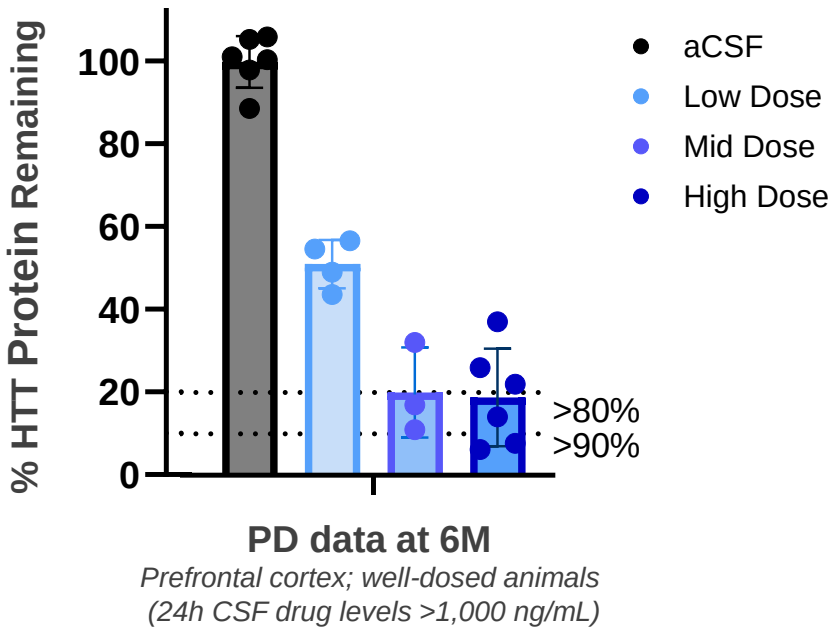
Multiple Doses of ALN-HTT02 Well Tolerated in NHP[1]

Safety Profile Supports Continued Development

Multiple IT Doses of ALN-HTT02



PD data at 6M

Prefrontal cortex; well-dosed animals (24h CSF drug levels >1,000 ng/mL)

Observations following multiple doses of ALN-HTT02 at 3 dose levels:

- **Encouraging safety profile through 6 months**
  - No in-life neurological abnormalities
  - No adverse CSF parameter changes
  - No adverse microscopic findings
- ALN-HTT02 has been evaluated in 4 independent NHP studies to date
  - **No adverse findings, even after deep HTT-lowering (>90%)**

aCSF, artificial cerebrospinal fluid; CSF, cerebrospinal fluid; HTT, huntingtin; IT, intrathecal; NHP, non-human primates; PD, pharmacodynamic, Q3M, every 3 months.

1. Sloan K, et al. Oral Presentation at the European Huntington's Disease Network and Enroll-HD 2024 Meeting. September 12-14, 2024. Strasbourg, France (recording available online at EHDN.org).

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Ph1b Study of ALN-HTT02 Underway in Adult Patients with HD[1]

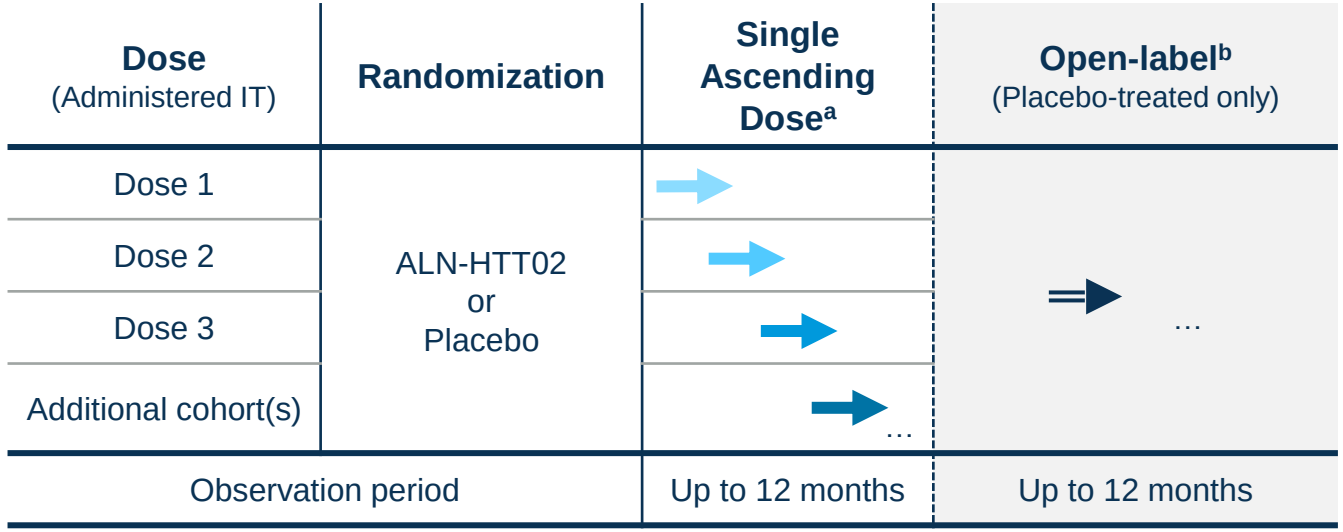
Placebo-Controlled Single Ascending Dose Study Evaluating Safety, Tolerability, and PK/PD

Study Population

- Age 25 to 70 years with >39 CAG repeats
- HD-ISS Stage 2 or early Stage 3

Endpoints

- Primary endpoint
  - Safety and tolerability
- Secondary endpoints
  - PK: CSF and plasma profile of ALN-HTT02
  - PD: Change in mHTT levels in CSF
- Exploratory endpoints
  - Clinical, imaging and biomarker measures of disease progression and safety



a. The decision to proceed to the next dosing cohorts is determined by the Safety Review Committee
b. After all patients in the double-blind cohort have reached Month 6, cohort is unblinded and placebo-treated patients may receive a single open-label dose of ALN-HTT02

clinicaltrials.gov

Protocol reviewed and accepted by Enroll-HD CTC and endorsed by EHDN EC

Study initiating in the UK, Canada & Germany

Initial participants dosed Q4'24

CAG, cytosine-adenine-guanine; CSF, cerebrospinal fluid; HD, Huntington's disease; HD-ISS, HD Integrated Staging System; IT, intrathecal; mHTT, mutant huntingtin; PD, pharmacodynamic; PK, pharmacokinetic.

1. ClinicalTrials.gov. NCT06585449. Available from: https://clinicaltrials.gov/study/NCT06585449 (Accessed Oct 16, 2024).

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ALN-HTT02 Holds Promise for Huntington's Disease

- C16-siRNA platform offers a **new approach for HTT-lowering** in the CNS
  - Broad distribution, infrequent dosing, encouraging safety profile
- ALN-HTT02 is an investigational RNAi therapeutic designed to **durably lower all forms** of mHTT, including shorter HTT1a (exon 1) isoform
  - Engagement of the HTT1a isoform may be critical to maximize efficacy of HTT-lowering
- HTT-lowering in the CNS **appears well tolerated in NHPs** after IT dosing with ALN-HTT02
  - Deep & sustained HTT-lowering, broad distribution, encouraging safety & tolerability across four studies
- **A Phase 1b study of ALN-HTT02 is ongoing** in people with Huntington's disease[1]
  - Potential to optimize depth & duration of HTT-lowering via clinical dosing regimens, to maximize efficacy while preserving safety

If you are seeking additional scientific information related to Alnylam therapeutics, US HCPs may visit the Alnylam US Medical Affairs website at RNAiScience.com. Non-US HCPs should contact medinfo@alnylam.com.

C16, 2'-O-hexadecyl; CNS, central nervous system; CSF, cerebrospinal fluid; HD, Huntington's disease; HTT, huntingtin; IT, intrathecal; mHTT, mutant huntingtin; NHP, non-human primate; PD, pharmacodynamic; RNAi, RNA interference; SAD, single ascending dose; siRNA, small interfering RNA; wtHTT, wild-type huntingtin.

1.ClinicalTrials.gov. NCT06585449. Available from: https://clinicaltrials.gov/study/NCT06585449 (Accessed Oct 16, 2024).

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Progress Toward Building a Neuroscience Pipeline

- **First human translation of RNAi in the CNS** and encouraging clinical profile of mivelsiran unlocks our ability to tackle many serious neurodegenerative diseases
- We now have **3 molecules in active clinical studies**, leveraging the C16-siRNA platform
  - **Mivelsiran** (ALN-APP) – CAA & Alzheimer's
  - **ALN-HTT02**[1] – Huntington's
  - **ALN-SOD**[2] – ALS
- **Additional molecules in CTA-enabling development**, rapidly approaching clinic
  - **MAPT**[1] – tauopathies, including Alzheimer's
  - **SNCA**[3] – Parkinson's
- Research team is **actively pursuing additional targets** and **evolving the delivery platform** with new approaches including systemic brain shuttles
- Partnership with Regeneron; supporting **rapid growth of a neuroscience pipeline**

1. Partnered, Alnylam-led with profit split; 2. Partner-led with profit split; 3. Out-licensed with milestones and/or royalties;


Alnylam®

Q&A

11:00 – 11:30a ET

TOPIC		PRESENTER
Spring-loaded for Growth		**Pushkal Garg, M.D.,** Chief Medical Officer
TTR Amyloidosis – Market Leadership With Rapid Knockdown		**John Vest, M.D.,** SVP, ATTR Development Lead
Cardiovascular – Zilebesiran: Continuous Control of Hypertension		**Simon Fox, Ph.D.,** VP, Program Lead, Zilebesiran
Neuroscience	**Mivelsiran: A Differentiated Approach for Alzheimer's Disease and Cerebral Amyloid Angiopathy** **Overview of Huntington's Disease Unmet Need** **ALN-HTT02: Hope for Huntington's Disease Patients**	**Julia Shirvan, M.D., Ph.D.,** Senior Director, Mivelsiran Clinical Lead **Professor Sarah Tabrizi, M.D., Ph.D.** FMedSci FRS, UCL **Kevin Sloan, Ph.D.,** VP, Early Neuroscience Programs


Alnylam®

Durable Leadership in RNAi Therapeutics

Kevin Fitzgerald, Ph.D.
Chief Scientific Officer

Alnylam Drove the First Phase of the RNAi Revolution

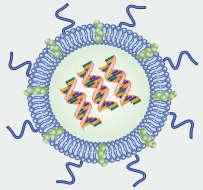
We Conquered Delivery to the Liver and Discovered the World's First Five RNAi Therapeutics

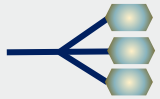
1998 — Fire and Mello report gene silencing effect in worms, coined RNAi interference[1]

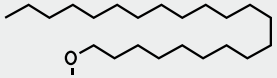
1999 — Sharp proposes using siRNA and RNAi process to treat disease[2]

2002 — Alnylam founded

Delivery Delivery Delivery







Lipid Nanoparticles (LNPS)

GalNAc, C16
Small molecule ligands

2018 — onpattro® (patisiran) lipid complex injection 10 mg/5 mL

2019 — GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL

2020 — OXLUMO® (lumasiran) for injection 94.5 mg/0.5 mL

2021 — LEQVIO® (inclisiran) injection 284 mg/1.5 mL
Global rights held by Novartis[3]

2022 — amvuttra® (vutrisiran) injection 25 mg/0.5 mL

1. Fire A et al. Nature. 1998;391(6669):806-811. 2. Sharp P. Genes & Development. 1999. 13: 139-141. 3. Alnylam formed a collaboration to develop inclisiran with The Medicines Company in 2013; Novartis completed acquisition of The Medicines Company in 2020

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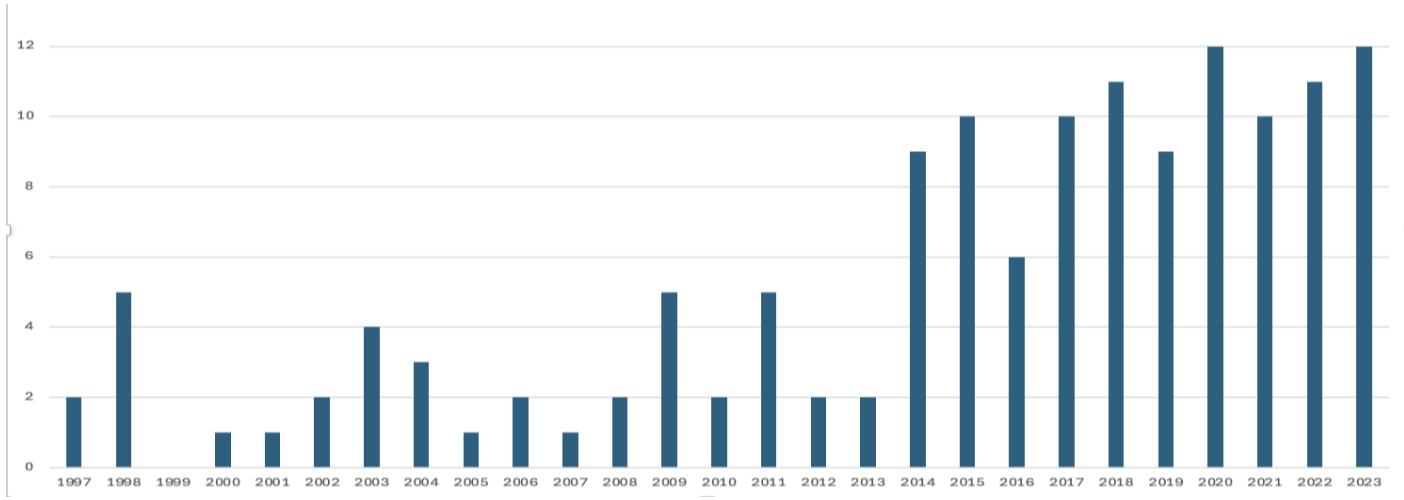
RNAi Therapeutics – A Generational Technology

Following the Trajectory of Another Generational Technology

Antibody-Based Biologics Approved by FDA[1]



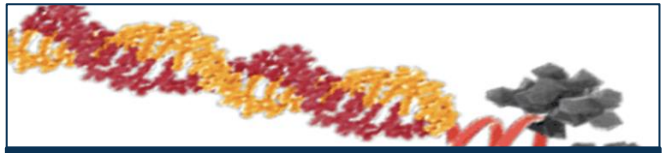
145 siRNA Programs in Development Across the Industry[2]

95 distinct assets in development across 85 indications

1. Strohl. "Structure and function of therapeutic antibodies approved by the US FDA in 2023." Antibody Therapeutics, Volume 7, Issue 2, April 2024, Pages 132–156, https://doi.org/10.1093/abt/tbae007.
2. EvaluatePharma (1/28/2025) cross-referenced with TrialTrove and ClinicalTrials.gov data sets (1/29/2025).

Alnylam is Positioned to Continue Leading the Field Into the Future

Unmatched Depth of Expertise, Experience and Innovation in RNAi

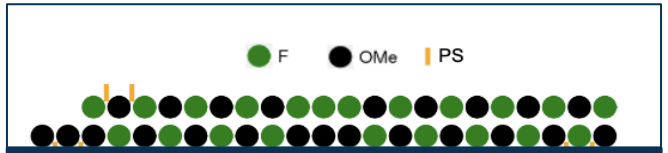


Largest database of active siRNAs interrogated with AI;
Proven innovation in delivery

+

From idea to IND in 9-12 months for many high priority projects

+



20+ years experience in clin. dev. across multiple tissues, including emerging profile in CNS

+

The NEW ENGLAND JOURNAL of MEDICINE

450+ publications, including 13 NEJM articles and 37 articles in Nature journals

+

State of the art manufacturing with innovation on the way

+

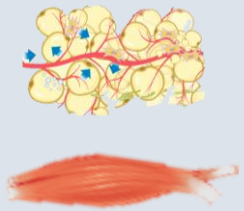
(10) International Publication Number
WO 2019/217459 A1

Broad and foundational IP

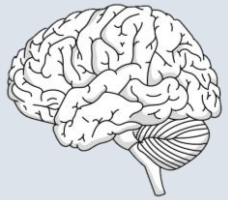
Alnylam

On Track to Meet Our Ambitious 2-2-5 Pipeline Expansion Goals

15 New Programs in Clinic (2024-2025) Across Wholly-owned and Partner-led Programs

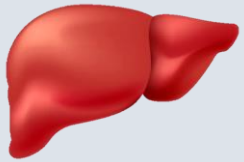


2 **new tissues** with INDs



2 new **CNS** INDs

+1 or more partner-led programs



5 new **liver** INDs

+5 or more partner-led programs

8 INDs/CTAs filed in 2024

- ALNY-led: 4 (3 Liver: **ALN-6400/plasminogen (POC)**, **ALN-4324/GRB14**, ALN-AGT-**REVERSIR**; 1 CNS: **ALN-HTT02**)
- Partner-led: 4 (3 Liver, 1 CNS)
- Dosed first patient with **ALN-BCAT** in hepatocellular carcinoma
- **9+ development candidates** identified, providing optionality

Looking Ahead

- **Continue to follow our strategic principles in decision making:**
  - Strong biologic rationale, informed by human genetics
  - Biomarkers, early POC
  - Potential to halt or reverse severe disease, and be best-in-class
- **Expect 2025 filings to be a mix of liver, CNS and extra-hepatic tissues (adipose and muscle)**

Alnylam

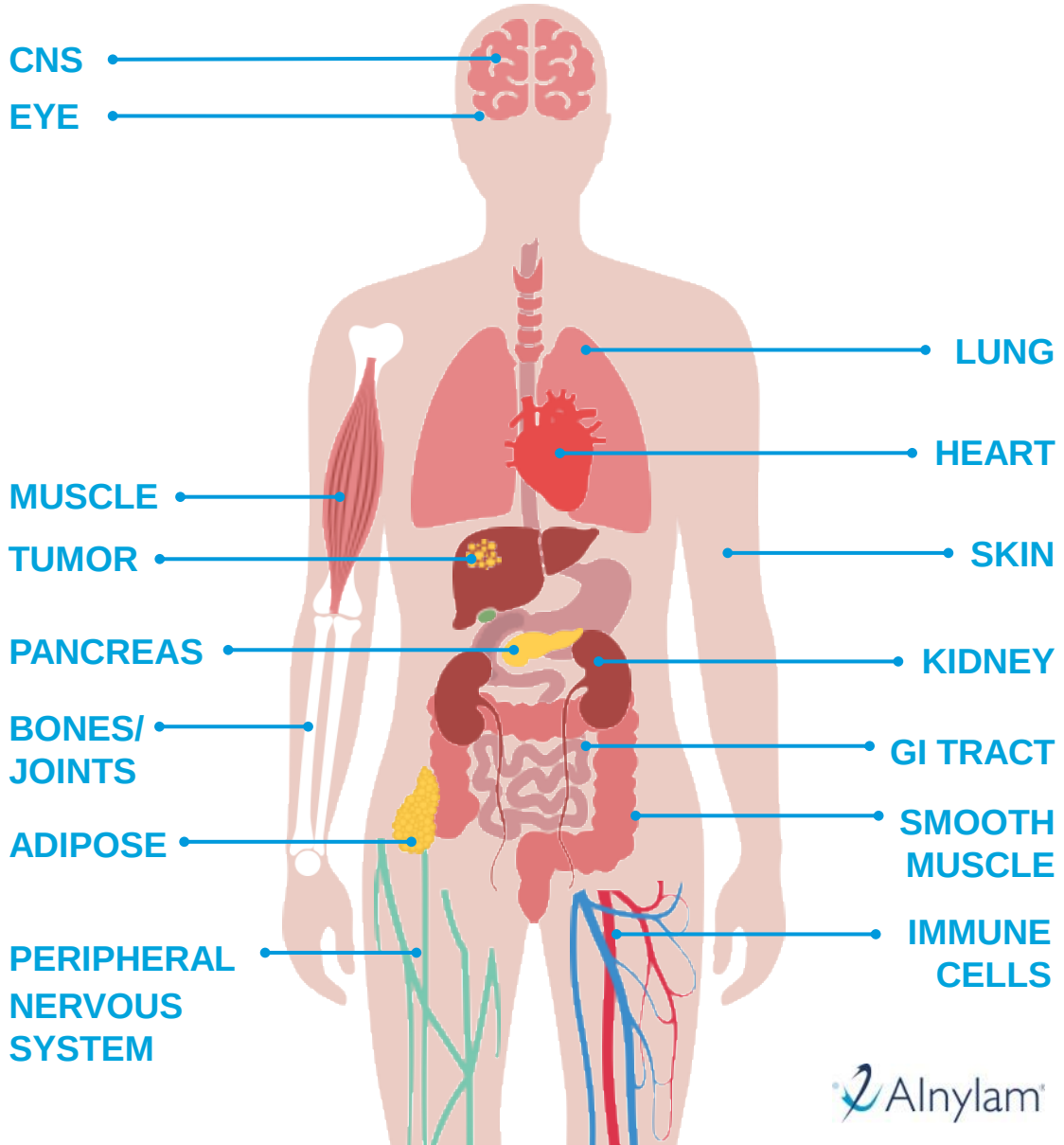
Our Delivery Ambition: Unlock All Major Tissues by 2030

- RNAi is at work in every cell of your body
- RNAi therapeutics have the potential to silence any gene in the genome
- Delivery to the liver was just the beginning.
- Tissues chosen through the lens of unmet patient need

Achieving Best-in-Class Delivery - Differentiated Profile

SC dosing → ≤ 3 mg/kg → Efficient Manufacturing

We're also pursuing combinations to realize the full potential of this technology.



