



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, mivelsiran, ALN-HTT02 and other product candidates; Alnylam's aspiration to become a top-tier biotech company and the planned achievement of its "Alnylam P<sup>5</sup>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<sup>5</sup>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.*

# || 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 *Anylam P<sup>5</sup>x25* Financial Goals

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

# 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 **nucesiran** (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

The Boston Globe

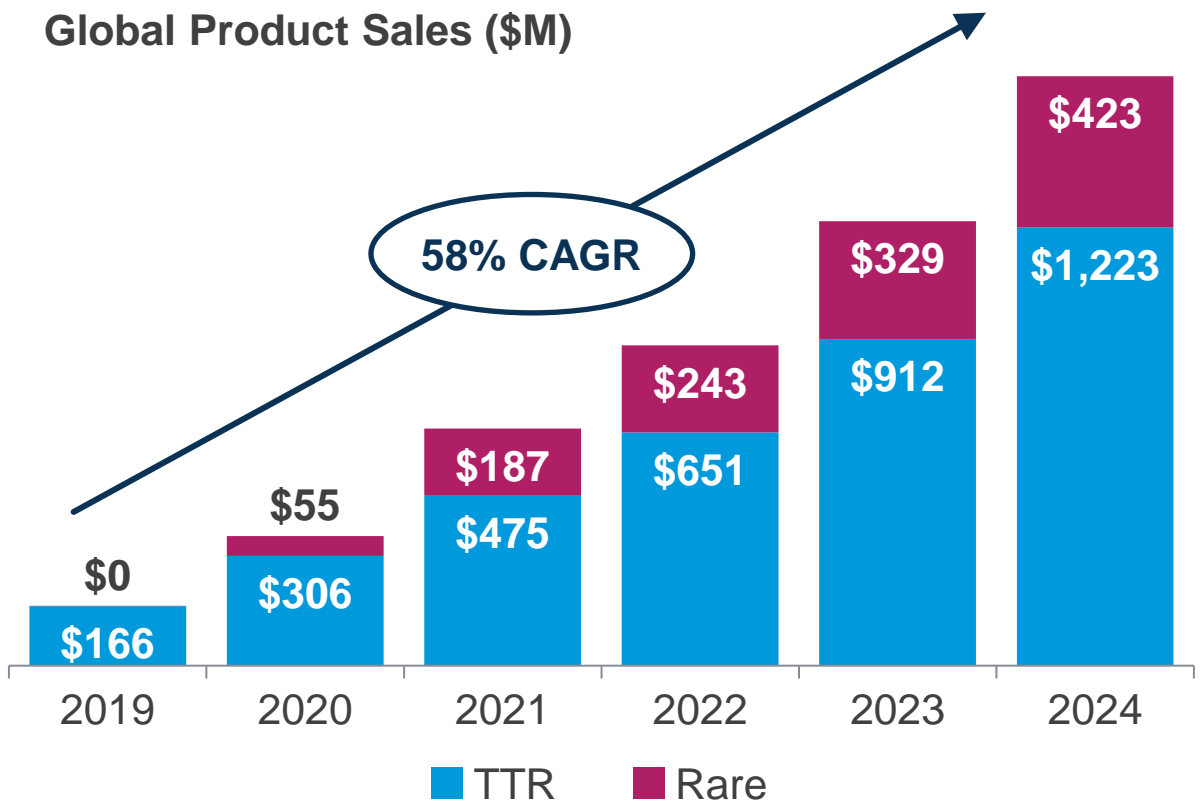
**TOP PLACES TO WORK**  
2015-2024

Continued recognition of **award-winning culture**

# Strong Commercial Performance, Exceptional Growth 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

onpatro (patisiran) amvuttra (vutrisiran)

**34%**

YoY growth in Total TTR revenues

Total Rare

GIVLAARI (givosiran) OXLUMO (lumiasiran)





**29%**

YoY growth in Total Rare revenues

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

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

# AInylam 2025 Goals

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

\* 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

# Alnylam 2025 Goals

|     |  | Combined Net Product Revenue Guidance<br>\$2,050M – \$2,250M | 2025                         |
|--|--|--|------------------------------|
| VUTRISIRAN   | ATTR Amyloidosis   | U.S. FDA Approval  | PDUFA date<br>March 23, 2025 |
| NUCRESIRAN*<br>(ALN-TTRsc04)   | <div style="background-color: #1a3d4d; color: white; padding: 20px; border-radius: 20px;"> <p><b>6 commercial products</b><br/>(4 WHOLLY OWNED)</p> <hr/> <p><b>3 Phase 3 study starts</b></p> <hr/> <p><b>Vutrisiran launch in ATTR-CM</b></p> <hr/> <p><b>≥4 new INDs</b></p> <hr/> <p><b>KARDIA<sub>3</sub></b><br/>Phase 2 results</p> <hr/> <p><b>Achieve sustainable non-GAAP profitability</b></p> </div> | Q2, Q3   |                              |
| ZILEBESIRAN*   |  | H1   |                              |
| MIVELSIRAN*  |  | H2   |                              |
| ALN-6400*  |  | H2   |                              |
| ADDITIONAL   |  | H2   |                              |
| FITUSIRAN* (Sanofi)  |  | H2   |                              |
| ELEBSIRAN* (Vir)   | Chronic HBV/HDV  | Initiate Phase 3 study in HDV                                | 2025                         |
|  |  | Phase 2 HBV Functional Cure Results                          | PDUFA date<br>March 28, 2025 |
| CEMDISIRAN* (Regeneron)  | Complement-Mediated Diseases   | Phase 3 MG Results   | H1                           |
|  |  |  | Q2                           |
|  |  |  | 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

# || Strong Progress Against Ambitious Five-Year Goals



P5  25

The graphic consists of the letters "P5" and "25" in a large, dark blue, sans-serif font. Between them is a network diagram icon with five circular nodes (three light blue, two dark blue) connected by lines, forming a central node with four branches.

**PATIENTS:** Over 0.5 million on Anylam 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

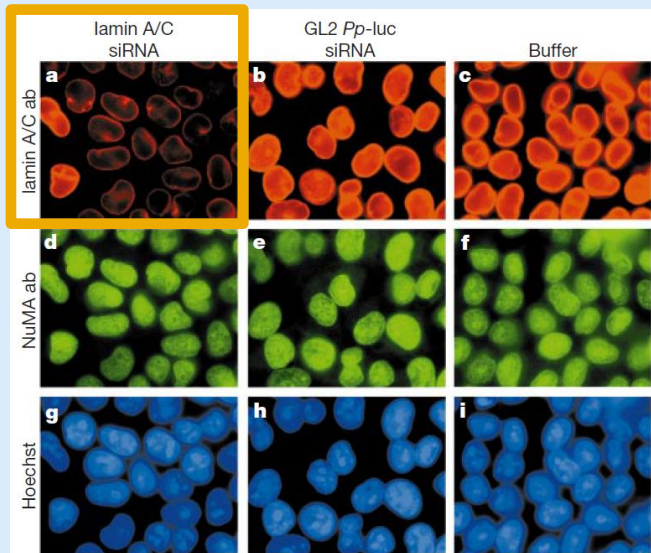


# Spring-Loaded for Growth

**Pushkal Garg, M.D.**  
**Chief Medical Officer**

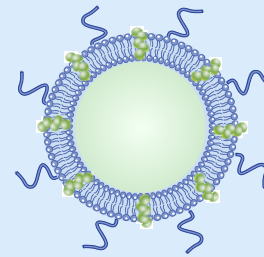
# Alnylam – Pioneering a Generational Class of Medicines Based on RNAi

## RNA Interference



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

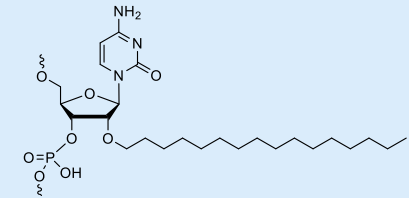
## State-of-the-Art Delivery



**LNPs**



**GaINAC**



**C16**

**Building a Portfolio of RNAi Therapeutics with Transformational Patient Impact**

# ||| 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

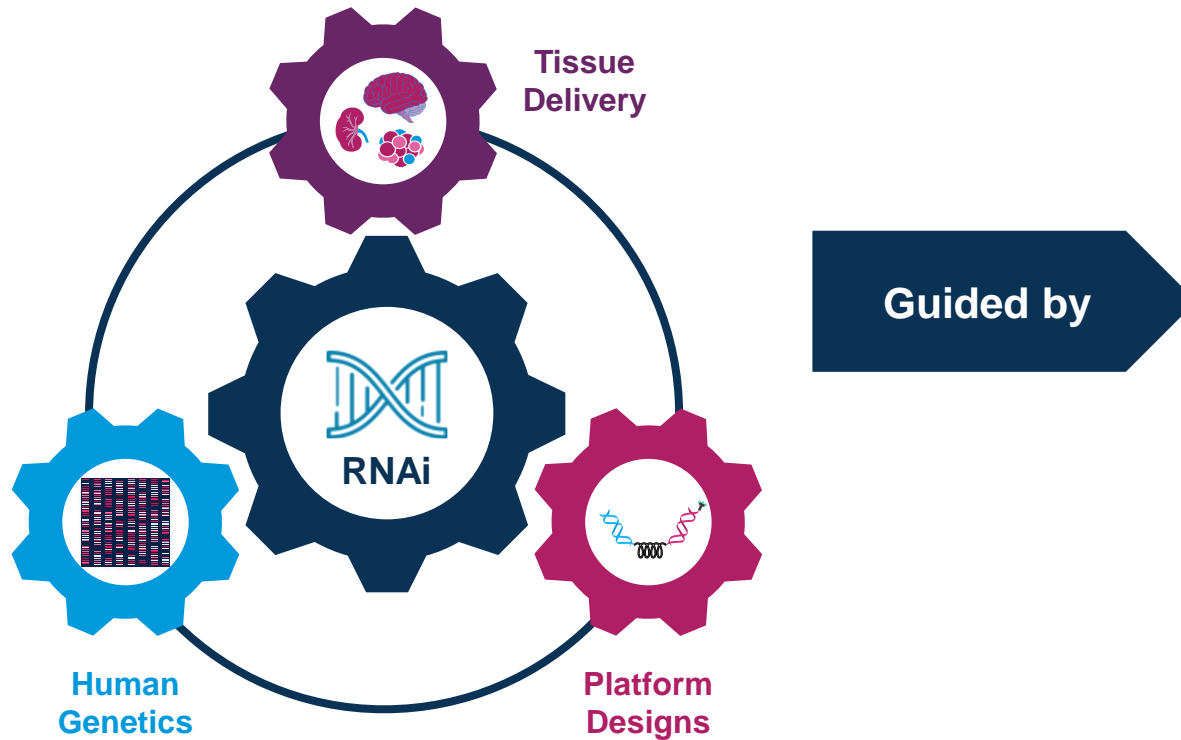
# Five Marketed Products Based on our Technology & Approach

Track Record of Successful Execution



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

## Sustainable Innovation Engine



## 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

# || Anylam 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**
- Anylam 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

biobank<sup>uk</sup>

+  
Our  
Future  
Health

All  
of Us  
RESEARCH PROGRAM

discoverme  
SOUTH AFRICA

## Technology

Accessing new innovation to expand frontiers of opportunity



PeptiDream

ADIMAB

## Programs

Enhancing productivity and building capabilities with global partners

NOVARTIS

REGENERON

Roche

sanofi

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

# Robust and High-Value Pipeline of RNAi Therapeutics

|                |                                     | PHASE 1   | PHASE 2 | PHASE 3 | APPROVED |
|----------------|-------------------------------------|---|---------|---------|----------|
| TTR            | ONPATTRO® (patisiran)               | hATTR Amyloidosis with Polyneuropathy                   |         |         |          |
|                | AMVUTTRA® (vutrisiran)              | hATTR Amyloidosis with Polyneuropathy                   |         |         |          |
|                | Vutrisiran                          | ATTR Amyloidosis with Cardiomyopathy                    |         |         |          |
|                | Nucresiran (ALN-TTRsc04)            | ATTR Amyloidosis  |         |         |          |
| RARE           | GIVLAARI® (givosiran)               | Acute Hepatic Porphyria                                 |         |         |          |
|                | OXLUMO® (lumasiran)                 | Primary Hyperoxaluria Type 1                            |         |         |          |
|                | Fitusiran <sup>1</sup>              | Hemophilia  |         |         |          |
|                | Cemdisiran <sup>1</sup>             | Myasthenia Gravis                                       |         |         |          |
|                | Cemdisiran <sup>1</sup>             | Paroxysmal Nocturnal Hemoglobinuria                     |         |         |          |
|                | ALN-6400                            | Bleeding Disorders                                      |         |         |          |
| CARDIOVASCULAR | LEQVIO® (inclisiran) <sup>1</sup>   | Hypercholesterolemia                                    |         |         |          |
|                | Zilebesiran <sup>2</sup>            | Hypertension  |         |         |          |
|                | Zilebesiran + REVERSIR <sup>2</sup> | Hypertension  |         |         |          |
| METABOLIC      | Rapirosiran (ALN-HSD) <sup>1</sup>  | Metabolic Dysfunction-Associated Steatohepatitis (MASH) |         |         |          |
|                | ALN-4324                            | Type 2 Diabetes Mellitus                                |         |         |          |
|                | ALN-PNP <sup>3</sup>                | Non-Alcoholic Fatty Liver Disease (NAFLD)               |         |         |          |
|                | ALN-APOC3 <sup>1</sup>              | Dyslipidemia  |         |         |          |
| NEUROLOGIC     | Mivelsiran <sup>4</sup>             | Cerebral Amyloid Angiopathy                             |         |         |          |
|                | Mivelsiran <sup>4</sup>             | Alzheimer's Disease                                     |         |         |          |
|                | ALN-HTT02 <sup>5</sup>              | Huntington's Disease                                    |         |         |          |
|                | ALN-SOD <sup>3</sup>                | SOD1 Amyotrophic Lateral Sclerosis                      |         |         |          |
| OTHER          | Cemdisiran <sup>1</sup>             | Geographic Atrophy                                      |         |         |          |
|                | Elebsiran <sup>6</sup>              | Hepatitis B Virus Infection                             |         |         |          |
|                | Elebsiran <sup>6</sup>              | Hepatitis D Virus Infection                             |         |         |          |
|                | ALN-BCAT                            | Hepatocellular Carcinoma                                |         |         |          |
|                | ALN-ANG3 <sup>1</sup>               | Healthy Volunteers                                      |         |         |          |