Combos Hold Enormous Promise for Common Diseases

Embracing Complexity to Address the Leading Drivers of Death and Disability in the World

Proving Ground for RNAi Tx

First approved in **rare and select prevalent diseases** impacted by targeting a single gene.

Examples:

- ATTR amyloidosis
- Primary hyperoxaluria type 1
- Acute hepatic porphyria
- High LDL cholesterol

Impacting Human Health at Scale in Areas of High Unmet Need

Most **common diseases** have **multiple genetic drivers** requiring targeting multiple genes and tissues.

Examples:

- Cardiovascular disease
- Metabolic disease
- Neurodegenerative disease

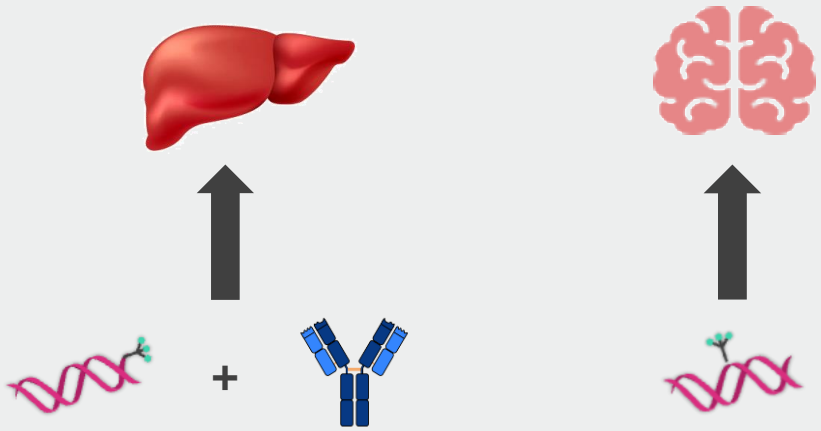
1 in 4 people
in the world has metabolic syndrome[1]

1. *IDF estimate included in O'Neill, S. & O'Driscoll, L. J. O. R. Metabolic syndrome: A closer look at the growing epidemic and its associated pathologies. Obes. Rev. 16(1), 1–12 (2015).*

Exponentially Expanding Patient Impact with Combinations

We’re actively pursuing specific combinations and investing in technology to enable them

2024

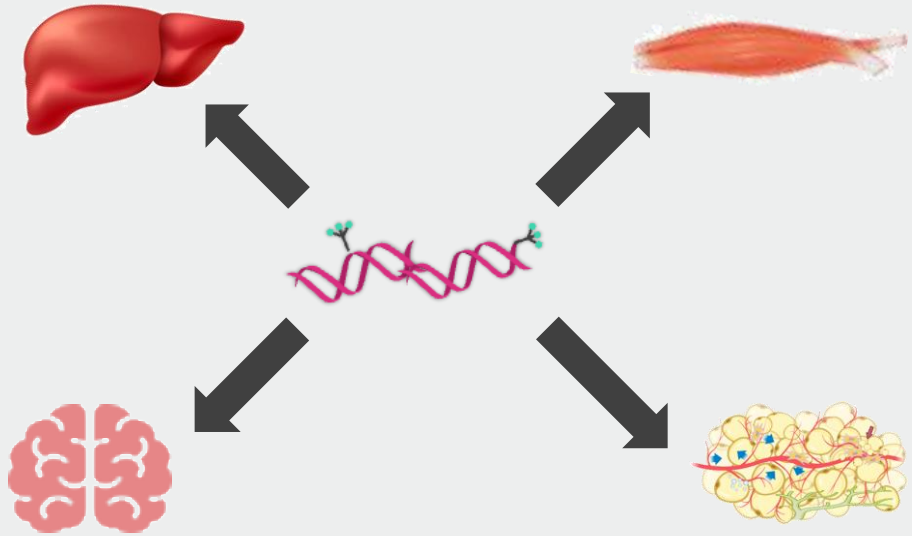


Basic Combos with other agents

Example: cemdisiran + pozelimab[1]

Combos of existing RNAi Tx also possible

2025 Forward



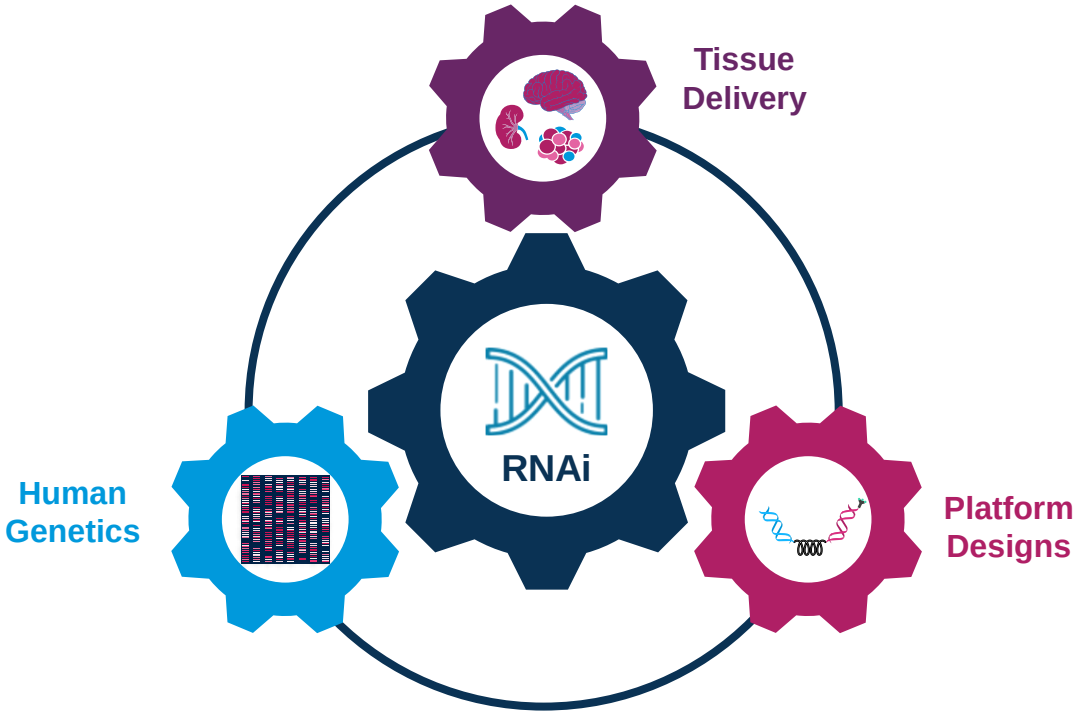
Accelerating Progress with multiple siRNAs delivered to one organ, or multiple organs simultaneously. May be combined with antisense, small molecule, antibody and peptide drugs.

Example: Delivery to Target A and Target B in liver
Preclinical data on knockdown will be presented today

1. Combination is being tested in myasthenia gravis, paroxysmal nocturnal hemoglobinuria and geographic atrophy. Out-licensed to Regeneron with milestones and/or royalties

Driving the RNAi Revolution into the Future

Sustainable Innovation Engine



- **Well on track for 2-2-5 initiative!**
- **Our pace of innovation and drug discovery is rapid and accelerating!**
  - High-quality programs based on human genetics
  - 20 years clinical development experience and track record of success
  - CNS, CV/Metabolic, Hematology, Ocular
  - Innovative: best-in-class delivery and RNAi technology, including manufacturing
    - Subcutaneous, low dose, durable, scalable

We make disciplined, data-driven choices to fill our portfolio with potential best-in-class therapies that address diseases with high unmet need

Alnylam

Next Wave of Innovation in Metabolic Diseases

Sandeep Menon, M.D., Ph.D.
Chief Development Officer

Aligning Alnylam's Strategic R&D Principles to Metabolic Strategy

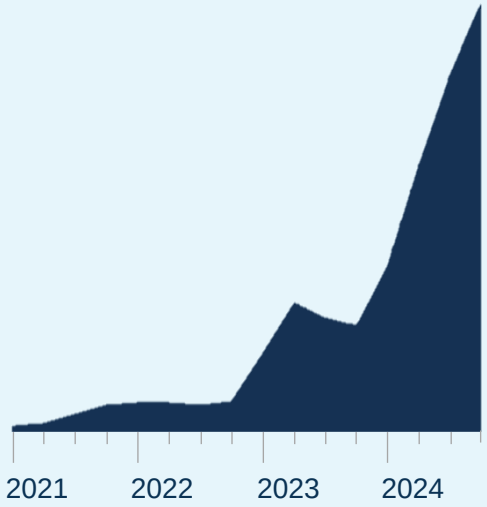
Prioritization Principles	Obesity	Diabetes
Address diseases with high morbidity and mortality	✓	✓
Demonstrate capacity to halt or reverse disease and best-in-class potential	Address unmet needs not adequately served by incretins	Addressing Insulin Resistance – precursor and primary driver for Type 2 Diabetes
Pursue high-conviction targets with strong biological rationale informed by human genetics	ACVR1C INHBE GPR75* "Gene X" Novel siRNA combinations	GRB14 Novel siRNA combinations

*Partnered program

Significant Unmet Need Remains in Obesity Despite Innovation and Growth Achieved with Incretins

First Wave of Innovation

GLP-1 Treatment Rate Since Approval[1]



- **Rapid uptake of GLP-1s** since approval, driving obesity market growth
- Obesity 2031 estimated market potential **>$130B**

Emerging Unmet Needs

Sub-optimal GI tolerability	**~50%** of patients discontinue therapy
Durability of weight loss	**>60%** of weight loss regained within 1 year
Muscle preservation & improved body composition	**15% - 60%** reduction in lean mass

Ongoing Innovation: Largely Incretin-Based Combinations

1. IQVIA NPA retrieved on Jan. 29, 2025; Time range: January 2019 to December 2024 | GLP-1 Obesity drugs include: Saxenda (liraglutide), Wegovy (semaglutide), Zepbound (tirzepatide)

Targeting the Inhibin/Activin Pathway with the Aim to Achieve Safe and Sustained Weight Loss

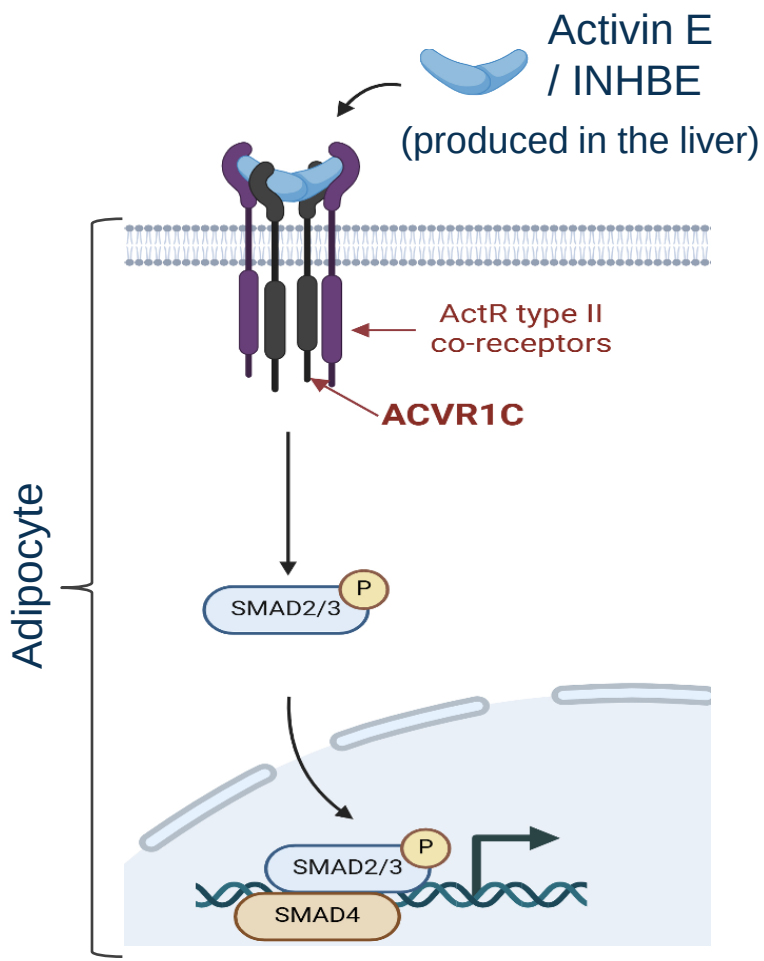
Alnylam Portfolio Addresses Key Unmet Needs
as monotherapy or novel siRNA combinations or with low dose incretins

- Strong genetics
- Exquisite tissue selectivity
- Long acting (biannual / annual dosing)
- Strong pre-clinical data
  - Monotherapy
  - Combinations with novel siRNAs
    - Multiple tissue
    - Multiple targets
  - Combinations with low dose incretin

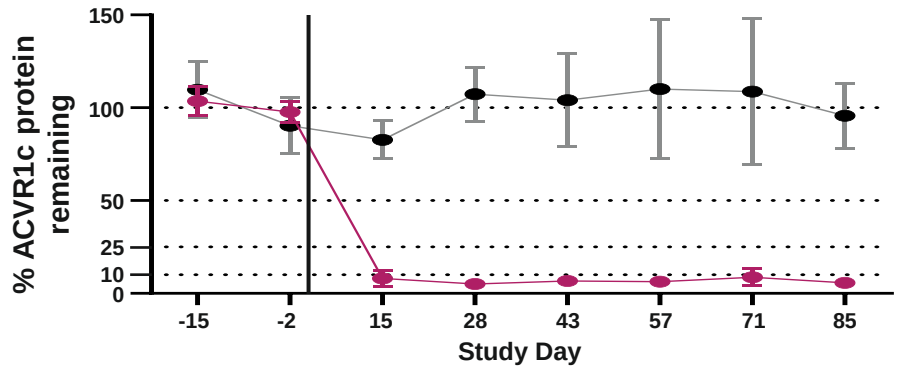
- **Durable** weight loss
- Improve **quality of weight loss**
  - Prevent muscle loss
  - Improved body composition
- **Improve tolerability**
- **Reduce discontinuation rate**

Long-acting siRNA with the Aim to Achieve Safe and Sustained Weight Loss

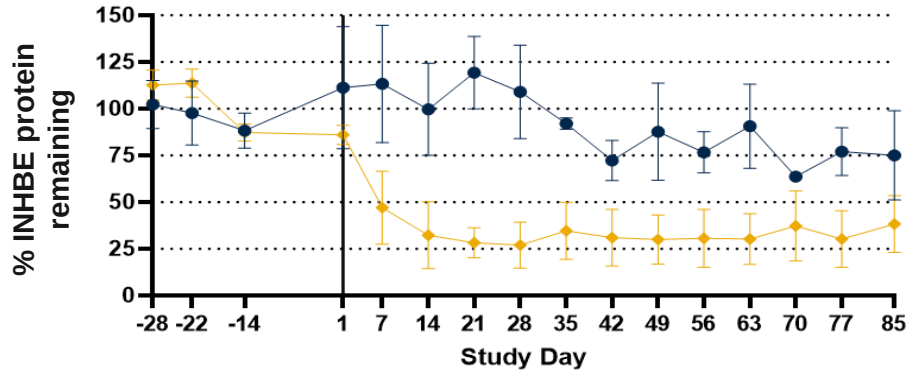
Ligand/Receptor Inhibin/Activin Pathway: INHBE (in liver) and ACVR1c (in adipose)



95% ACVR1c Knockdown in NHP Adipose



INHBE Knockdown in NHP Liver



- Deep and durable knockdown with single dose
- Highly potent with exquisite tissue specificity
- Infrequent, sub-cutaneous dosing
- Fat loss, lean mass preservation & weight regain attenuation