# Key Near- to Midterm Growth Drivers

Potential For Three Blockbuster Franchises



**ATTR  
Amyloidosis**



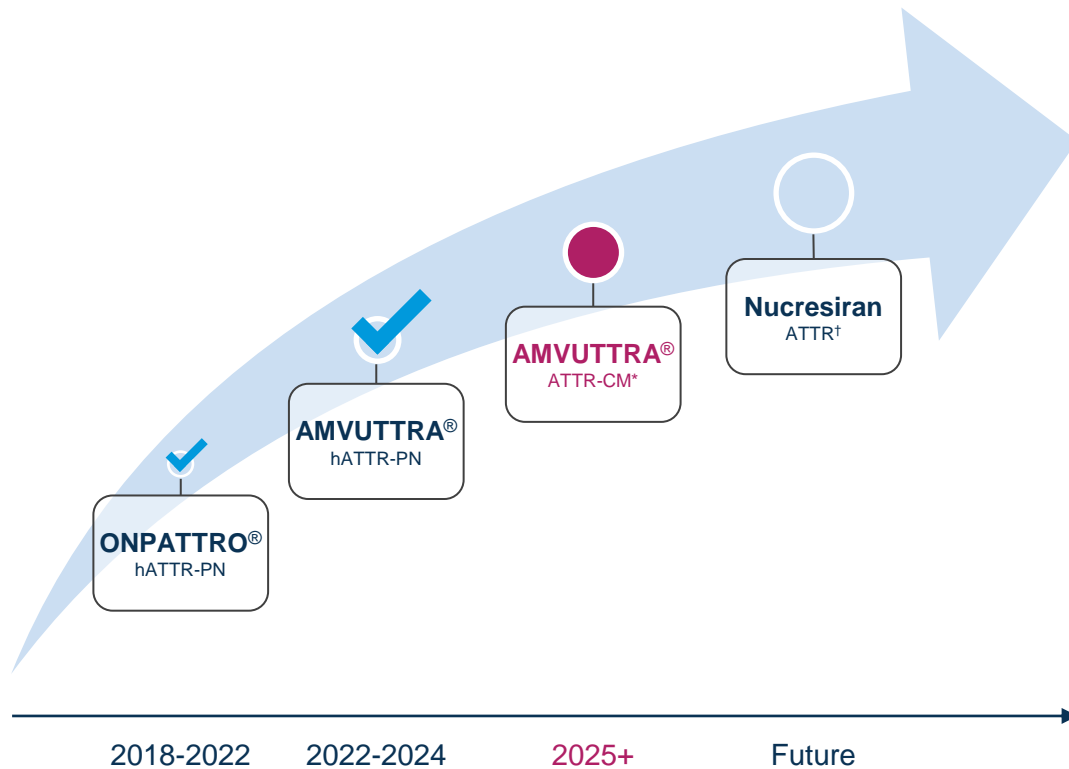
**Cardiovascular**



**Neuroscience**

# Building on Our Leadership in ATTR Amyloidosis

## A Durable, Blockbuster Franchise

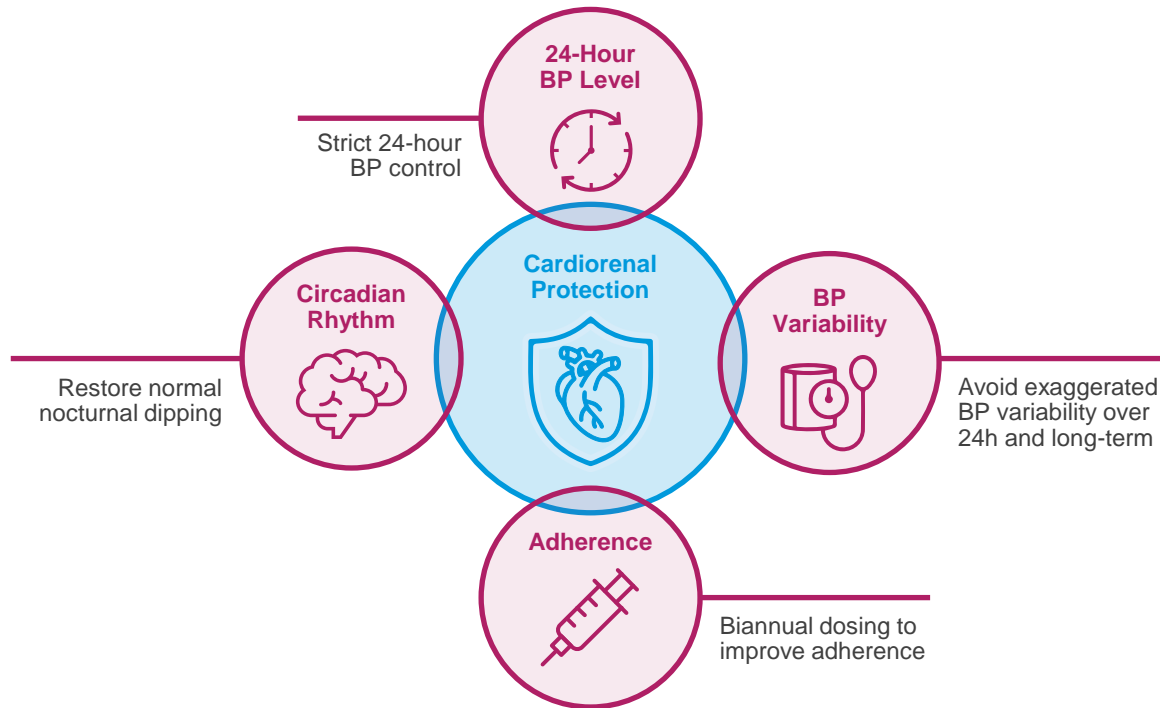


### John Vest, M.D.

- 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 nucesiran in ATTR-CM and hATTR-PN

# Reimagining Hypertension & Atherosclerotic Cardiovascular Disease

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



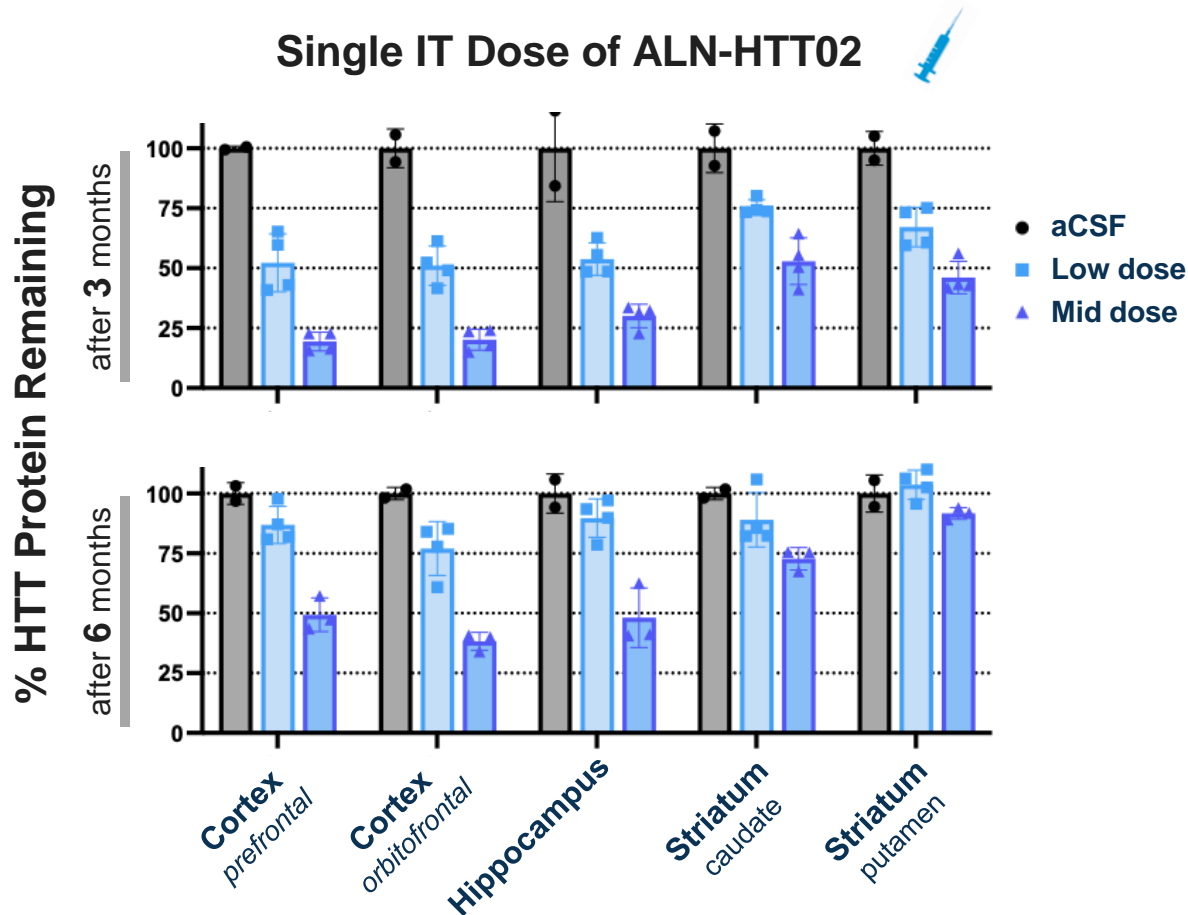
**Therapeutic Goal to Improve Quantity and Quality of Blood Pressure Control**

## 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

# || 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



Liana, Brazil  
Diagnosed with hATTR  
amyloidosis

# 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<br>Mivelsiran: A Differentiated Approach for Alzheimer’s Disease and Cerebral Amyloid Angiopathy<br>Overview of Huntington’s Disease Unmet Need<br>ALN-HTT02: Hope for Huntington’s Disease Patients | Julia Shirvan, M.D., Ph.D., Snr. Dir., Mivelsiran Clinical Lead<br>Professor Sarah Tabrizi, M.D., Ph.D.<br>FMedSci FRS, UCL<br>Kevin Sloan, Ph.D., VP, Program Lead, Early CNS Programs |
| 10:50 – 11:00a ET  | <i>Intermission</i>   |   |
| 11:00 – 11:30a ET  | Q&A   | Pushkal Garg, M.D., Chief Medical Officer ( <i>moderator</i> )  |
| 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<br>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 ( <i>moderator</i> )  |
| 12:55 – 1:00p ET   | Closing Remarks   | Pushkal Garg, M.D., Chief Medical Officer   |

# 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



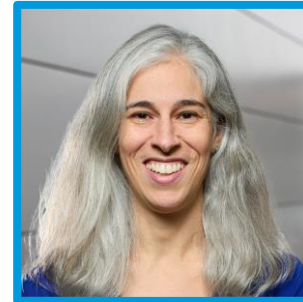
**Vasant Jadhav, Ph.D.**  
Chief Technology Officer



**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



# **Anylam 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**

# 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<sup>1</sup>

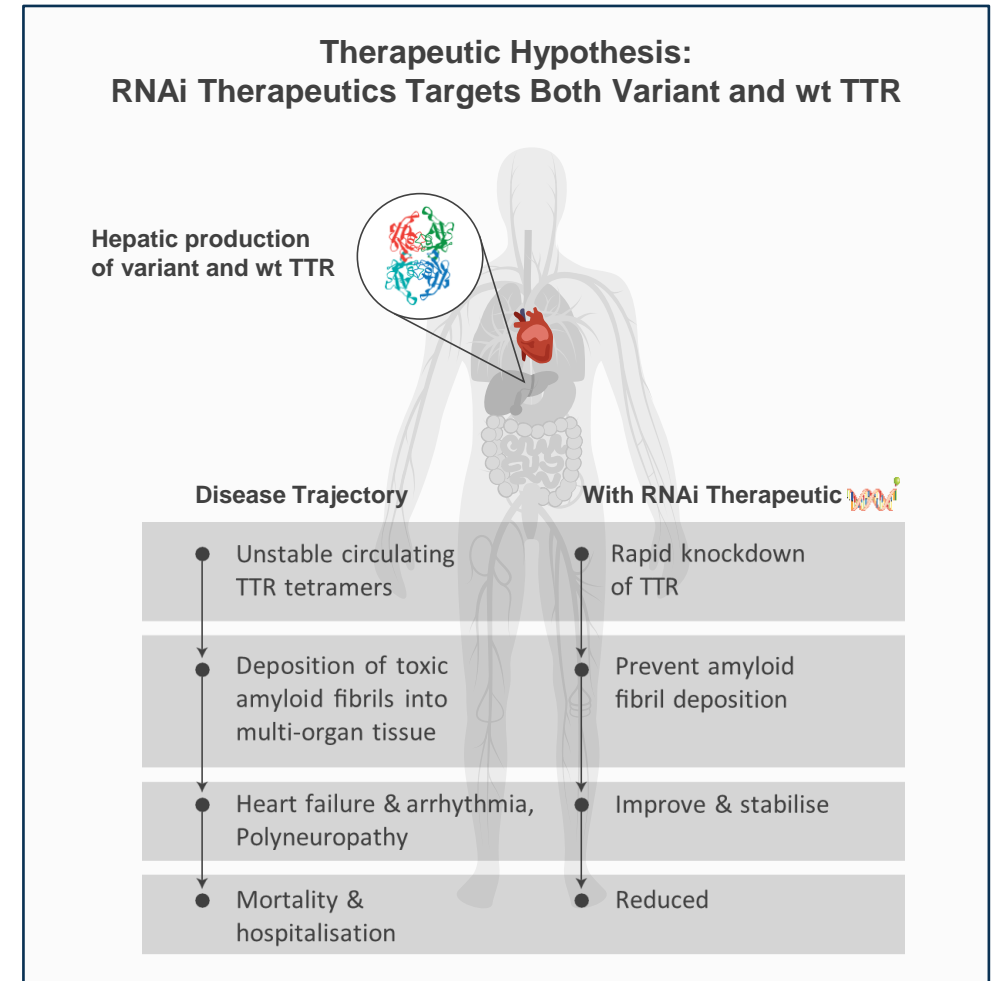
Predominantly manifests as cardiomyopathy and/or polyneuropathy