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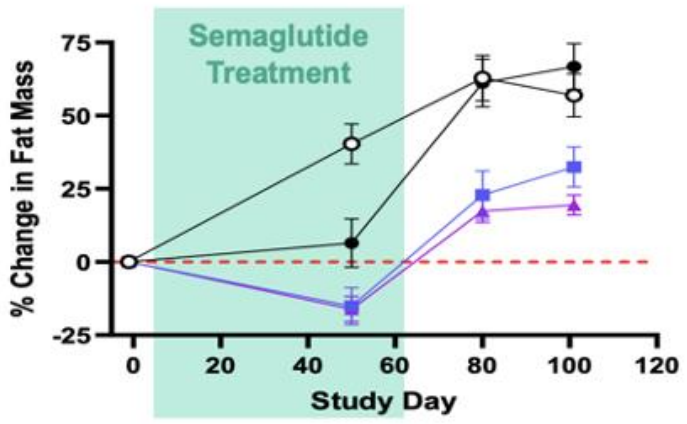
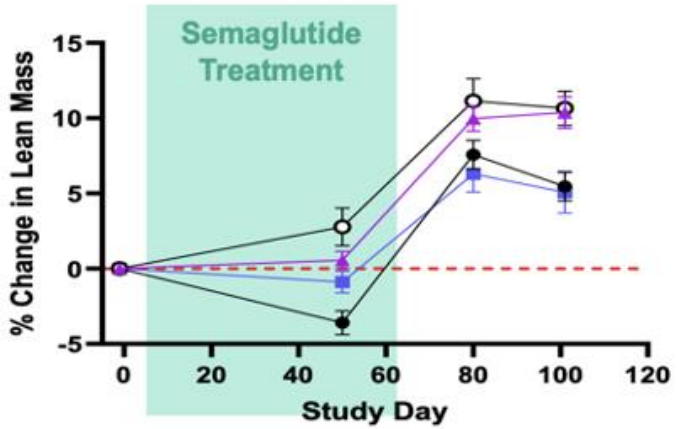
Combining Long-acting siRNAs with Low Dose Semaglutide Gives Greater Fat Loss, Lean Mass Preservation and Attenuated Weight Regain

Rodent models

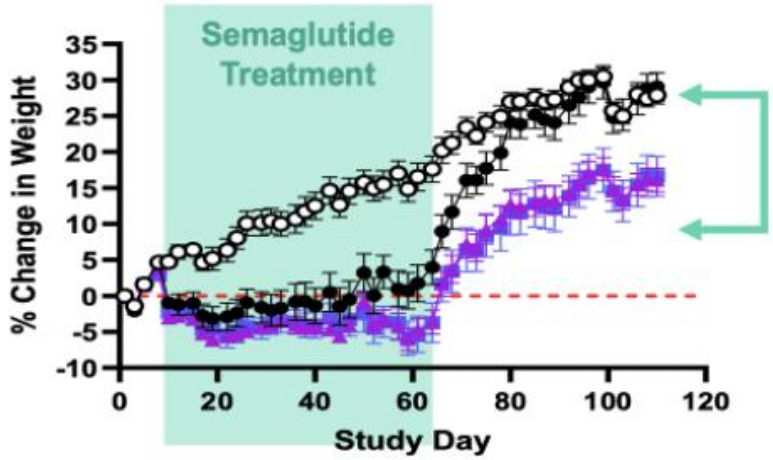
Greater Fat Loss



Lean Mass Preservation



Attenuated Weight Regain



PBS + Vehicle PBS + Semaglutide si-INHBE + Semaglutide si-ACVR1C + Semaglutide

N=9/group HFD Mice, each point represents the mean +/- error
Semaglutide dosed IP at 8ug/kg

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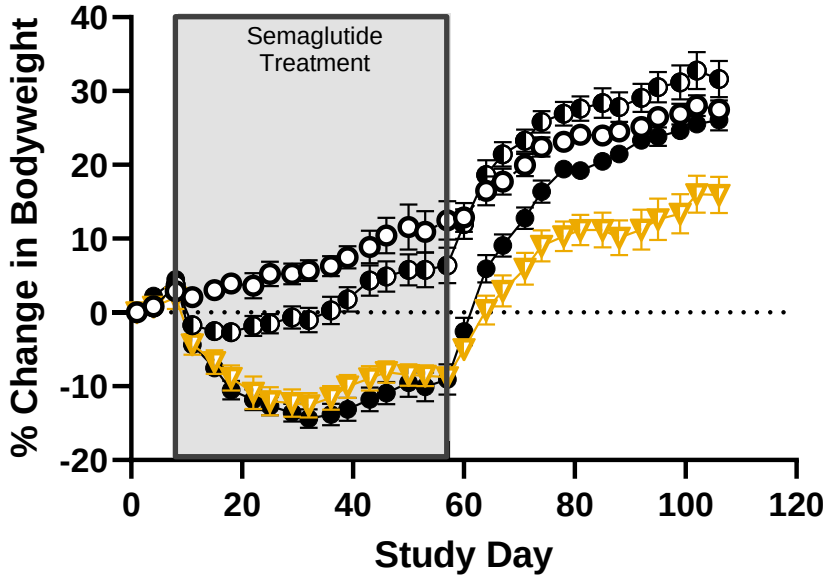
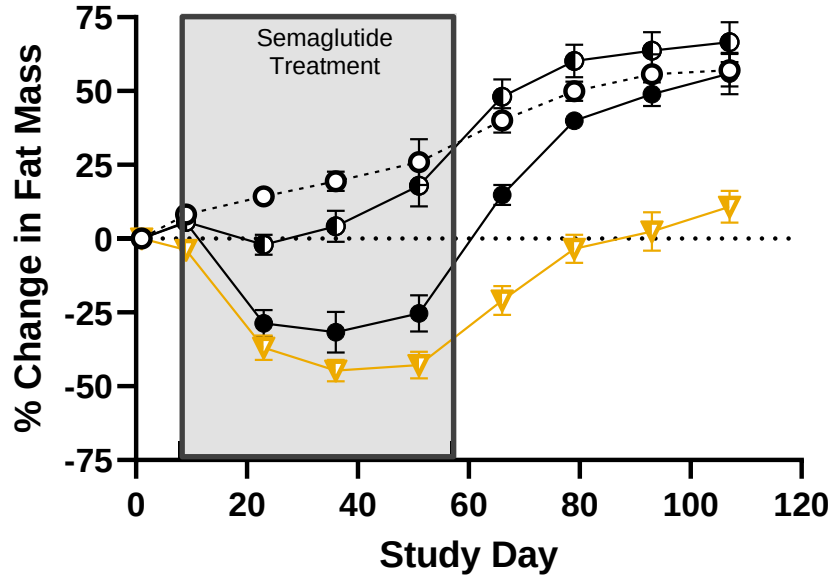
Novel siRNA Combinations Enhances Fat Loss with Sustained Weight Loss

Rodent models

Weight Loss



Fat Loss



PBS + vehicle

PBS + low dose semaglutide

PBS + high dose semaglutide

ACVR1C siRNA + "Gene X" siRNA + low dose semaglutide

Emerging Potential Profile	Enhanced fat loss (~45%)	Sustained weight loss	Increased lean mass	Prevention of weight regain

Plan to progress ALN-2232 (ACVR1c), the first Alnylam adipose tissue program, into the clinic in 2025

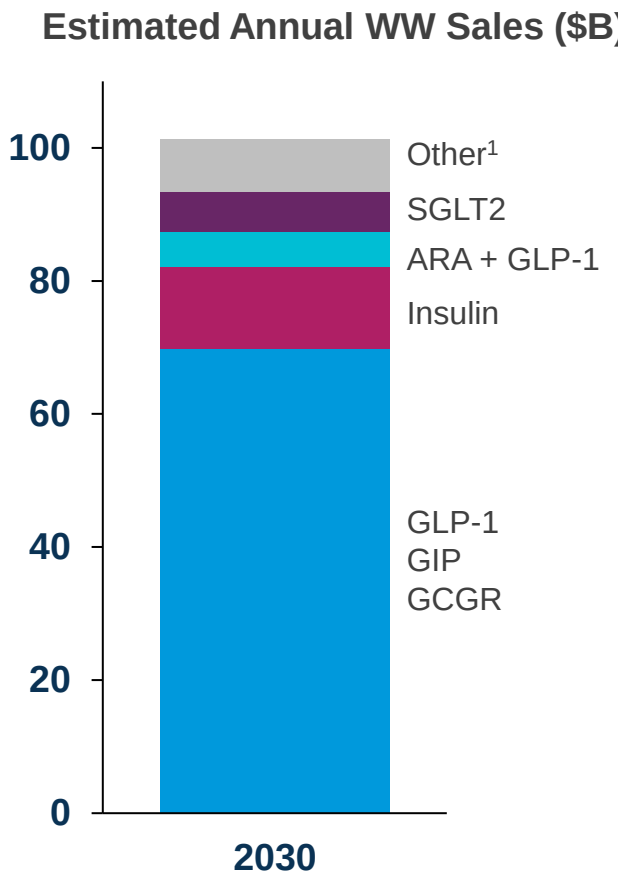
Doses of semaglutide are 8ug/kg/day and 40ug/kg/day for low and high doses respectively

Alnylam

Type 2 Diabetes Represents Significant Opportunity

Alnylam Portfolio Provides Optionality for Both Monotherapy and Combination Approaches

Large Market Opportunity



Unmet Needs

Poor Glycemic Control

~45% not at target

Comorbidity Management

Up to **40%** of patients with at least 3 comorbidities

Treatment Adherence

Sub-optimal adherence to oral anti-diabetic agents

Alnylam Strategy

- ✓ 1st insulin sensitizer in 30 years
- ✓ Novel combinations with SOC and siRNAs to address orthogonal MOA
- ✓ Long-acting siRNA potentially enables annual, bi-annual SC dosing

1. Other includes DPP4 inhibitors, AMPK inhibitors, OXPHOS inhibitors, PPAR agonists, and Alpha-glucosidase inhibitors. ARA: Amylin Receptor Agonist.
Source: Basu. Health Action International. 2019; Fang. NEJM. 2021; Freemantle. Diabetes, Obesity and Metabolism. 2015; Hegland. JAMA. 2024; Pitak; Public Heath; 2023; Person-Stuttard. Lancet. 2022; Puneet. Diabetes and Endocrinology. 2023; Cowen Reports; Evaluate Pharma; ClearView Analysis.

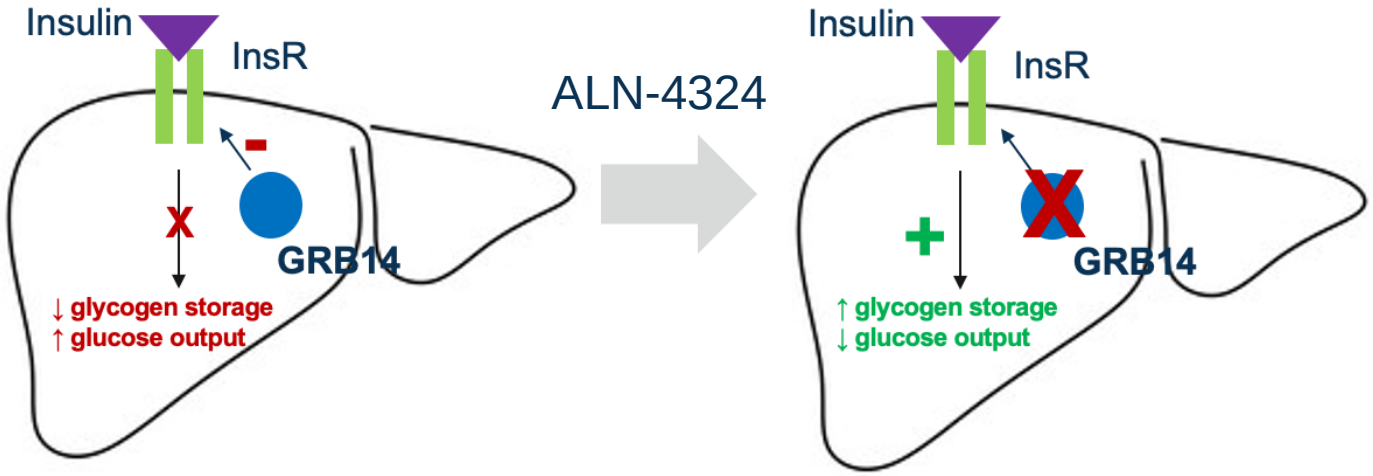
ALN-4324: Aiming to Deliver the First Long-Acting and Safe Novel Insulin Sensitizer in 30 years

Targets Growth Factor Receptor-Bound Protein 14 (GRB14)

Insulin Resistance

- One of the primary drivers of Type 2 Diabetes (T2D)
- Targeting Insulin Resistance can delay or prevent T2D
- Available Insulin sensitizers effective…
  BUT limited in use by adverse effects (e.g., weight gain)

Target GRB14: Negative Regulator of IR Signaling



Emerging Potential Profile

- Liver targeted insulin sensitizer with strong human genetics
- Preclinical validation showing impressive HbA1C lowering without liver fat accumulation
- Weight Neutral
- Long acting
  - Q3M to Q6M dosing
- Potential for insulin sensitization in muscle

IR: Insulin Receptor

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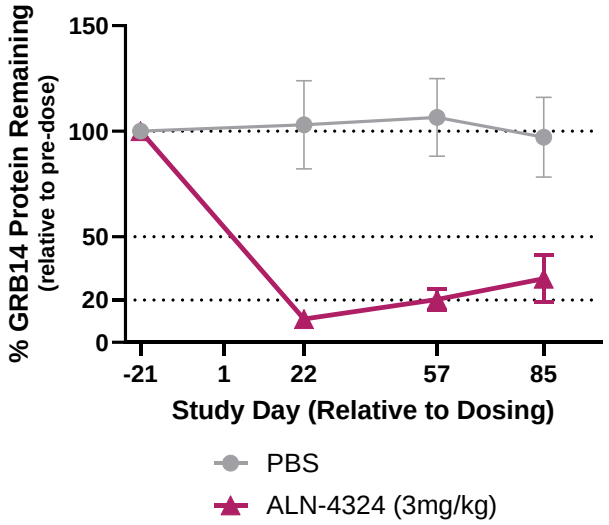
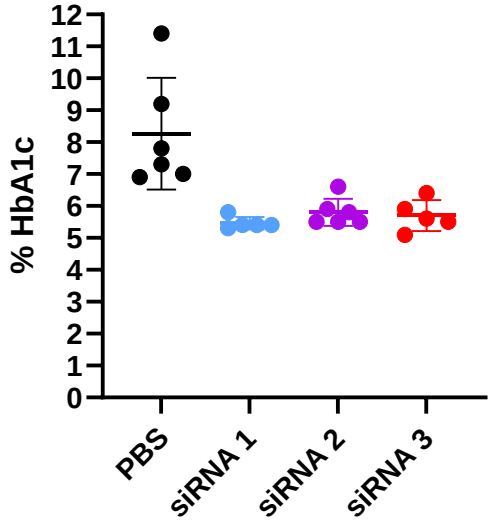
ALN-4324 Demonstrates Desired Potency, Specificity, and Durability

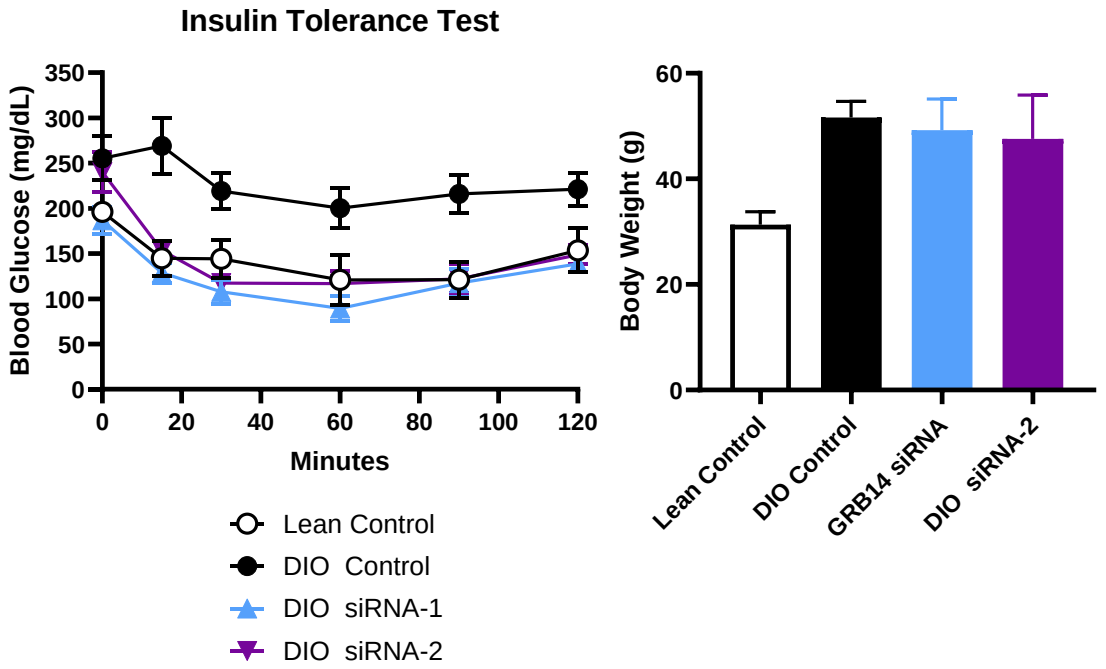
Achieves ~90% GRB14 Knockdown at Day 22 (NHP)



Normalizes HbA1c (Ob/Ob mice)



Improves Insulin Sensitivity Without Weight Gain (DIO mice)



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ALN-4324 Phase 1 Study Overview

Healthy Overweight or Obese Subjects

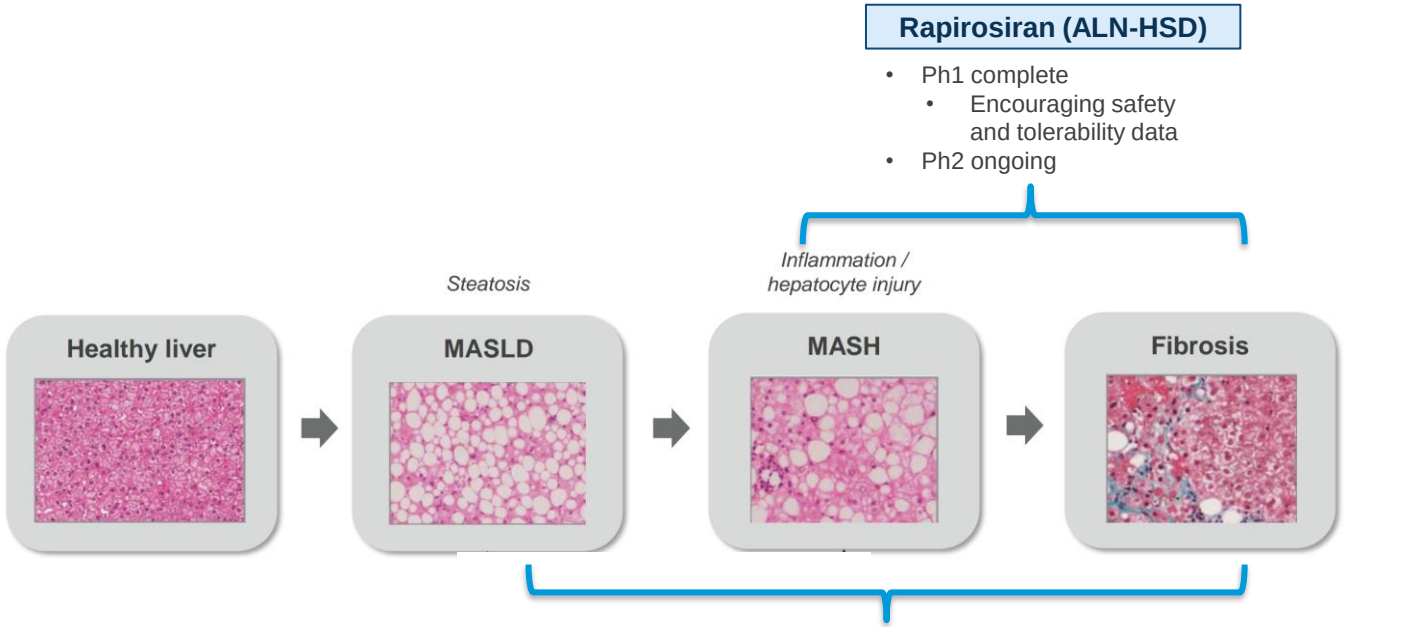
- **Primary Objective:** Safety & Tolerability
- **Exploratory Objective:** PD effect assessed by insulin sensitivity and biomarkers
- **Population:**
  - HbA1c <6.5%
  - 18 to 65 yrs., BMI 27 to 40
  - 5 dose cohorts (N=40; 8/Cohort)
- **First Patient First Dose expected Q1 2025**

Obese Type 2 Diabetes Mellitus (T2DM)

- ALN-4324 vs Placebo (N=60; 30/Arm)
- **Primary Objective:** To evaluate HbA1c reduction at week 24
- **Population:**
  - 18 to 75 yrs; BMI 30 to 45
  - HbA1c ≥7.0% to <10.5%
  - Background of SOC including GLP and SGLT2

Succeeding in MASH with RNAi Therapeutics

Genetically Validated Targets Offer Multiple Therapeutic Strategies



- Ph1 complete
  - Encouraging safety and tolerability data
- POC ongoing
  - Patient population: MASLD PNPLA3 p.I148M homozygotes
  - Initial data expected 2H 2025

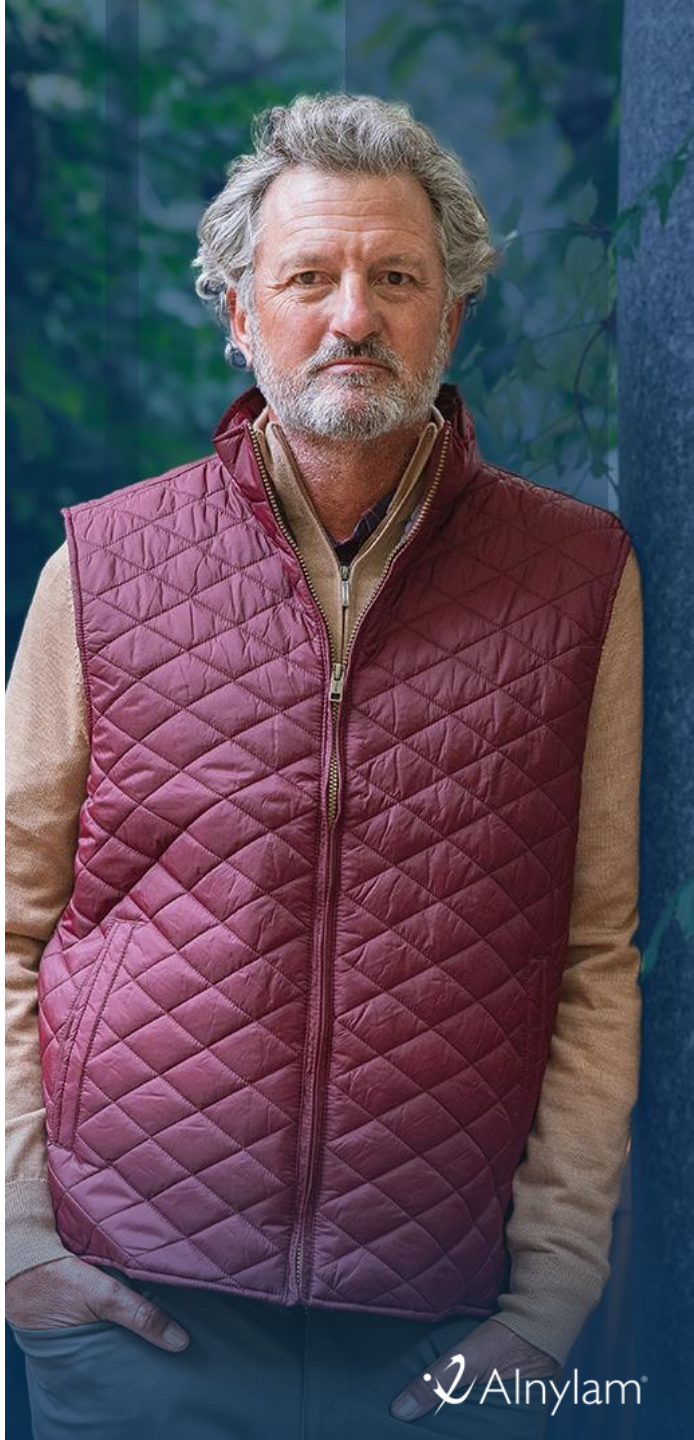
- On track for a CTA in Q1 2025

Development of rapirosiran, ALN-PNP, and ALN-CIDEB is being led by Regeneron Pharmaceuticals

REGENERON Alnylam

Well-Positioned To Deliver Innovations For Metabolic Diseases

- Unmet needs persist in diabetes, obesity, and other metabolic diseases despite incretin treatments
- Pursuing high-conviction targets with strong biologic rationale informed by human genetics with exquisite tissue selectivity
- RNAi therapeutics potentially offer differentiated approach
  - Extended durability enables infrequent dosing
  - Potential to improve adherence
  - siRNA combinations with standard of care could optimize clinical benefit
- Multiple programs advancing into clinical development in 2025

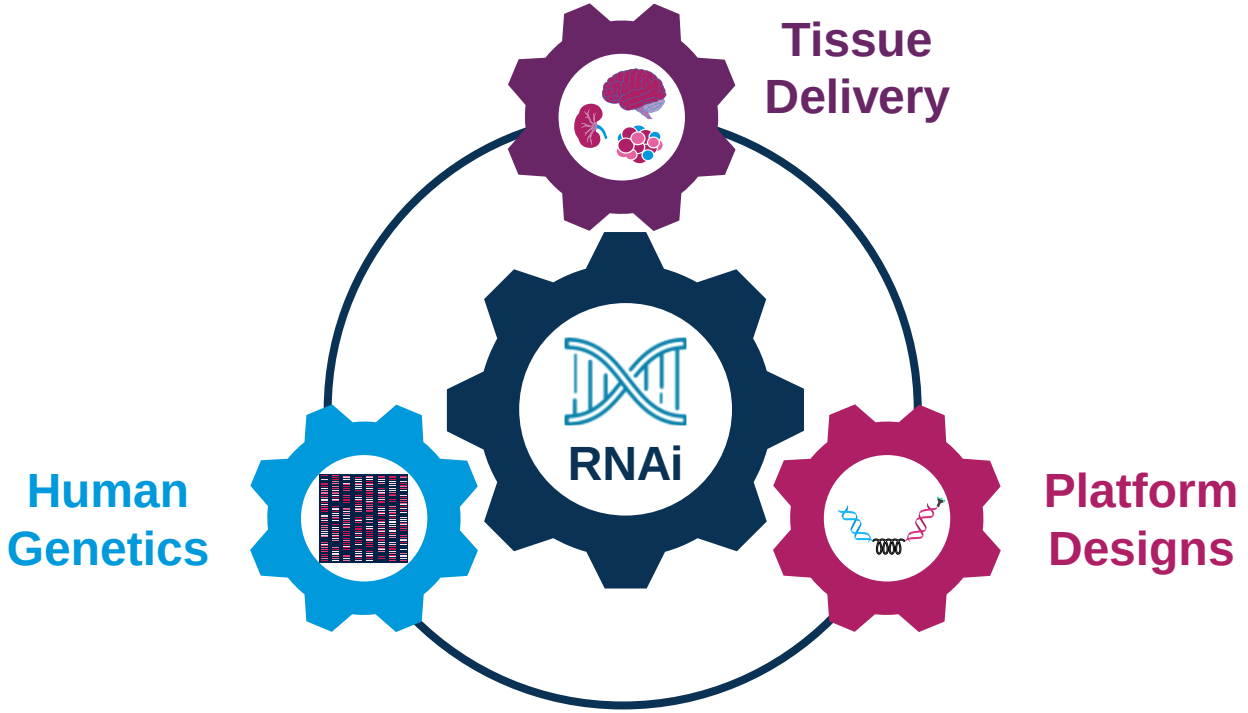


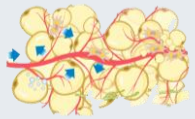
Next Wave of RNAi Therapeutics to Fuel a Robust Clinical Pipeline

Paul Nioi, Ph.D.
SVP, Research

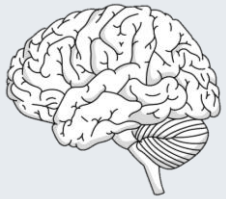
Anna Borodovsky, Ph.D.
VP, Research

Multiple Sources of Sustainable Innovation Drive a Robust Pipeline



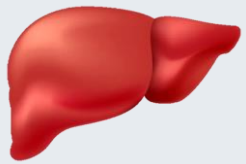


2 **new tissues** with INDs



2 new **CNS** INDs

+1 or more partner-led programs



5 new **liver** INDs

+5 or more partner-led programs

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Genetic Insights from > 1M People Fuel Our Differentiated Pipeline

Unique Amongst Technology Peers in Terms of Data Access and Expertise in Genetics

Data Access

Our Future Health

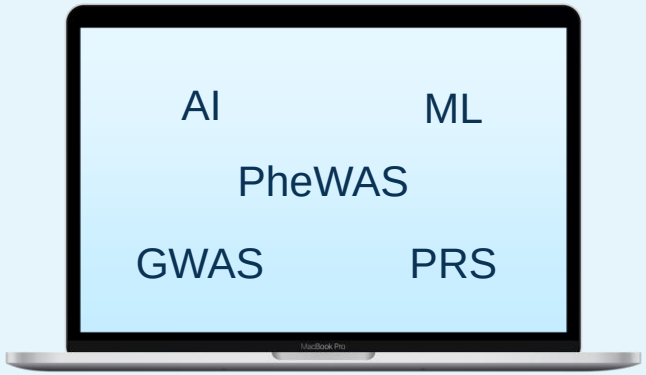
biobank uk

discoverme

All of Us RESEARCH PROGRAM

1M Individuals scaling to > 6M by 2030

Analytical Expertise



High Probability of Success Targets

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We Are On Track with Our 2-2-5 Strategy

Significant Opportunities in a Range of Conditions with High Unmet Need

DC = Development Candidate

Target	Indication	Stage or goal at R&D day '23	Achieved?	Current Stage
PLG	Bleeding disorders	IND-enabling	✓	Ph1
Gene B	Cholestatic liver disease	DC 2024	✓	IND-enabling
ACVR1C	Obesity	DC 2024	✓	IND-enabling
Gene D	Obesity	DC 2024	✓	IND-enabling
INHBE	Obesity	DC 2024	✓	IND-enabling
Gene F	Glutaric Acidemia	DC 2024	✓	IND-enabling
Gene G	Dry AMD	DC 2023	✓	IND-enabling
Gene H	Pruritus	DC 2024	✓	IND-enabling
Gene I	Genetic muscle disease	New program	✓	IND-enabling
GRB-14	T2DM	IND-enabling	✓	Ph1
HTT	Huntington's disease	DC 2023	✓	Ph1
MAPT	Alzheimer's disease	DC 2024	✓	IND-enabling
Genetically Validated Targets				

Liver program | Adipose program | Muscle program | CNS program

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ALN-6400
An Investigational Drug For Bleeding Disorders

Alnylam®

Majority of Bleeding Disorders Lack Treatment

ALN-6400 is a Potential Universal Hemostatic Agent

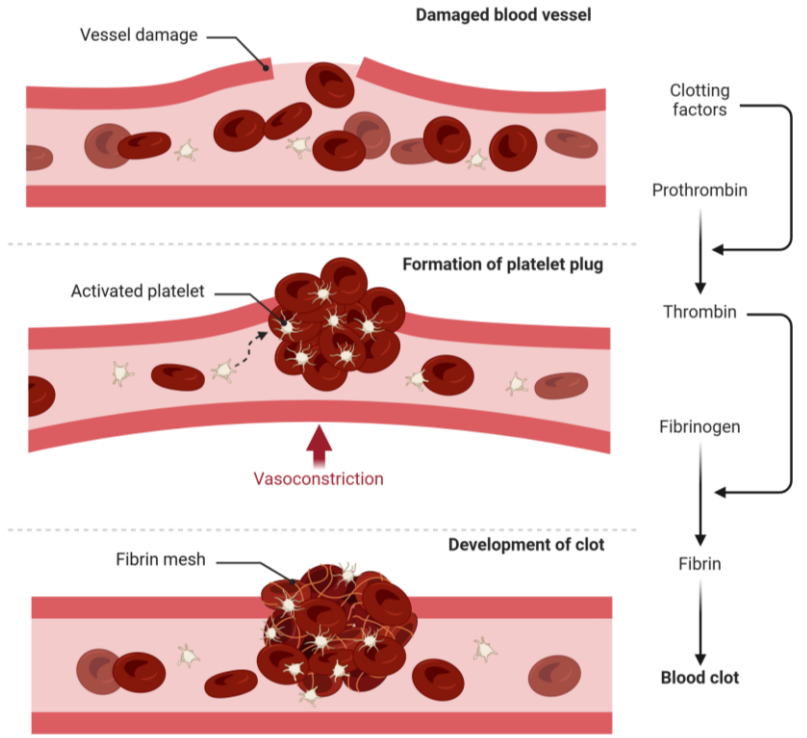
Bleeding disorder patients experience:

- Anemia
- ER Visits
- Anxiety & Depression
- Major Bleeding Events
- Hospitalization

~3 million people in the US are affected by bleeding disorders

Existing treatments are burdensome and can increase risk of thrombosis

Hemostasis



Modulation of fibrinolysis may allow the development of a universal hemostatic agent

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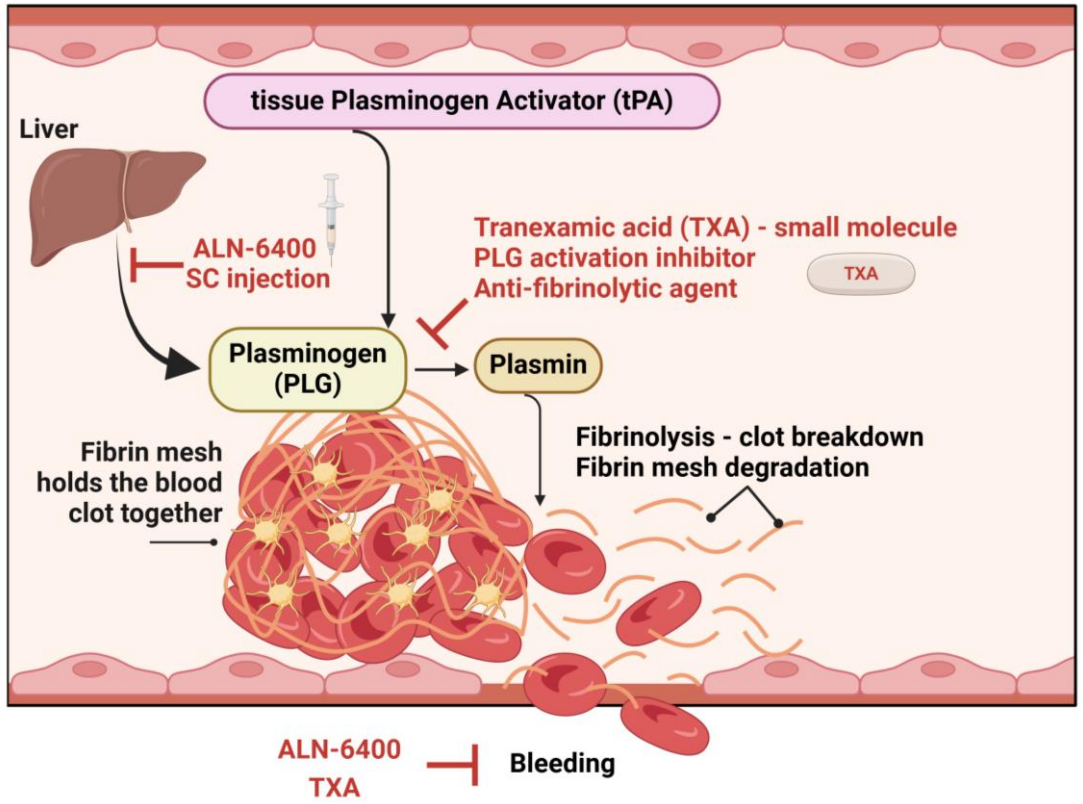
ALN-6400 - Lowering Plasma Plasminogen (PLG) to Reduce Bleeding



PLG is activated to plasmin and drives fibrinolysis: breakdown of fibrin mesh that holds together blood clots

Tranexamic acid (TXA) provides clinical validation for treating bleeding by inhibiting fibrinolysis

- Small molecule inhibitor of PLG activation
- Approved for treating heavy menstrual bleeding
- Frequently used off-label to treat bleeding disorders
- High pill burden, PK/PD variability and side effects limit use

ALN-6400 – a potential universal hemostatic agent that **opens the door to a "pipeline in a product" approach**

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UK Biobank Analyses Support Targeting PLG in Bleeding Disorders

↑ Circulating PLG protein levels

- ↑ GI and Nose bleeding
- ↑ Heavy menstrual bleeding

PLG loss of function

- ↓ GI and Nose bleeding
- ↓ Heavy menstrual bleeding
- ↔ No increase in risk of thrombosis

In house genetic analyses

No evidence of increased risk of thrombosis compared to known thrombophilic factors

Protein measured	Risk of thrombosis (OR per SD decrease in plasma level)	p value
Protein S	1.23	2e-24
Protein C	1.11	1e-06
Antithrombin	1.08	6e-05
PLG	**1.00**	**0.91**

In house proteomics analyses

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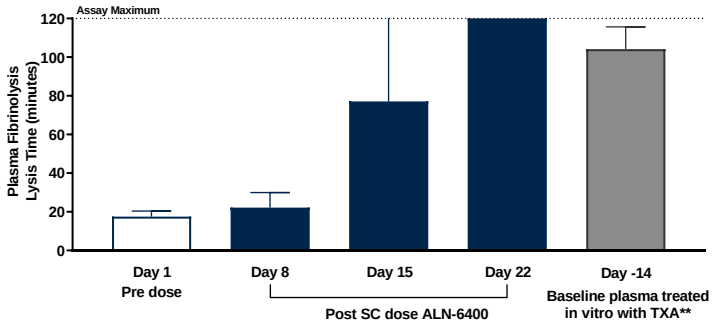
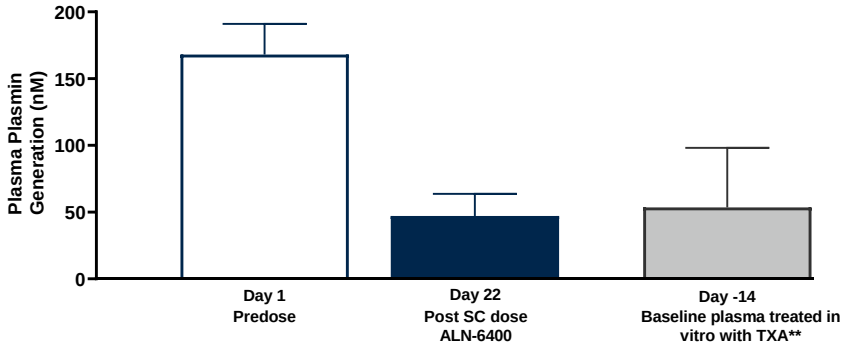
Treatment of NHPs With ALN-6400 Reduces Plasmin Generation, Fibrinolysis and Mucosal Bleeding