**Hereditary ATTR (hATTR)  
Amyloidosis**

**~50,000**  
patients worldwide<sup>2</sup>

**Wild-Type ATTR (wtATTR)  
Amyloidosis**

**>300,000**  
patients worldwide<sup>3</sup>



# 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<sup>1</sup>

- Based on APOLLO data, commercially available in >30 countries for hATTR amyloidosis with polyneuropathy
- Positive results from APOLLO-B<sup>3</sup>
- 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<sup>2</sup>

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

**Nucresiran**  
(ALN-TTRsc04)

An **Investigational** RNAi  
Therapeutic for Potential  
Treatment of ATTR Amyloidosis

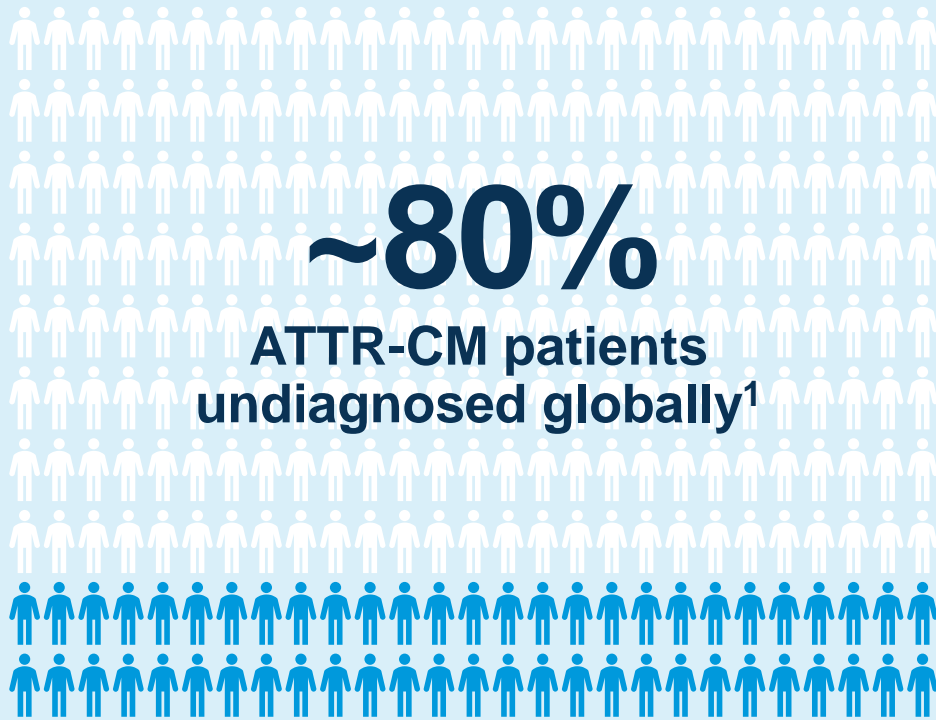
- Phase 1 study ongoing
- Potential for >90% serum TTR reduction with biannual dosing
- No third-party royalties; exclusivity expected beyond 2040

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

# Opportunity for Significant Impact in ATTR-CM

## Significant Unmet Patient Need in ATTR-CM

>300K patients globally<sup>1</sup>



## 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

# Readout of the Landmark HELIOS-B Study

## Transformational Profile Expected to Drive a Robust and Growing Market



**ESC Congress  
2024 London**



### Primary Results from HELIOS-B, a Phase 3 Study of Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy



M. Fontana<sup>1</sup>, J. L. Berk<sup>2</sup>, J. D. Gillmore<sup>3</sup>, R. Witteles<sup>4</sup>, M. Grogan<sup>5</sup>, B. Drachman<sup>6</sup>, T. Damy<sup>6</sup>, P. Garcia-Pavia<sup>7</sup>, S. D. Solomon<sup>8</sup>, N. Tahara<sup>9</sup>, P. Van der Meer<sup>10</sup>, L. Yang<sup>11</sup>, S. A. Eraly<sup>11</sup>, K. L. Boyle<sup>11</sup>, J. Vest<sup>11</sup>, M. S. Maurer<sup>12</sup>

<sup>1</sup>Division of Medicine, University College London, Royal Free Hospital, London, UK; <sup>2</sup>Boston University School of Medicine, Boston, MA, USA; <sup>3</sup>Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA, USA; <sup>4</sup>Department of Cardiovascular Diseases, Mayo Clinic College of Medicine, Rochester, MN, USA; <sup>5</sup>Department of Cardiovascular Medicine, Penn Presbyterian Medical Center, Philadelphia, PA, USA; <sup>6</sup>Referral Center for Cardiac Amyloidosis, Hôpital Henri Mondor, Créteil, France; <sup>7</sup>Department of Cardiology, Hospital Universitario Puerta de Hierro Majadahonda, GIBEROV, Madrid, Spain; <sup>8</sup>Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA; <sup>9</sup>Division of Cardiovascular Medicine, Department of Medicine, Kurume University School of Medicine, Kurume, Japan; <sup>10</sup>Universitair Medisch Centrum Groningen, University of Groningen, Groningen, The Netherlands; <sup>11</sup>Alnylam Pharmaceuticals, Cambridge, MA, USA; <sup>12</sup>Columbia University Medical Center, New York, NY, USA

30 August–2 September 2024 | European Society of Cardiology Congress 2024, London, UK

ESC Congress 2024  
London & Online



The NEW ENGLAND  
JOURNAL of MEDICINE

ORIGINAL ARTICLE

### Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy

M. Fontana, J.L. Berk, J.D. Gillmore, R.M. Witteles, M. Grogan, B. Drachman, T. Damy, P. Garcia-Pavia, J. Taubel, S.D. Solomon, F.H. Sheikh, N. Tahara, J. González-Costello, K. Tsujita, C. Morbach, Z. Pozsonyi, M.C. Petrie, D. Delgado, P. Van der Meer, A. Jabbour, A. Bondue, D. Kim, O. Azevedo, S. Hvitfeldt Poulsen, A. Yilmaz, E.A. Jankowska, V. Algalarrondo, A. Slugg, P.P. Garg, K.L. Boyle, E. Yureneva, N. Silliman, L. Yang, J. Chen, S.A. Eraly, J. Vest, and M.S. Maurer, for the HELIOS-B Trial Investigators\*

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

# || 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<sup>1</sup>

### 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<sup>1</sup>

**~50%**

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

**~30%**

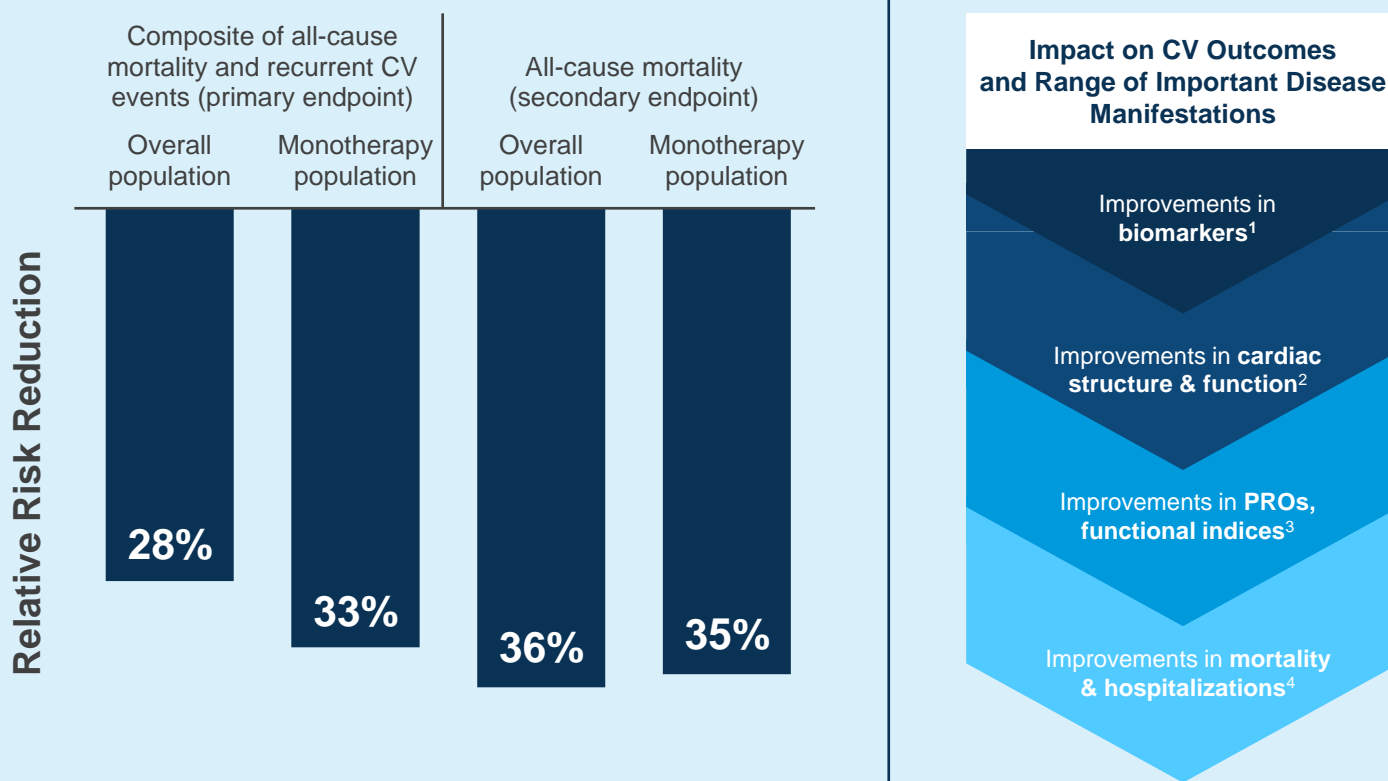
of patients started SGLT2 inhibitors during the DB period