- ALN-6400 is a GalNAc-conjugated siRNA targeting PLG
- Highly selective for targeting of PLG transcript
- >90% reduction of circulating PLG achieved in NHP
- No evidence for increased risk of thrombosis in preclinical studies

Inhibition of Fibrinolysis (NHP plasma)

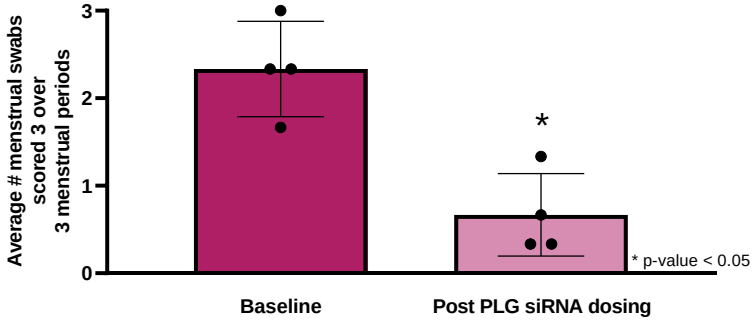


Reduced Plasmin Generation (NHP plasma)



Plasmin is an activation product of PLG

Reduced Menstrual Bleeding

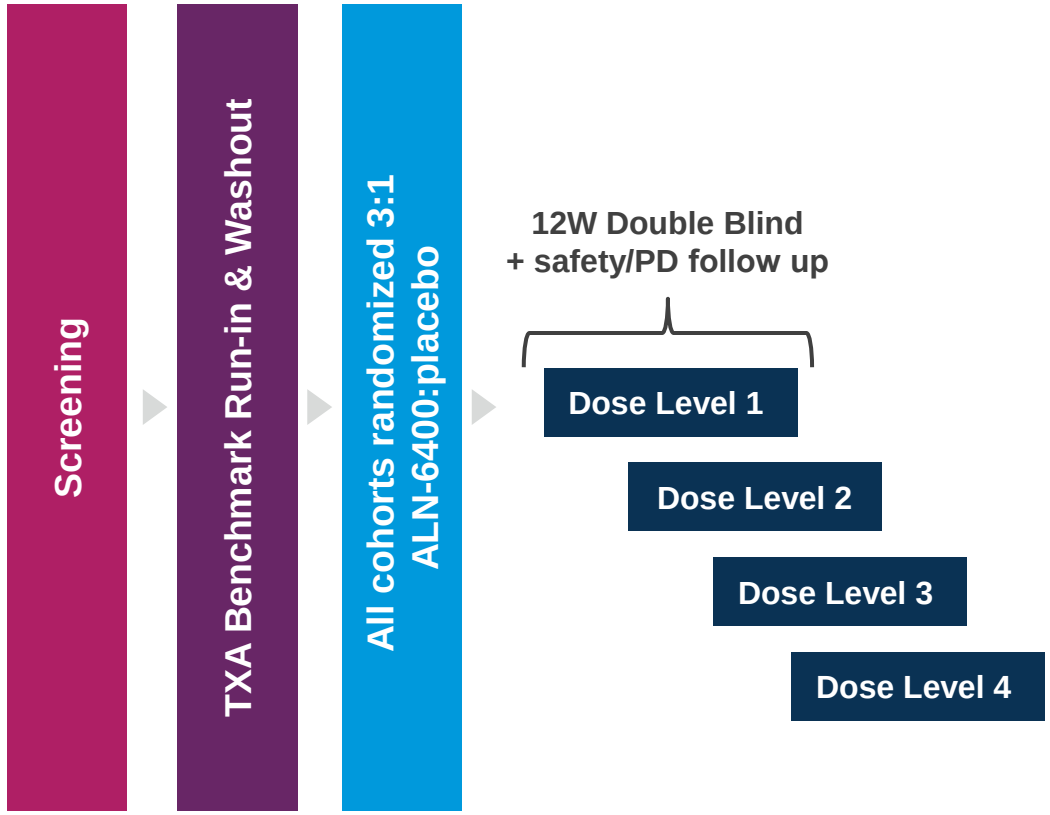


Daily monitoring of menstrual bleeding scored 0-3

*** TXA added in vitro to plasma from baseline samples (from Day -14) before Fibrinolysis or plasmin generation assays.*
Concentration of TXA added represents the C_{max} in human plasma at steady state after standard of care oral dosing (1300mg TID).

ALN-6400 Phase 1 Study in Healthy Volunteers

With Proof of Mechanism for Fibrinolysis Inhibition (Currently Enrolling)



Primary Objective

To evaluate the safety and tolerability of single ascending doses of ALN-6400

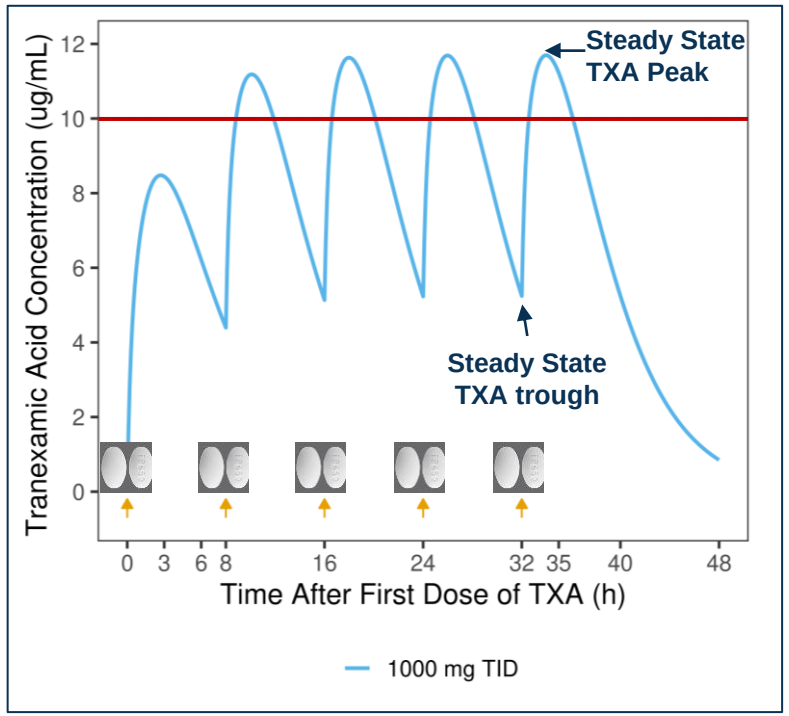
Includes SOC oral TXA dosing prior to SC ALN-6400/Placebo to evaluate impact on ROTEM (antifibrinolytic effect) and benchmark the antifibrinolytic response of TXA to ALN-6400

https://clinicaltrials.gov/study/NCT06659640

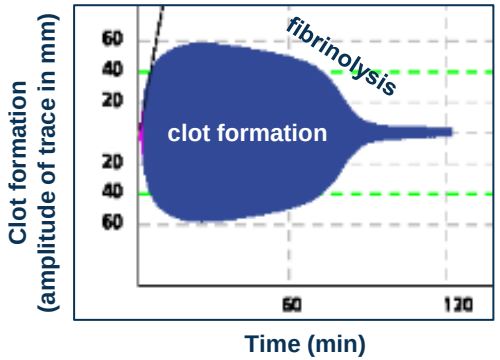
Evaluation of Fibrinolysis Using Ex-Vivo ROTEM Assay

Clinical Whole Blood Assay of Clot Formation and Fibrinolysis

Predicted PK Profile of TXA



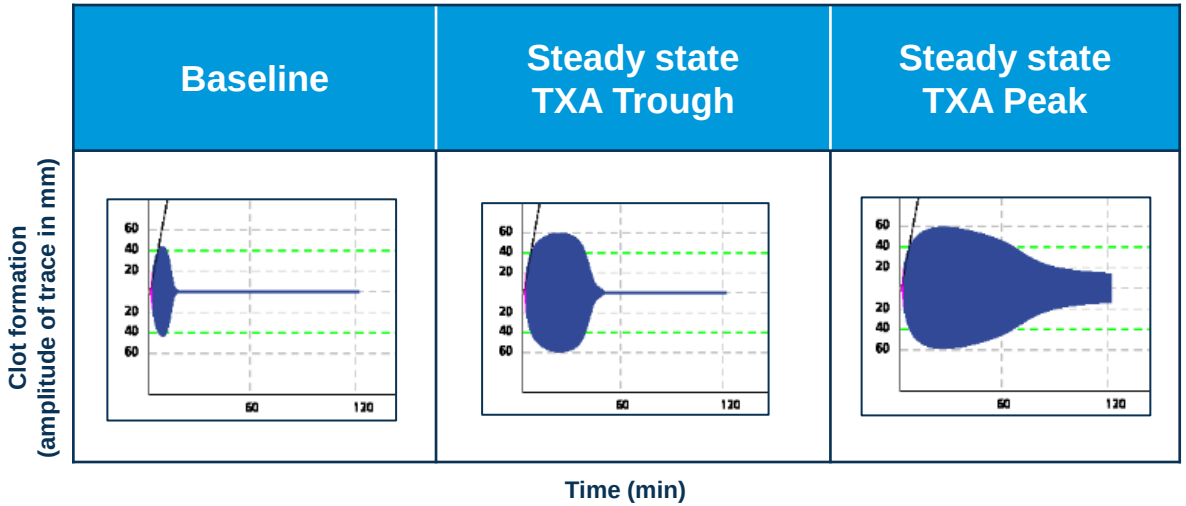
High pill burden and variable PK



tPA-ROTEM traces

- Whole blood clot formation and fibrinolysis over time
- Amplitude of trace represents the extent of clot formation and lysis

Healthy Volunteer dosed with oral TXA*



Clot formation is not affected, clot breakdown (fibrinolysis) is delayed

*SOC dose of TXA given orally during the run-in phase of the study
Steady state of TXA reached after 5th dose

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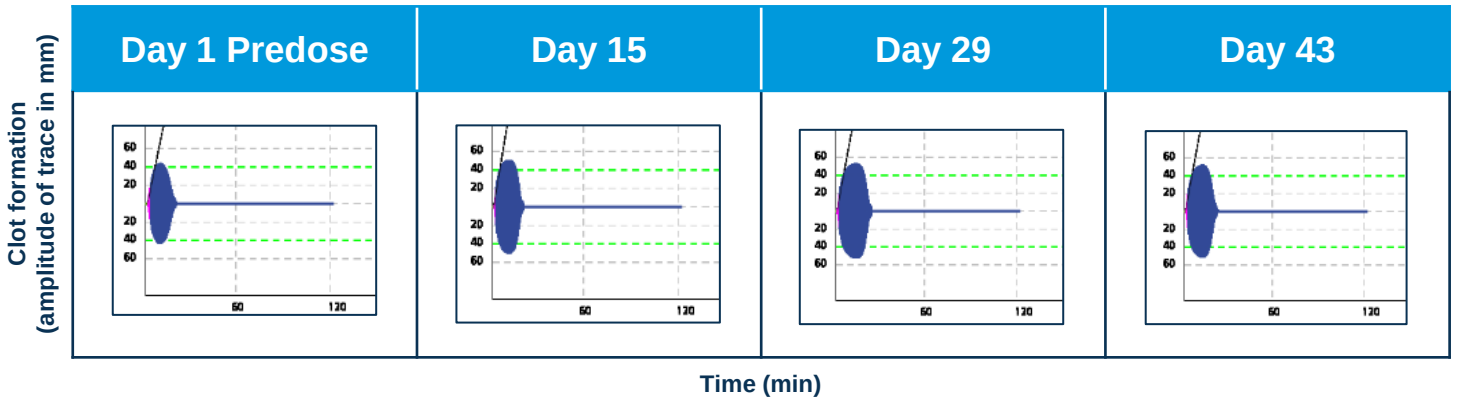
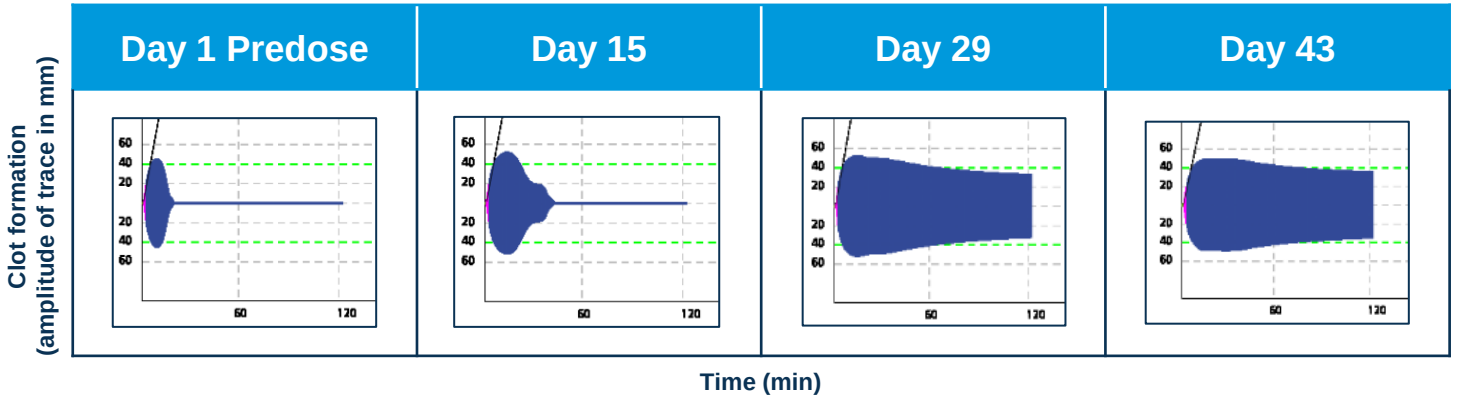
Initial Clinical POM: Inhibition of Fibrinolysis with ALN-6400

Four Months From CTA Filing to Clinical POM Data

Healthy Volunteer dosed with placebo



Healthy Volunteer dosed with ALN-6400



Plan to initiate a Phase 2 study in a bleeding disorder in the second half of 2025

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ALN-Gene G:
An Investigational Subcutaneously Administered Therapeutic to Treat AMD

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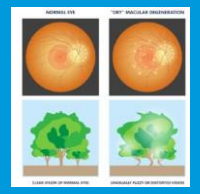
Dry Age-related Macular Degeneration is the Most Common Cause of Vision Loss in Older Adults

10M diagnosed patients in the US; 4.25M with early AMD; 4.25M with intermediate AMD; 1.5M with late AMD (50% wet, 50% dry)



Characterized by progressive impairment and loss of vision due to degeneration of photoreceptors

Risk factors include genetics, heart disease, obesity

Treatments exist for wet AMD but there are **no approved therapies that improve vision in dry AMD**

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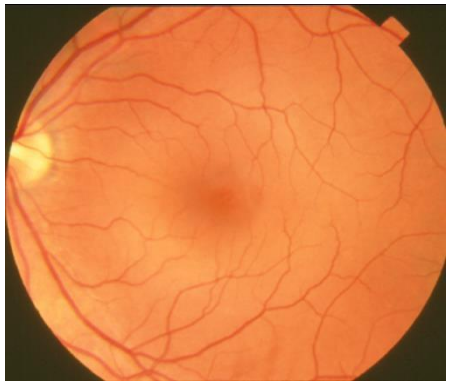
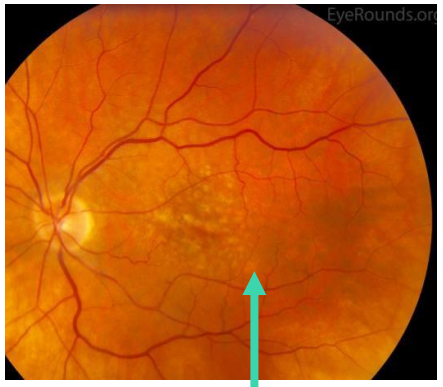
Significant Unmet Need Exists for Intermediate and Dry AMD Patients

Normal Fundus



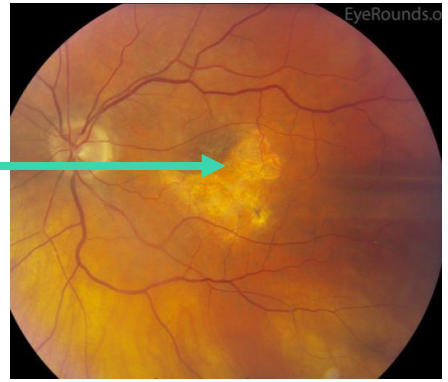
Intermediate AMD
No approved medicines



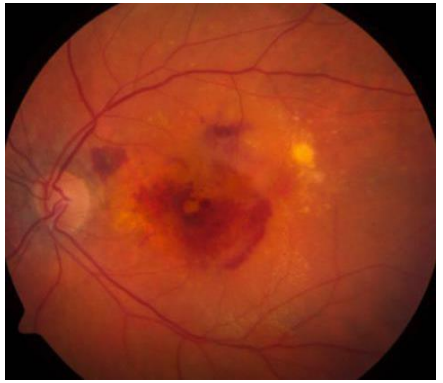
Drusen
Impaired dark adaptation
Blurring of vision

Geographic atrophy
Growing loss of central vision

Dry AMD
(Geographic atrophy)



Wet AMD (choroidal neovascularization)



2 approved medicines

C3/C5 inhibitors

- No improvement in vision
- Subtle slowing of atrophy
- Rare blinding retinal vasculitis
- Intravitreal administration

Anti-VEGF Ab's
are standard of care

ALN-Gene G has the potential to fill the unmet needs in intermediate AMD and geographic atrophy

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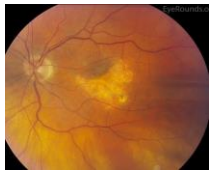
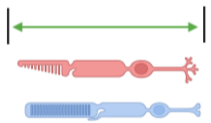
Gene G: A Differentiated Genetically Validated Target for AMD

Discovered Through In-house Human Genetics – Characteristics of Het Loss-of-function Carriers

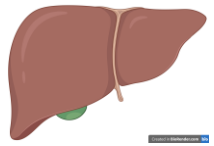
Disease/Trait	Effect of Gene G LOF	Pvalue
AMD (dry or wet)	OR = 0.50	7E-45
Dry AMD	OR = 0.49	1E-34
Wet AMD	OR = 0.49	2E-28
Photoreceptor IS/OS	+0.12 SD	3E-4