**~80%**

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

# 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

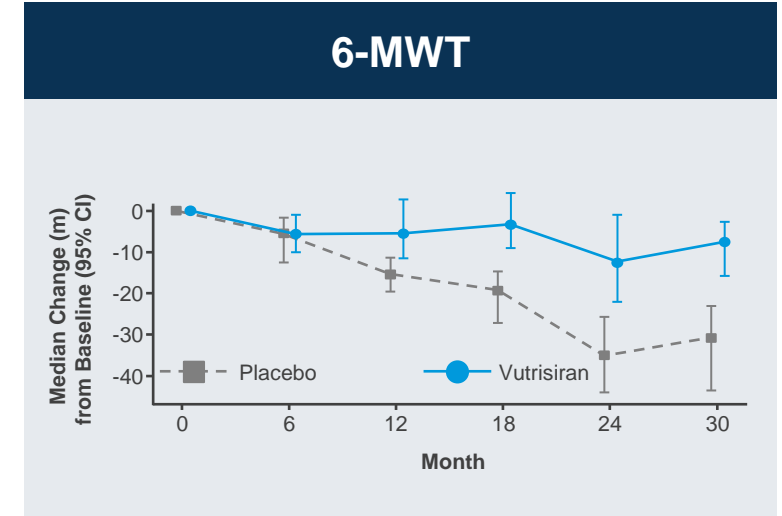
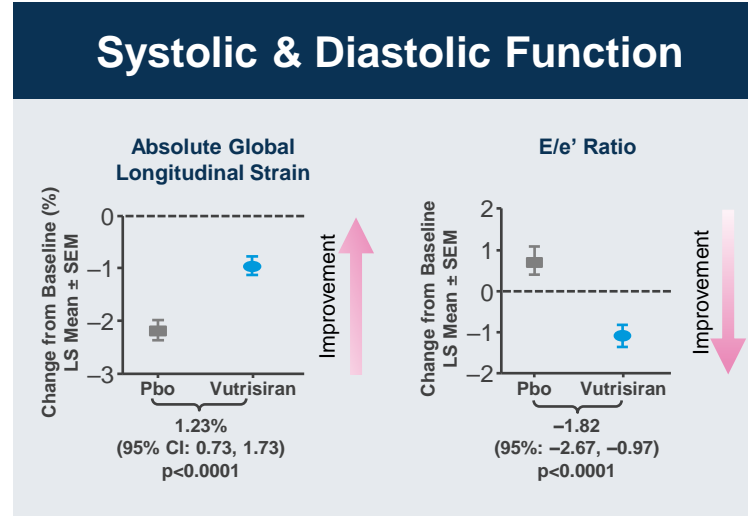
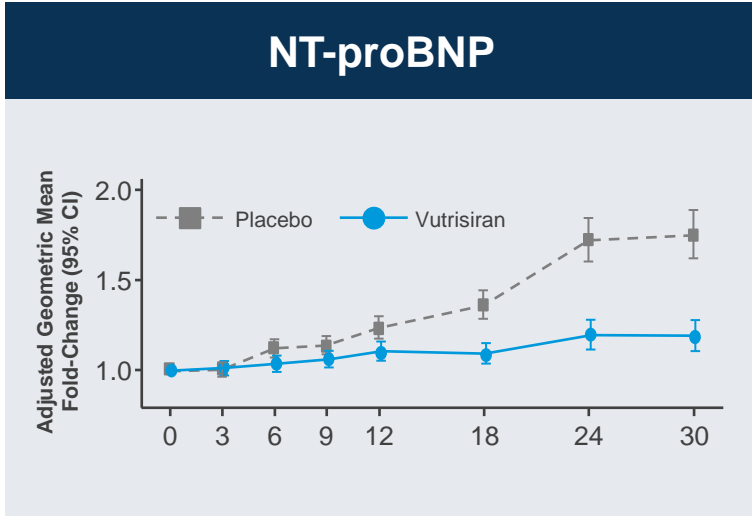
- Substantial effect despite extensive background therapy
- Disease modifying
- Works rapidly
- Evidence of stability over time
- Data support treating early; outsized benefit in milder disease
- Acceptable safety and tolerability profile, as previously established

HELIOS-B study, M. Fontana et al, NEJM September 2024; 1. 32% RRR for both NT-proBNP and Troponin 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



# Favorable Impact on Multiple Measures of Disease Progression

## Evidence for Disease Modifying Potential

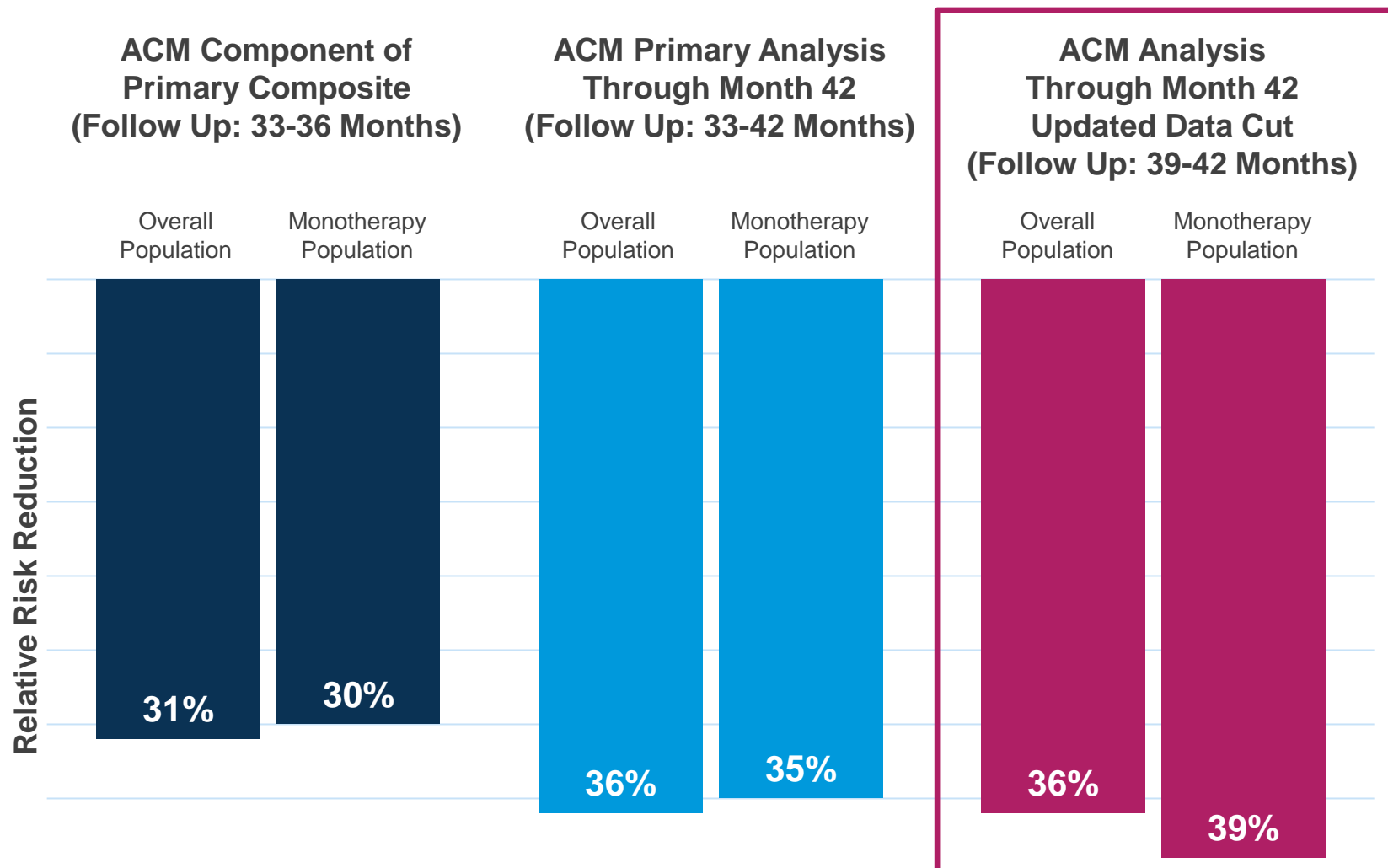


- Observed clinical benefits cascade in a biologically rational manner
- Effects on well established biomarkers of cardiac health seen early
- Improvements compared to placebo on cardiac structure, as well as systolic and diastolic function; all important elements of underlying pathophysiology
- Preservation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

# Updated Data Cut Corroborates Primary Analysis of Mortality

Consistent results across analyses of all-cause mortality

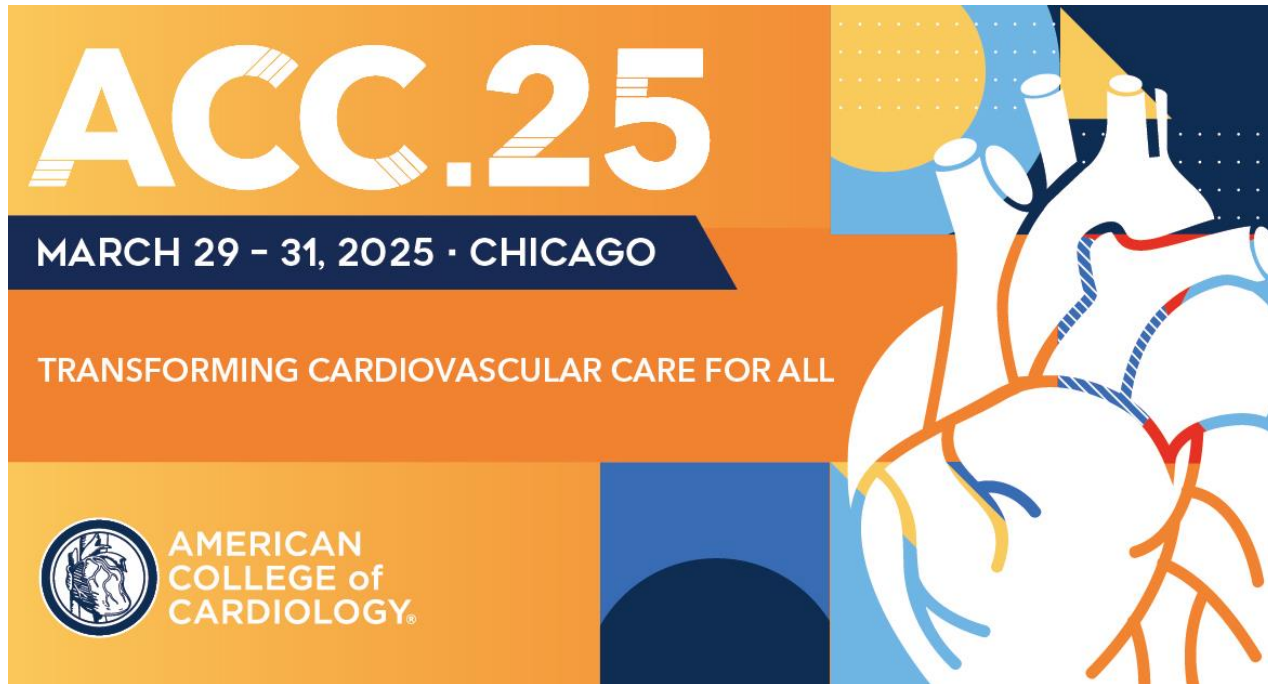


- Analysis with near complete data for ACM through month 42
- >99% ascertainment of vital status
- Further details in planned publication

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.



# 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



**Potential to be 1st  
Line SOC for both  
ATTR-CM and  
hATTR-PN**

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



**U.S. PDUFA Date  
March 23, 2025**



**Additional global  
regulatory submissions  
ongoing**

# 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<sup>1</sup>

- Based on APOLLO data, commercially available in >30 countries for hATTR amyloidosis with polyneuropathy
- Positive results from APOLLO-B<sup>3</sup>
- 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<sup>2</sup>

- Based on HELIOS-A data, approved in US, EU, UK, JP, and BR
- Positive HELIOS-B data in ATTR amyloidosis with CM<sup>4</sup>
- 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

# || Elevating Anylam's ATTR Leadership with Nucesiran

## 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

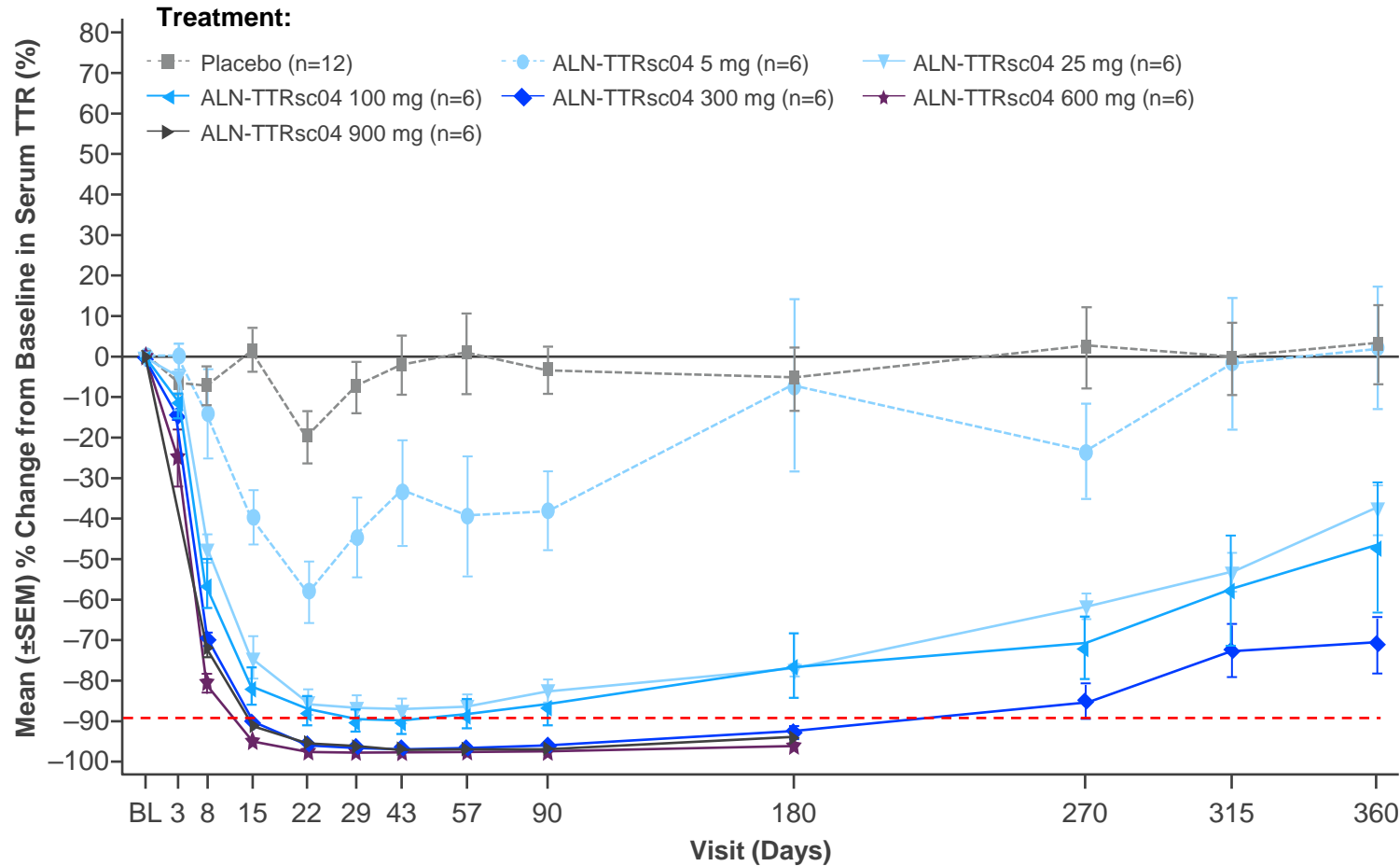
## Innovative Development Program Anticipating Future Category Dynamics

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

**Accelerating Speed to Market**  
hATTR Polyneuropathy potential fast to market

# Rapid, Deep and Sustained TTR Knockdown with Nucesiran

## 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)

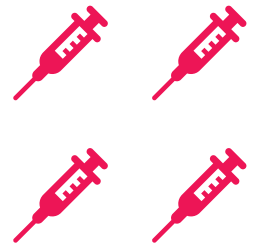
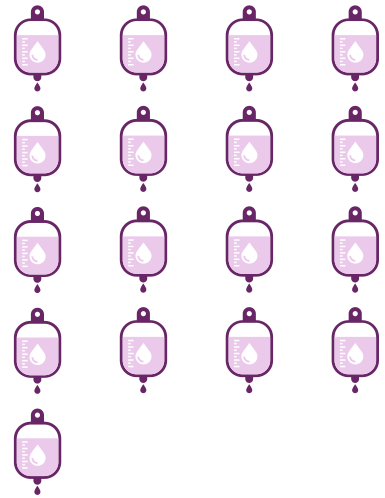
**Abbreviations:** BL, baseline; SEM, standard error of the mean; TTR, transthyretin

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>.