50% reduction in lifetime risk of developing AMD = potential to treat intermediate AMD



Thicker photoreceptor layer = potential to prevent vision loss

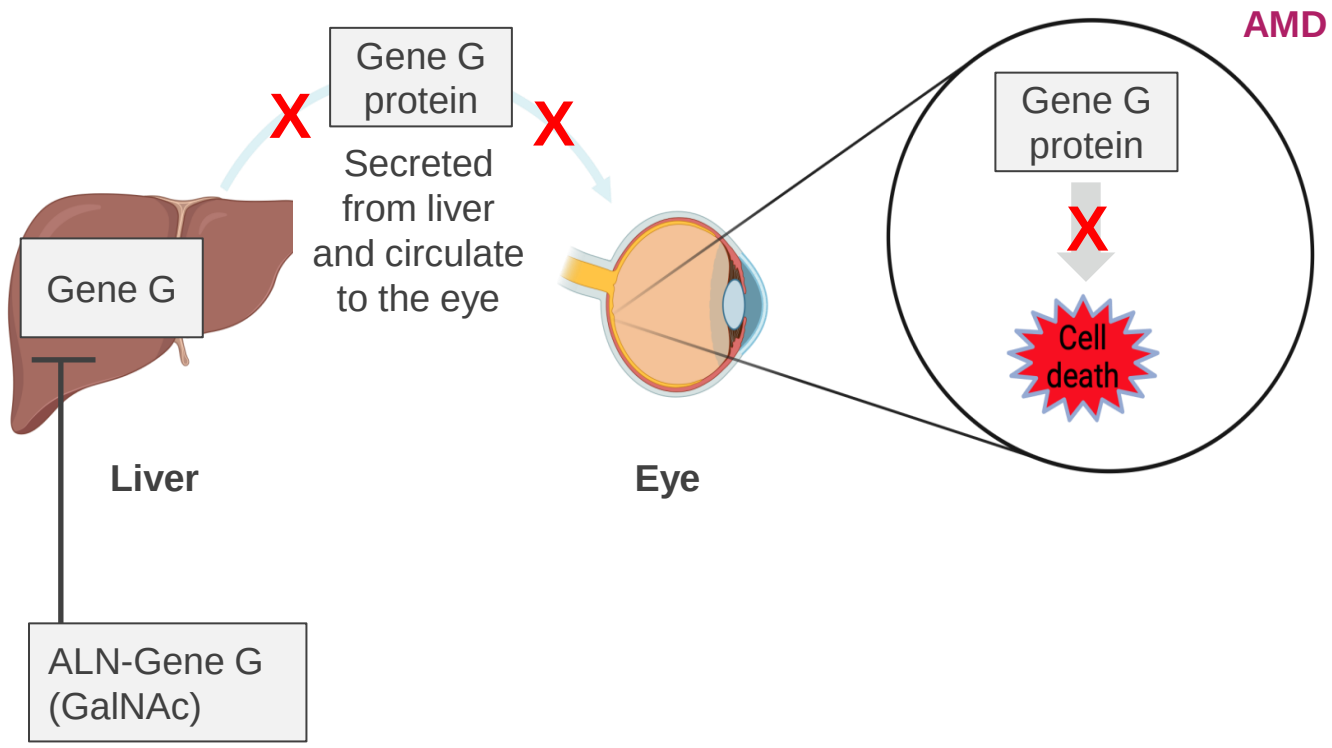


Exclusively liver expressed = targetable with GalNAc platform with infrequent subcutaneous dosing

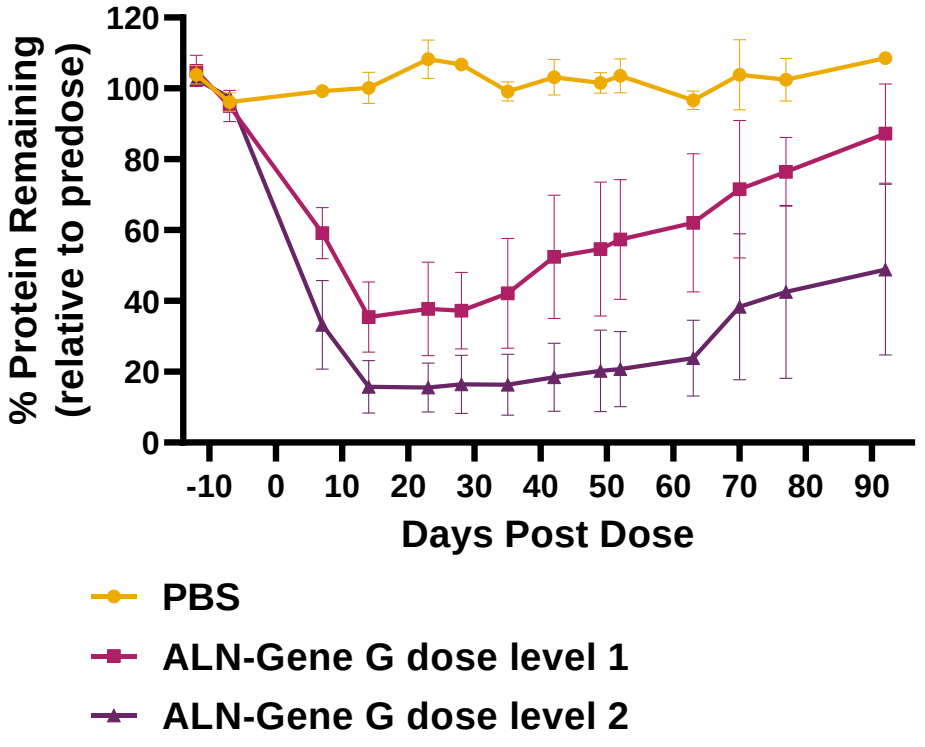
ALN-Gene G Effectively Knocks Down Gene G in the Liver

Profile Supports Q3-Q6M Subcutaneous Dosing

Therapeutic Hypothesis



Circulating Gene G Protein Levels in NHP



ALN-Gene G IND on track for ’25 filing

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Coming Attractions

Alnylam®

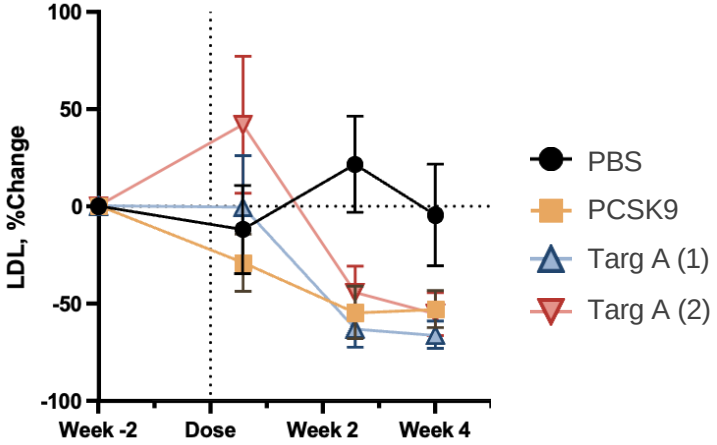
Genetic Discoveries Fuel Preclinical Pipeline Across Tissues

Liver

Target A – loss of function

Het LOF carriers ↓ 28mg/dl

PCSK9-independent LDL lowering in NHP



Skeletal Muscle

Target B – loss of function

↑ Grip strength

↑ Muscle mass

↑ Basal metabolic rate

Distinct mechanism from myostatin

Adipose

Target C – loss of function

↓ Abdominal fat

↓ Risk of T2D

↓ Visceral fat
Insulin resistance

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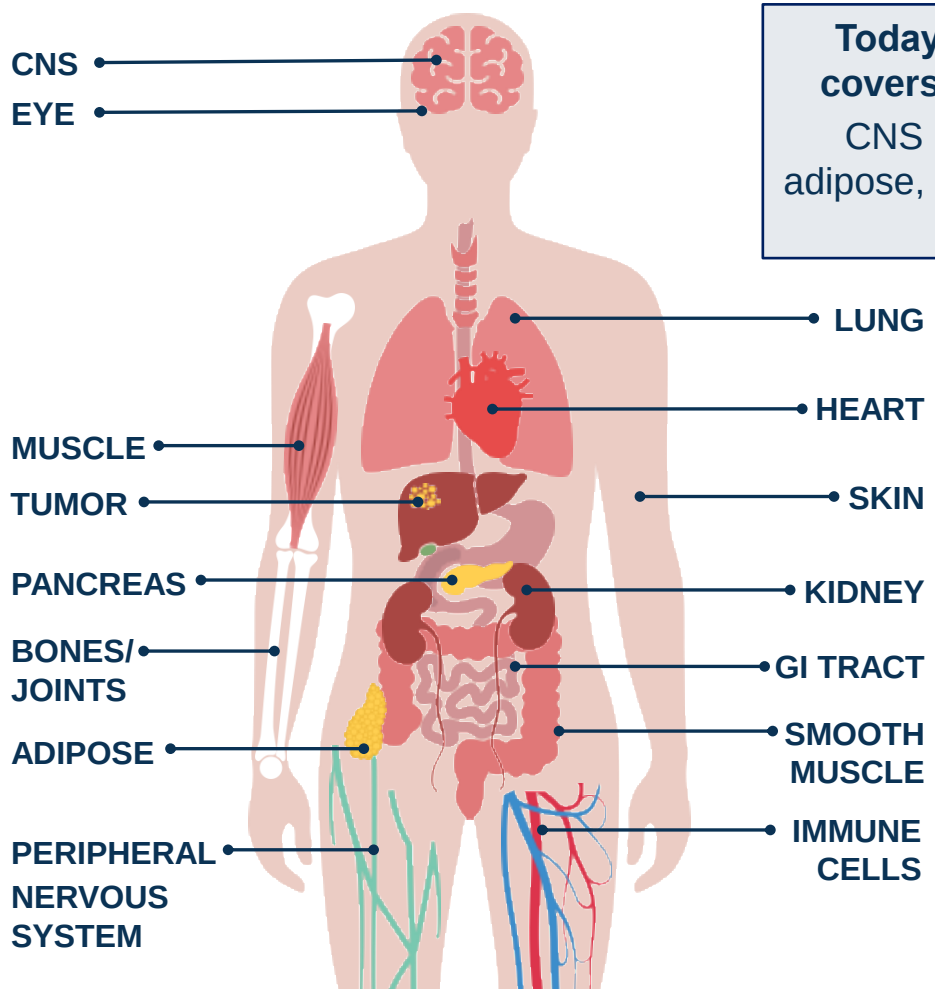
Unlocking Opportunities: Platform Innovation

Vasant Jadhav, Ph.D.
Chief Technology Officer

Continue to Define the Leading Edge of RNAi Technology

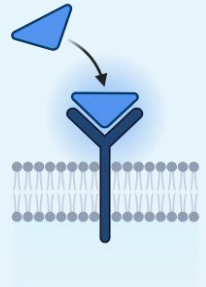
Expanding Delivery, Fine Tuning of siRNAs and Manufacturing

Our Ambition:
All Major Tissues with Therapeutic Target Opportunities by 2030
At least one CTA-enabling solution per year



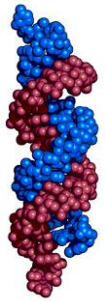
Today's delivery update covers 5 different tissues
CNS blood brain barrier, adipose, skeletal muscle, heart, and kidney

Best-in-Class Delivery Solutions



- SC dosing
- ≤ 3 mg/kg dose
- Efficient manufacturing

Continued Innovation
siRNA design and manufacturing



- Fine-tuning siRNA
- Revolutionize manufacturing

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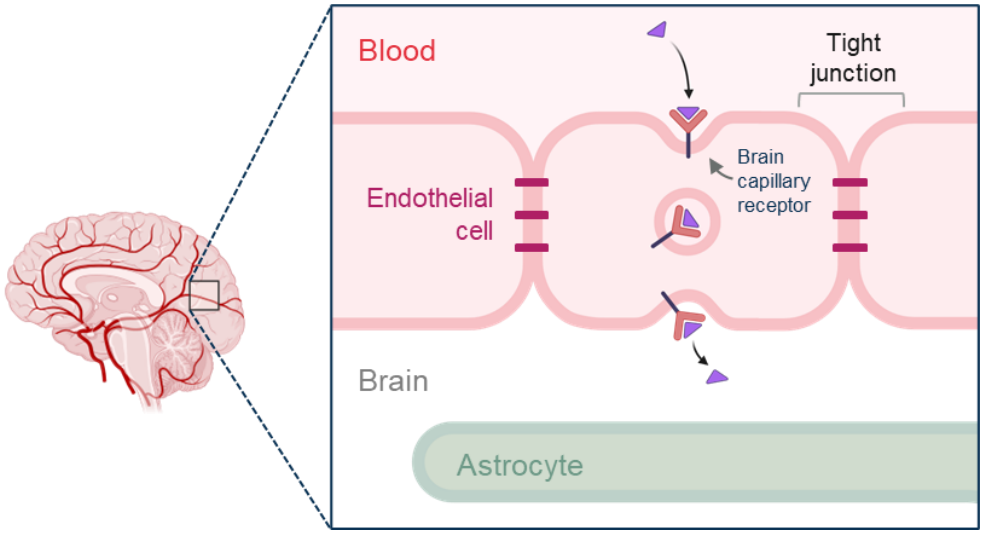
Overcoming Blood Brain Barrier (BBB): Expand CNS Opportunities via Systemic Dosing

Overcoming BBB Allows:

- IV or sub-cutaneous dosing
- Expanded indication opportunities
- More homogeneous biodistribution in CNS

BBB restricts direct access to brain cells



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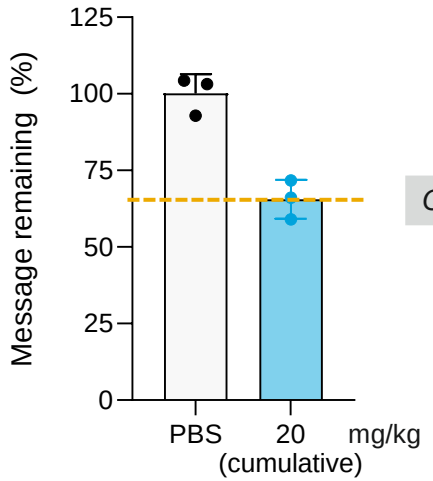
Overcoming BBB: Robust Activity After Systemic Dosing

Multi-log improvement in rodent activity through systematic optimization

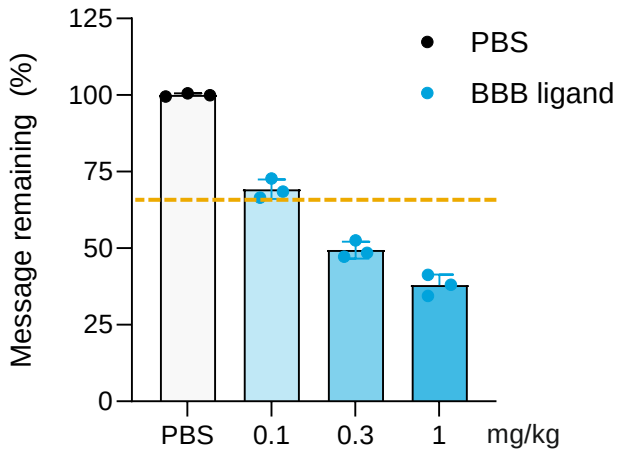
2023 R&D Day presentation

Mouse Cortex
QWx4 · 5 mg/kg · IV · D24



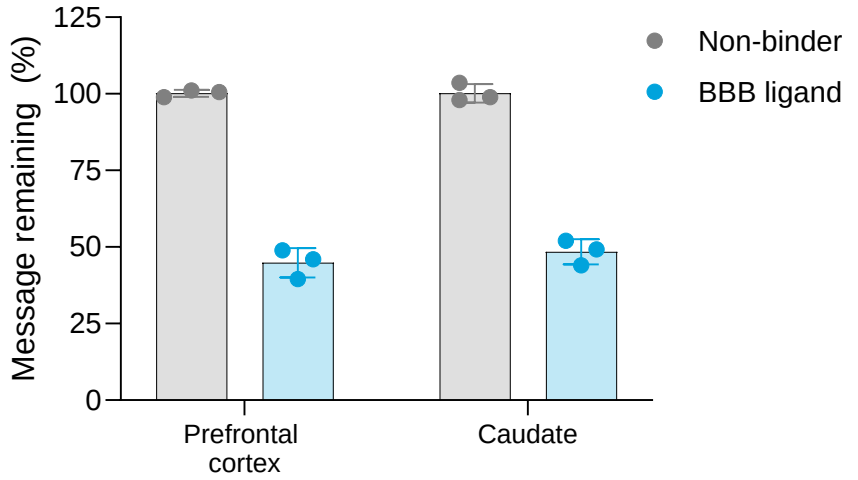
Optimization

Mouse Right Hemisphere
Single dose · IV · D14



Homogeneous activity across brain structures in non-human primates

Non-Human Primate
1 mg/kg x 3 · IV · D28



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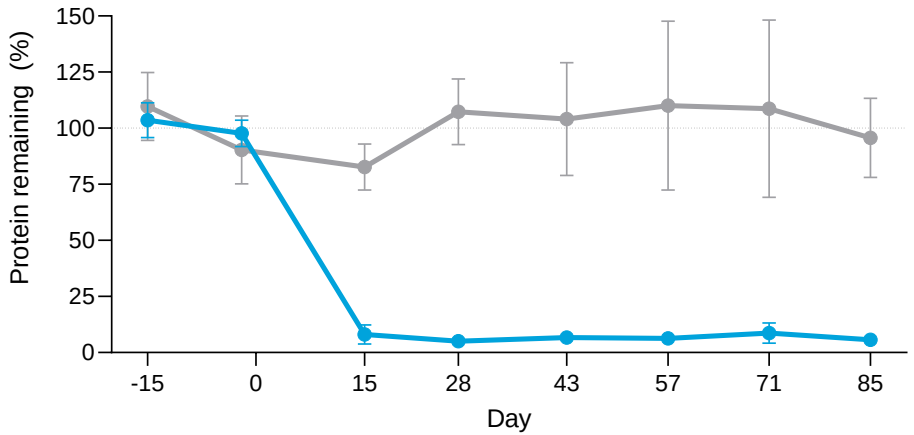
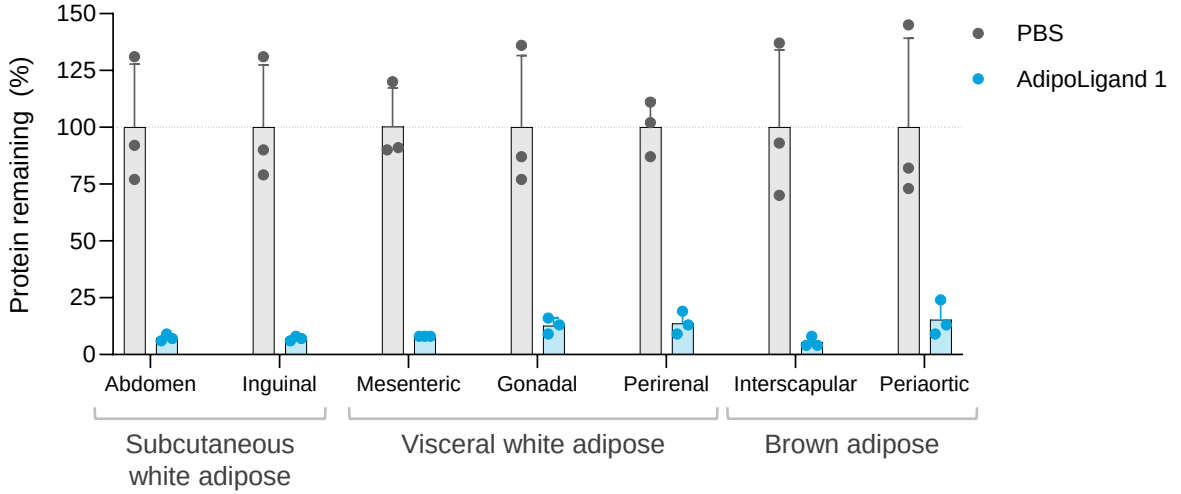
Adipose: Small Molecule Conjugate Elicits Robust Knockdown in NHP After SC Injection