# 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) |

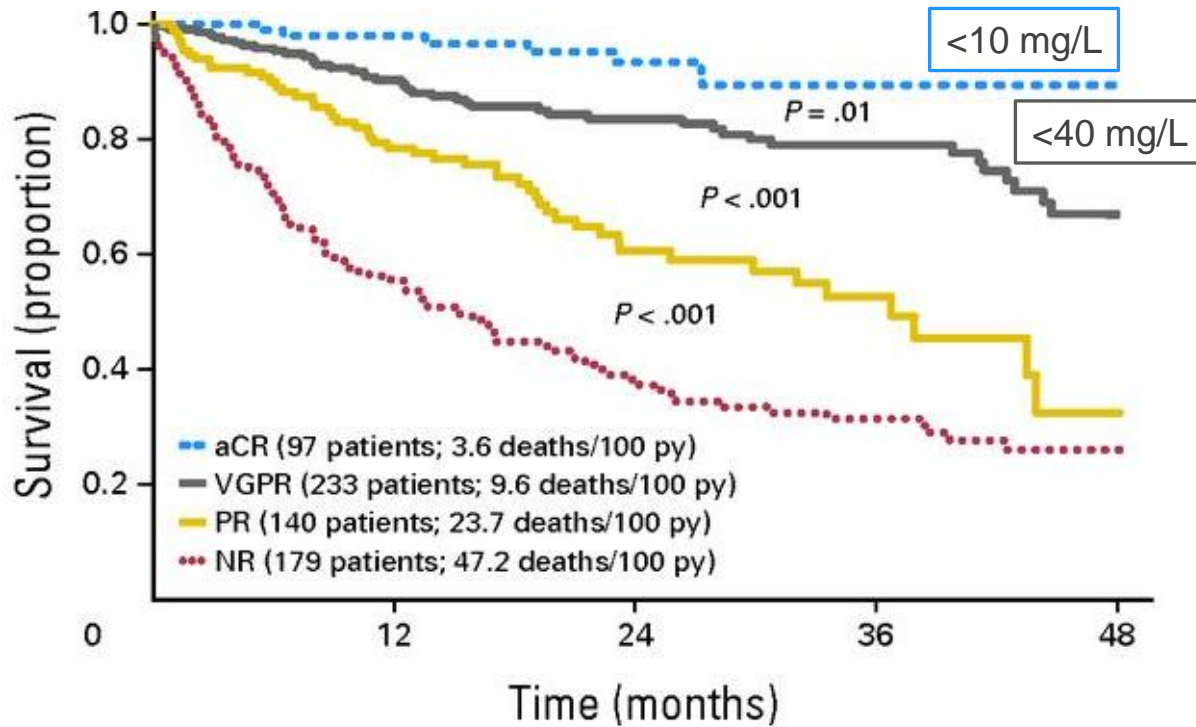


# AL and AA Amyloidosis: Maximal Knockdown → Best Outcomes

Proving the Therapeutic Hypothesis Required Decades of Clinical Experience

## AL Amyloidosis

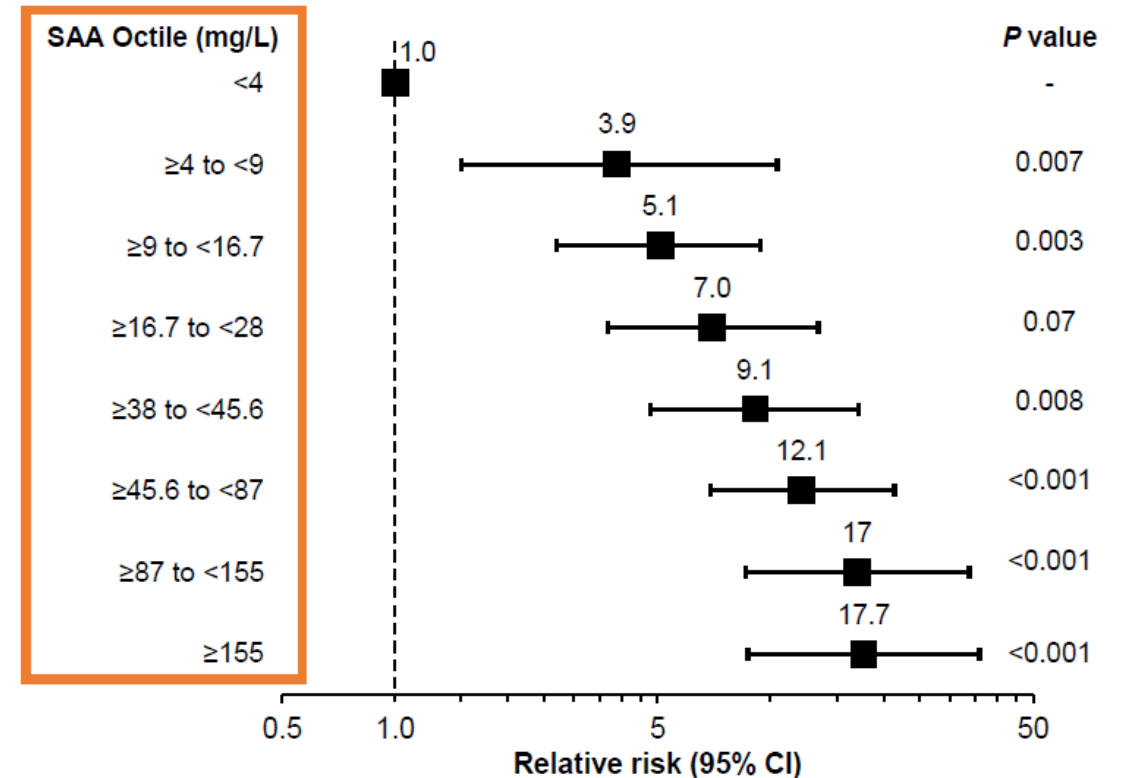
Survival Probability by Response to Therapy<sup>1</sup>



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

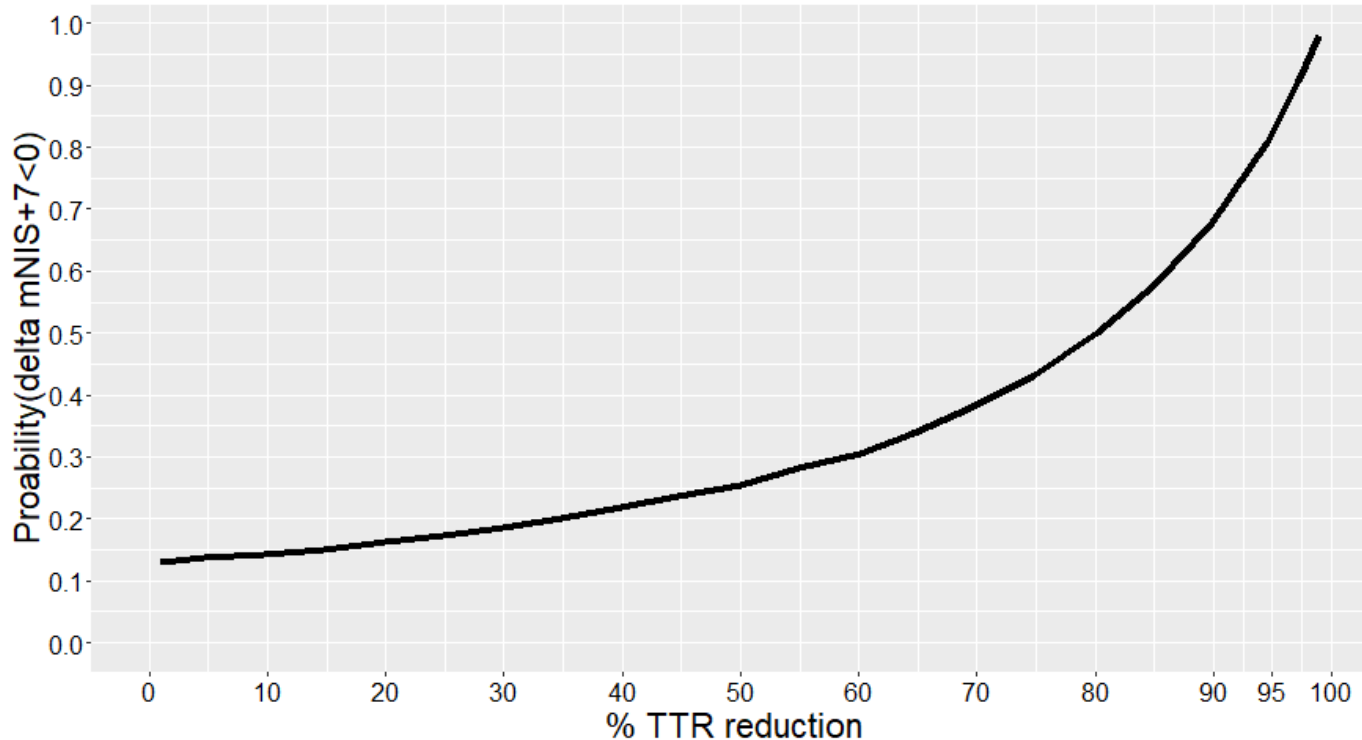
## AA Amyloidosis

Unadjusted relative risk of death associated with the most recent median annual SAA concentration during follow-up<sup>2</sup>