NHP Data from ACVR1C
Single dose · SC · 3 mg/kg

Deep and durable knockdown



Consistent activity across adipose depots at D85



AdipoLigand 1

- SC dosing ✓
- ≤ 3 mg/kg dose ✓
- Efficient manufacturing ✓

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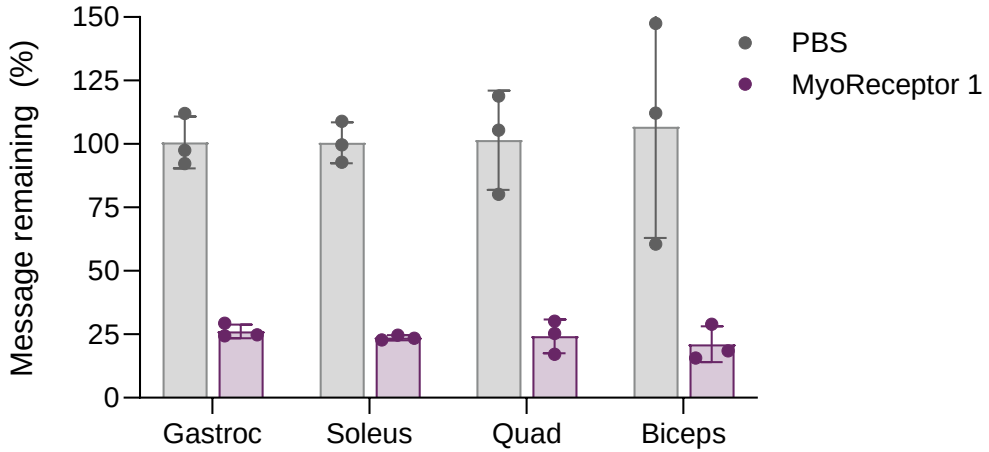
Skeletal Muscle: Novel Small Molecule Conjugate Elicits Robust Knockdown in NHP After SC Injection

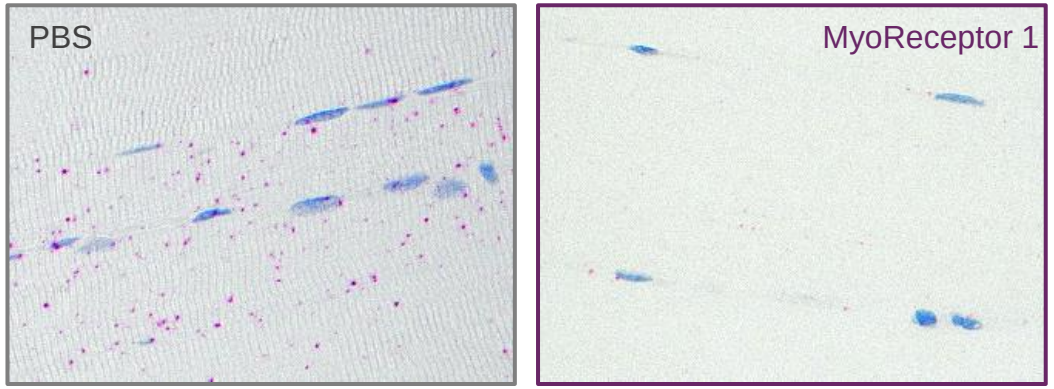
Overcomes Requirements for IV Infusions and High Doses of Antibody With TfR1 Based Approaches

NHP Data from CTA-enabling Program
Single dose · SC · 3 mg/kg · D84

Consistent activity across skeletal muscle types



Activity in biceps myofibers confirmed by in situ hybridization for target mRNA transcript



MyoReceptor 1 ligand

- SC dosing ✓
- ≤ 3 mg/kg dose ✓
- Efficient manufacturing ✓

CTA expected by YE 2025

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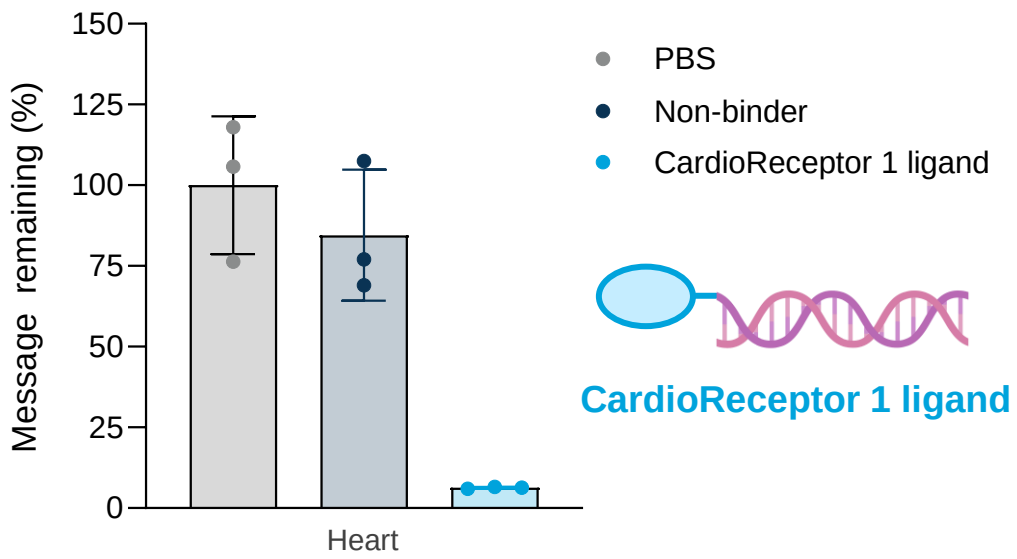
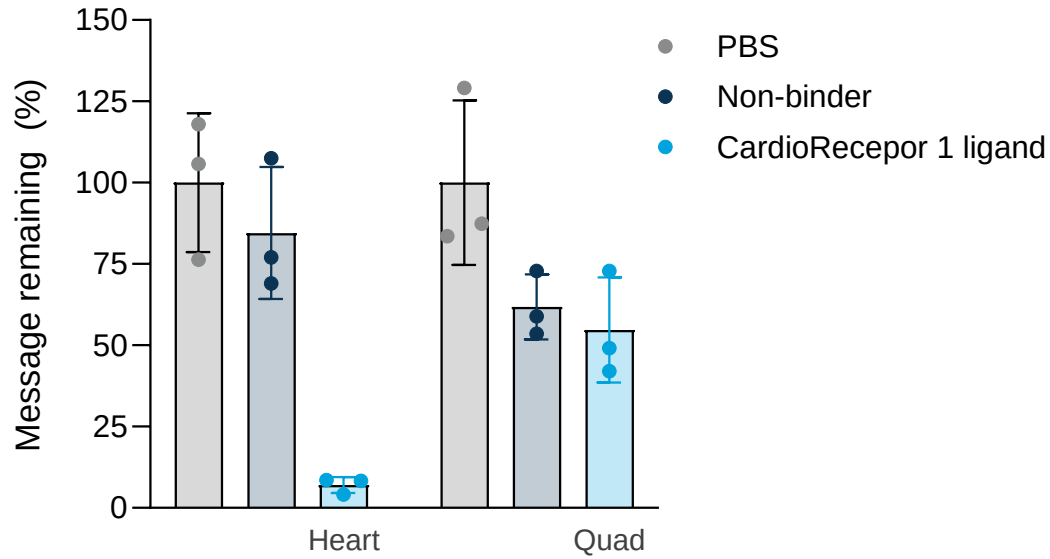
Heart: Ligands Targeting CardioReceptor 1 Demonstrate Potent and Selective Knockdown in Mice

Mouse

Heart Activity
Single dose · 2 mg/kg · SC · D21



Heart Specificity
Single dose · 2 mg/kg · SC · D21



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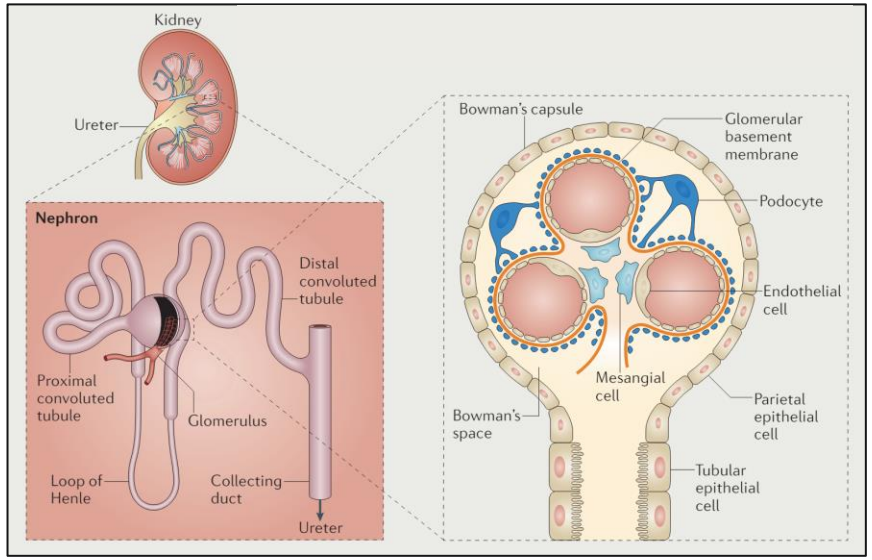
Kidney: Cracking the Delivery Puzzle – Functional Delivery of RNAi in Kidney

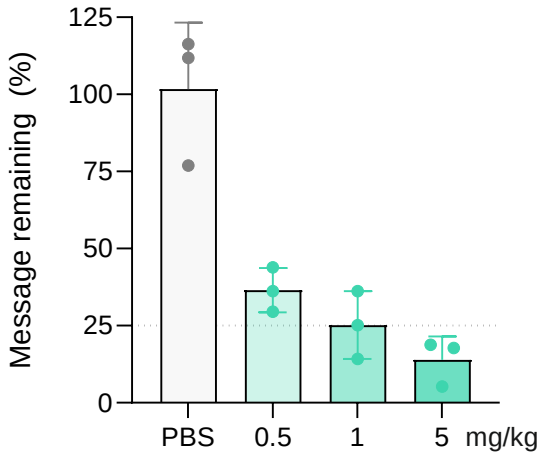
Anatomical and cellular complexity of kidney presents challenges for delivery of RNAi



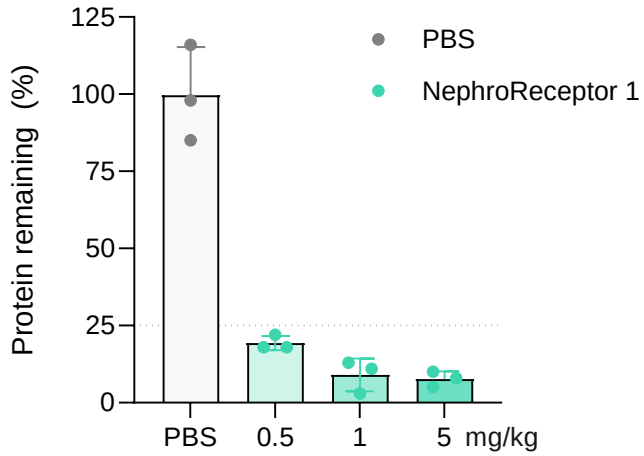
- **Filtration of ~200 liters of fluid a day from renal blood flow**
- **Multifunction organ system:**
  - Removal of metabolic waste products
  - Reabsorption of nutrients
  - Production of erythropoietin and renin
- **~30 unique cell types**

Mouse

mRNA
Single dose · SC · D7



Protein
Single dose · SC · D7



Functional delivery of siRNA conjugate

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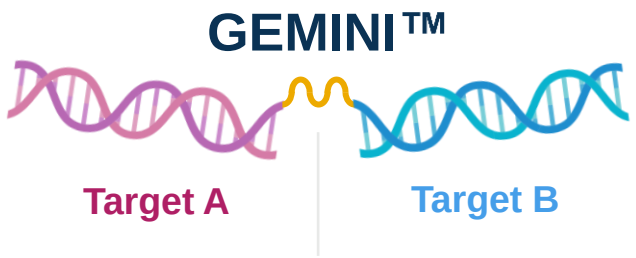
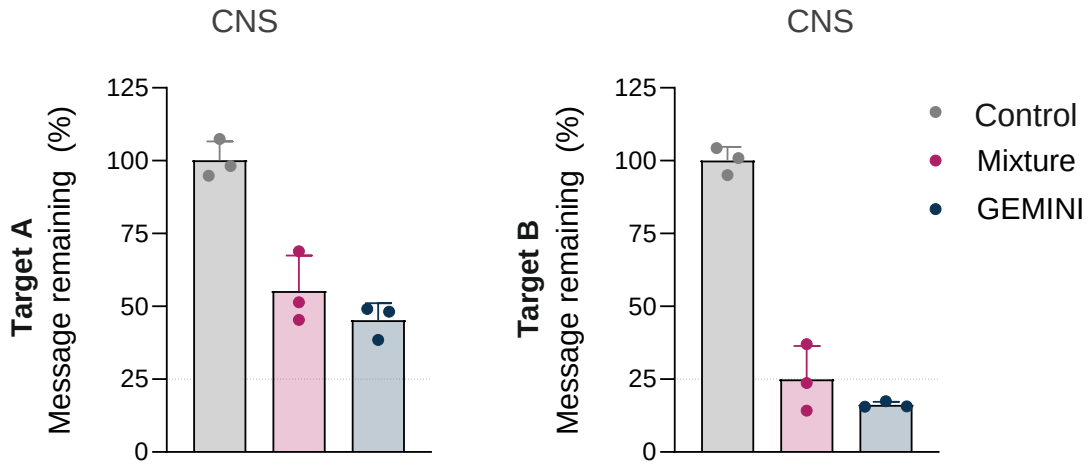
Multi-Tissue Targeting: Simultaneous Delivery to Address Multi-Organ Diseases

Simultaneous Knockdown of Multiple **Targets**

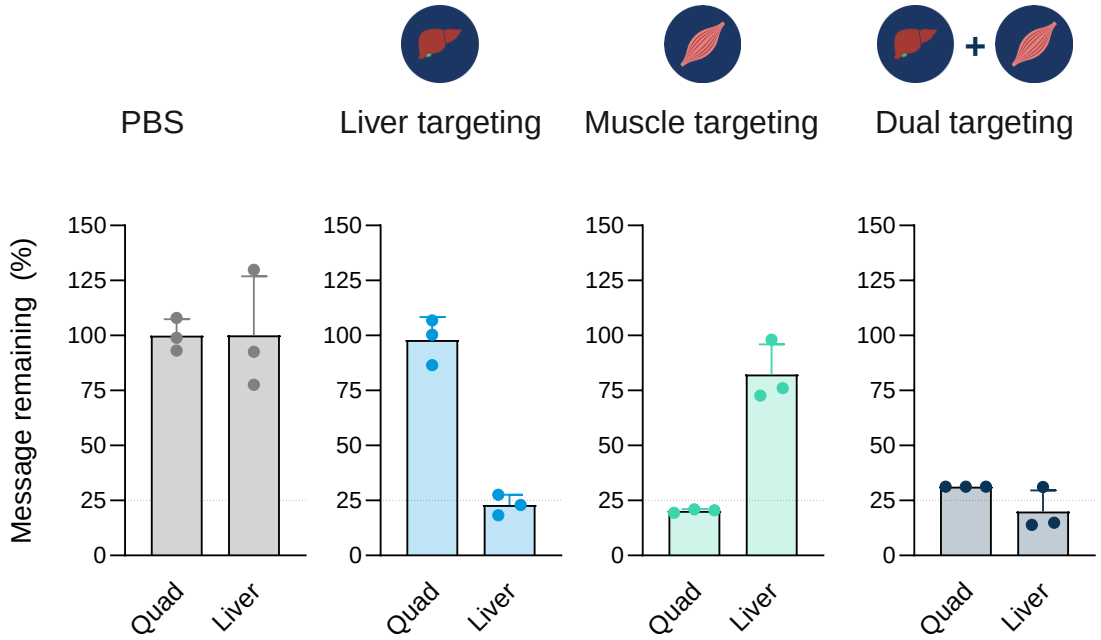




0.9 mg + 0.9 mg (mixture); 1.8 mg (GEMINI) · IT dosing in rats · D43

Simultaneous Targeted Delivery to Multiple **Tissues**

Single siRNA with dual-targeting



1 mg/kg; IV dosing in mice · D7

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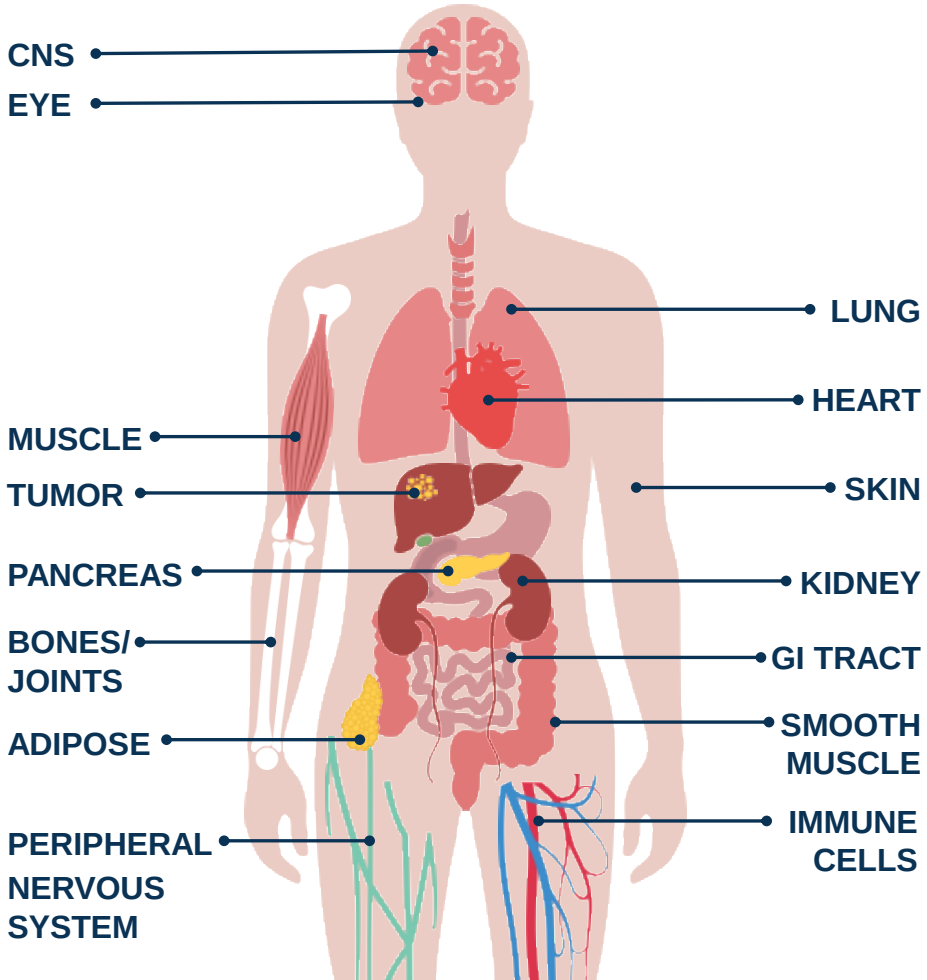
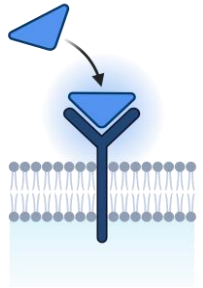
Continue to Define the Leading Edge of RNAi Technology

Expanding Delivery, Fine Tuning of siRNAs and Manufacturing

Our Ambition:
All Major Tissues with Therapeutic Target Opportunities by 2030
At least one CTA-enabling solution per year



Best-in-Class Delivery Solutions



- SC dosing
- ≤ 3 mg/kg dose
- Efficient manufacturing

Continued innovation
siRNA design and manufacturing

- Fine-tuning siRNA
- Revolutionize manufacturing

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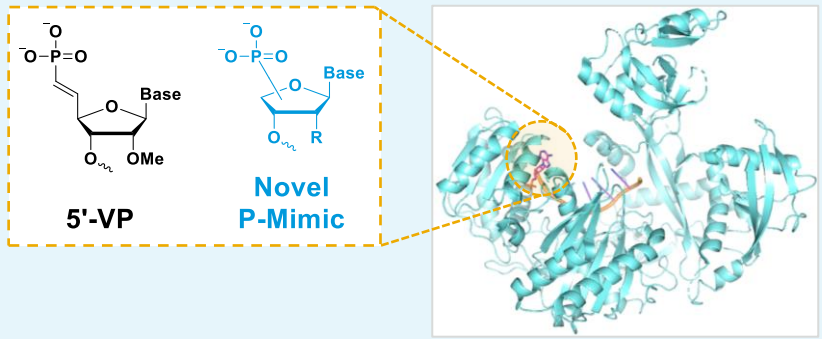
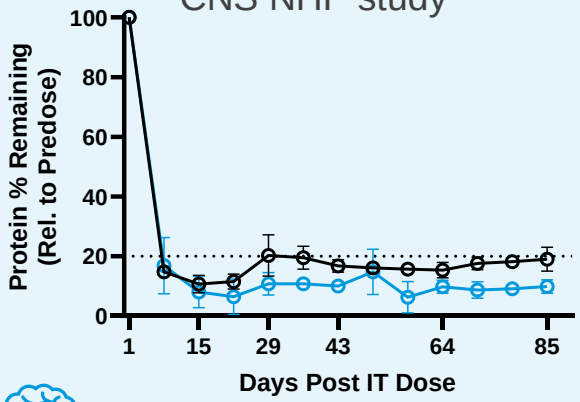
Fine-Tuning Alnylam's Best In Class siRNA Designs

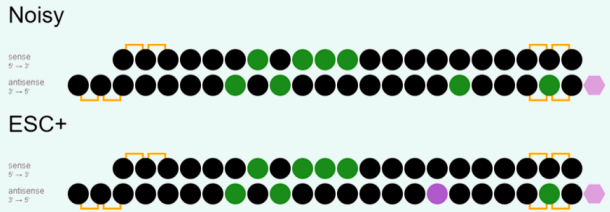
Ensuring Maximal Activity with Novel 5'-Phosphate Mimics



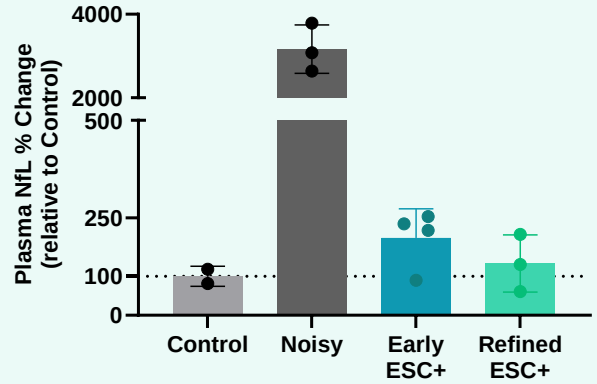
CNS NHP study



Optimizing Safety Through Novel Modification Patterns

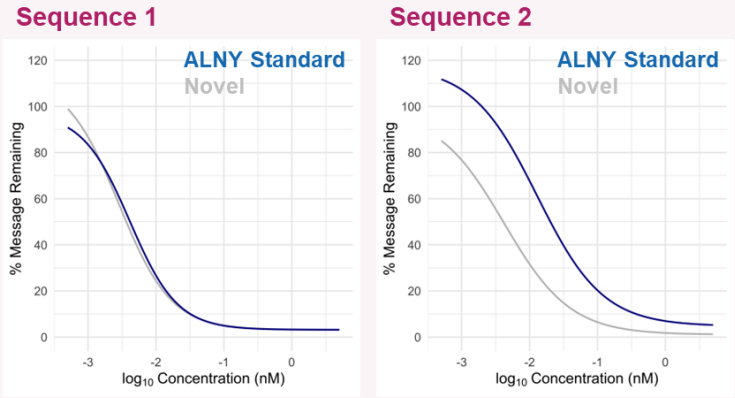


CNS rat study



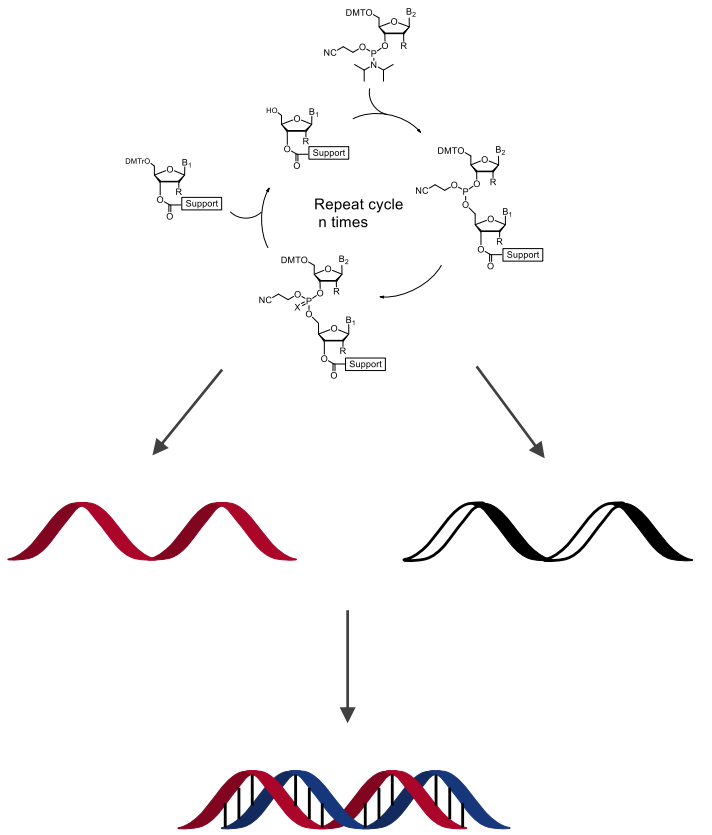
Fine-tuning siRNA Modification Pattern to Improve Potency

In vitro activity of siRNAs



Current Status of siRNA Manufacturing

Solid Phase Based (SPB) Process



Solid Phase Synthesis

Single Strands

Duplex

- Solid-phase synthesis is supporting our current pipeline and approved therapies
- Well-suited for low demand, shorter development time programs
- It will be challenging for solid-phase synthesis alone to meet the supply demand or COGS necessary for prevalent indications
- A new technology for manufacturing of oligonucleotides is needed

Enter Enzymatic Ligation

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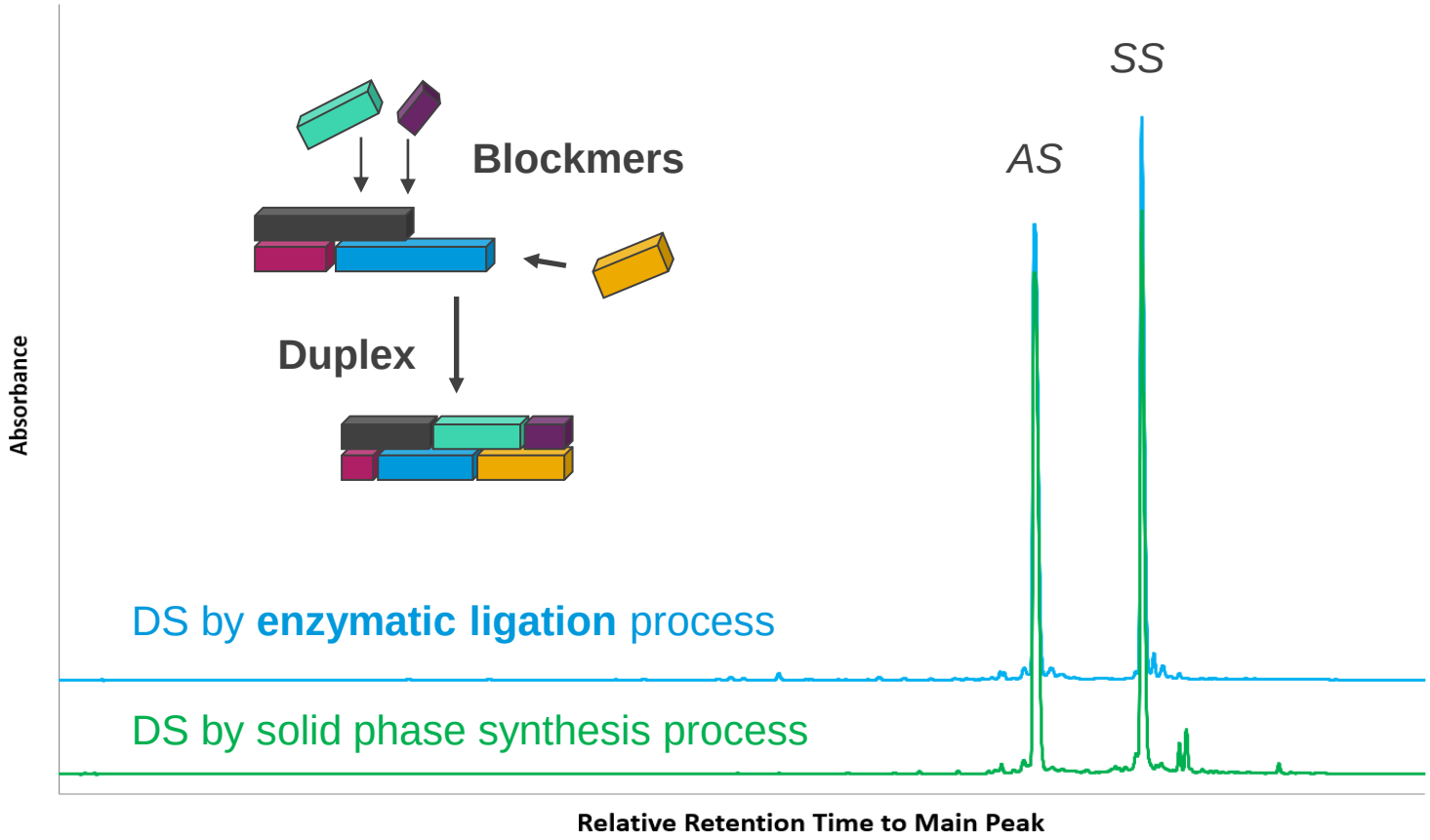
Enzymatic Ligation: Meet the Demand and Lower the Cost

Alnylam Continues to Lead a Revolution in Biology by Revolutionizing Oligonucleotide Manufacturing



Meet Demand

Decrease Cost

Expand Capability

Environmental Impact and Sustainability

- Achieved PoC yielding 90-95% pure drug substance (DS)
- No need for chromatographic purification
- Highly reproducible method

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We Continue to Define the Leading Edge of RNAi Technology

Expanding Delivery, Fine Tuning of siRNAs and Manufacturing

- Delivery to all major tissues with therapeutic targets by 2030
  - Focused on best-in-class delivery solutions
  - Reported progress on 5 different tissues
  - Two CTAs in 2025 based on adipose and skeletal muscle delivery
- Demonstrated dual tissue delivery of siRNA as single entity
- Continuing to fine tune siRNA designs for improved potency and specificity
- Enzymatic ligation approach to meet the demands of broad indications
  - Represents a key advance in oligonucleotide manufacturing


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Q&A

12:30 – 12:55p ET

TOPIC	PRESENTER
Durable Leadership in RNAi Therapeutics	**Kevin Fitzgerald, Ph.D.,** Chief Scientific Officer
Metabolic – Next Wave of Innovation	**Sandeep Menon, M.D., Ph.D.,** Chief Development Officer
Next Wave of RNAi Therapeutics to Fuel a Robust Clinical Pipeline	**Paul Nioi, Ph.D.,** SVP, Research **Anna Borodovsky, Ph.D.,** VP, Research
Platform Innovation	**Vasant Jadhav, Ph.D.,** Chief Technology Officer


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Closing Remarks

Pushkal Garg, M.D.
Chief Medical Officer

Alnylam 2025 Goals

onpattro (patisiran) / amvuttra (vutrisiran) / GIVLAARI (givosiran) / OXLUMO (lumasiran)		Combined Net Product Revenue Guidance $2,050M – $2,250M	**2025**
VUTRISIRAN	ATTR Amyloidosis	U.S. FDA Approval	**PDUFA date March 23, 2025**
		Additional Global Approvals (Japan, EU)	**Q2, Q3**
NUCRESIRAN* **(ALN-TTRsc04)**	ATTR Amyloidosis	Initiate Phase 3 Study in ATTR-CM	**H1**
		Initiate Phase 3 Study in hATTR-PN	**H2**
ZILEBESIRAN*	Hypertension	KARDIA-3 Phase 2 Results	**H2**
		Initiate Phase 3 CVOT	**H2**
MIVELSIRAN*	Cerebral Amyloid Angiopathy and Alzheimer's Disease	Interim Phase 1 Part B Data in EOAD	**H2**
		Initiate Phase 2 Study in AD	**H2**
ALN-6400*	Bleeding Disorders	Initiate Phase 2 Study	**H2**
ADDITIONAL PROGRAMS		File ≥4 New INDs	**2025**
KEY PARTNER-LED PROGRAM MILESTONES			
FITUSIRAN* (Sanofi)	Hemophilia	U.S. FDA Approval	**PDUFA date March 28, 2025**
ELEBSIRAN* (Vir)	Chronic HBV/HDV	Initiate Phase 3 study in HDV	**H1**
		Phase 2 HBV Functional Cure Results	**Q2**
CEMDISIRAN* (Regeneron)	Complement-Mediated Diseases	Phase 3 MG Results	**H2**

** Not approved for any indication and conclusions regarding the safety or effectiveness of these drugs have not been established.*
EOAD = Early Onset Alzheimer's Disease; MG = Myasthenia Gravis

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Alnylam 2025 Goals

onpattro (patisiran) amvuttra (vutrisiran) GIVLAARI (givosiran) OXLUMO (lumasiran)		Combined Net Product Revenue Guidance $2,050M – $2,250M	2025
VUTRISIRAN	ATTR Amyloidosis	U.S. FDA Approval	PDUFA date March 23, 2025
			Q2, Q3
NUCRESIRAN* (ALN-TTRsc04)			H1
			H2
ZILEBESIRAN*			H2
			H2
MIVELSIRAN*			H2
			H2
ALN-6400*			H2
ADDITION			2025
FITUSIRAN* (Sanofi)			PDUFA date March 28, 2025
ELEBSIRAN* (Vir)	Chronic HBV/HDV	Initiate Phase 3 study in HDV	H1
		Phase 2 HBV Functional Cure Results	Q2
CEMDISIRAN* (Regeneron)	Complement-Mediated Diseases	Phase 3 MG Results	H2

6 commercial products (4 WHOLLY OWNED)

3 Phase 3 study starts

Vutrisiran launch in ATTR-CM

≥4 new INDs

KARDIA-3 Phase 2 results

Achieve sustainable non-GAAP profitability

** Not approved for any indication and conclusions regarding the safety or effectiveness of these drugs have not been established.*
EOAD = Early Onset Alzheimer's Disease; MG = Myasthenia Gravis

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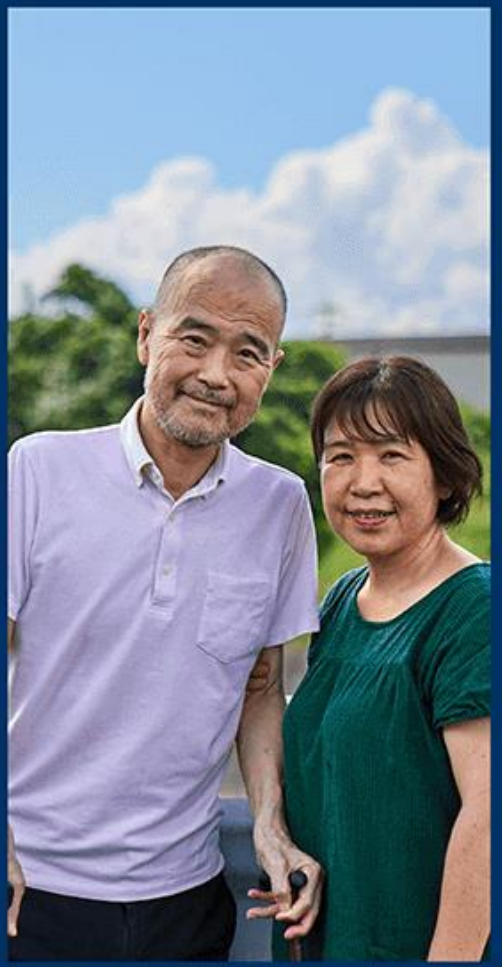



Silence disease
Amplify life™
Alnylam®


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