# 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**

# || 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

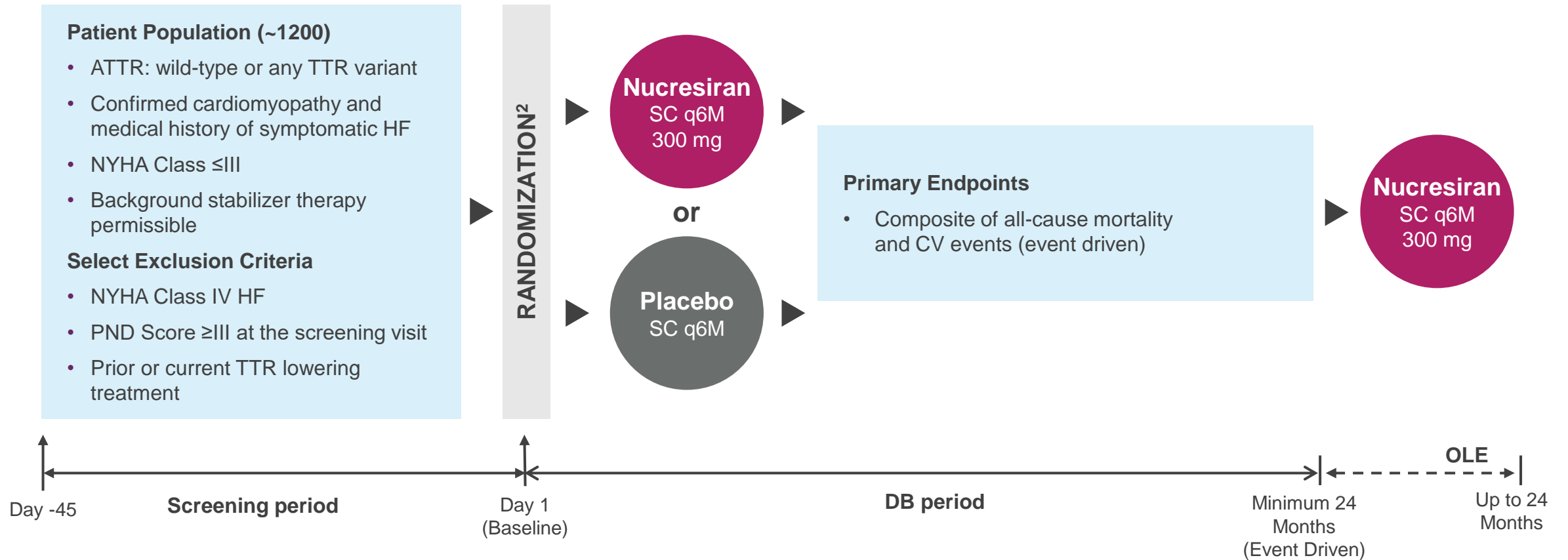
**Patients will be identified earlier and with milder disease**

- 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 Phase 3 Study

ATTR-CM CLINICAL STUDY

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



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.


# Nucresiran TRITON-PN Ph3 Study in hATTR Polyneuropathy

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

  
**TRITON-CM**  
ATTR-CM CLINICAL STUDY  
CVO primary endpoint  
(event driven)



*Assumed Launch  
~2030*

  
**TRITON-PN**  
hATTR-PN CLINICAL STUDY  
mNIS+7 primary  
endpoint



*Targeting Launch  
several years earlier*

- 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

# 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



**ATTR  
Amyloidosis**



**Cardiovascular**

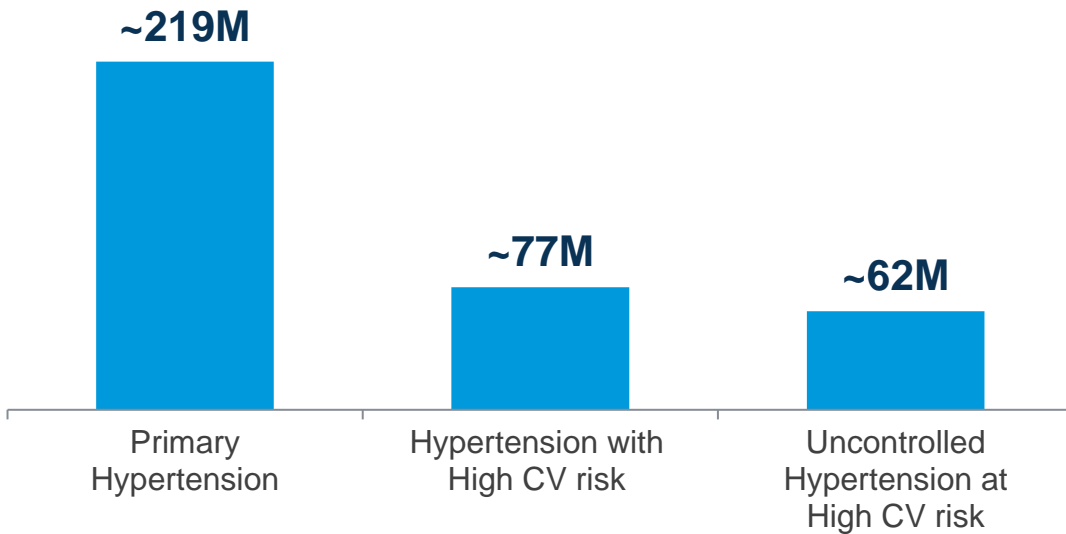


**Neuroscience**

# Uncontrolled Hypertension is a Global Health Crisis

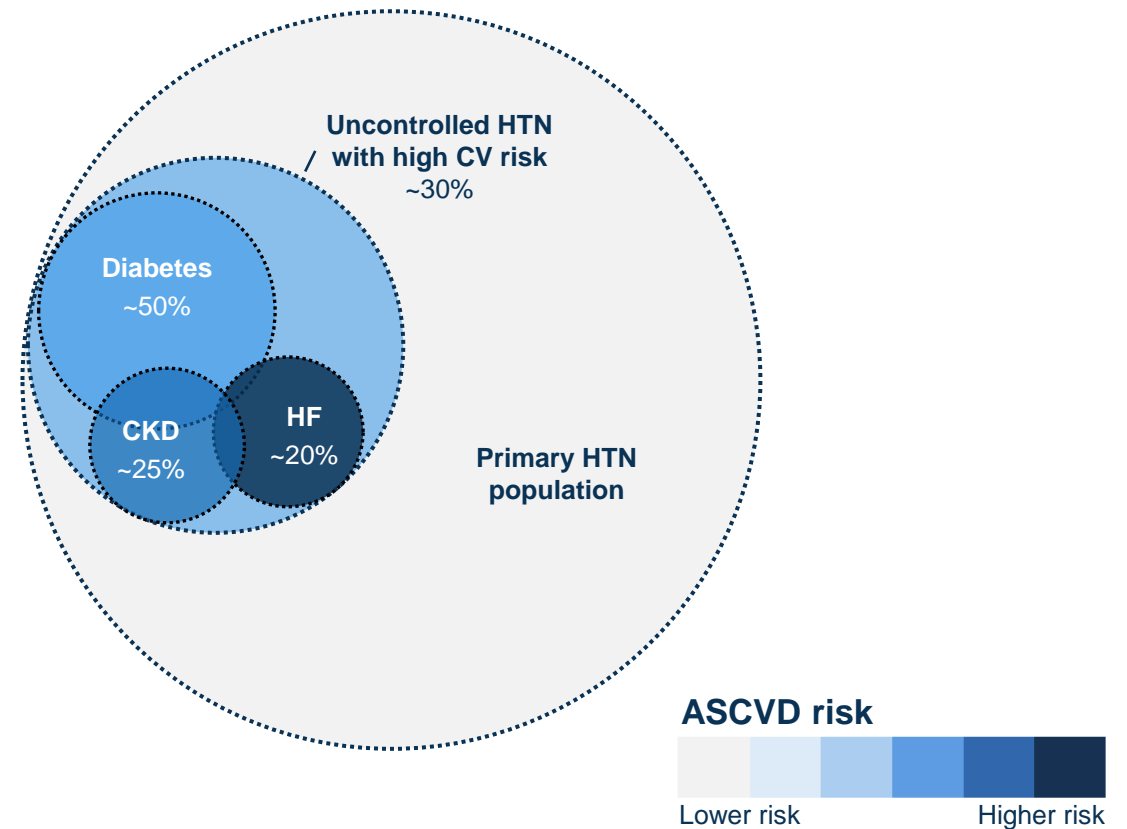
High Unmet Need with Many Patients Having Uncontrolled Hypertension and High CV Risk

## Number of Patients (7 Major Markets)



|                     | Risk Reduction per 5 mm Hg Decrease in SBP <sup>1</sup> |
|---------------------|---|
| Major CV Events     | 10%   |
| IHD                 | 8%  |
| Stroke              | 13%   |
| HF                  | 13%   |
| CV Mortality        | 5%  |
| All Cause Mortality | 2%  |

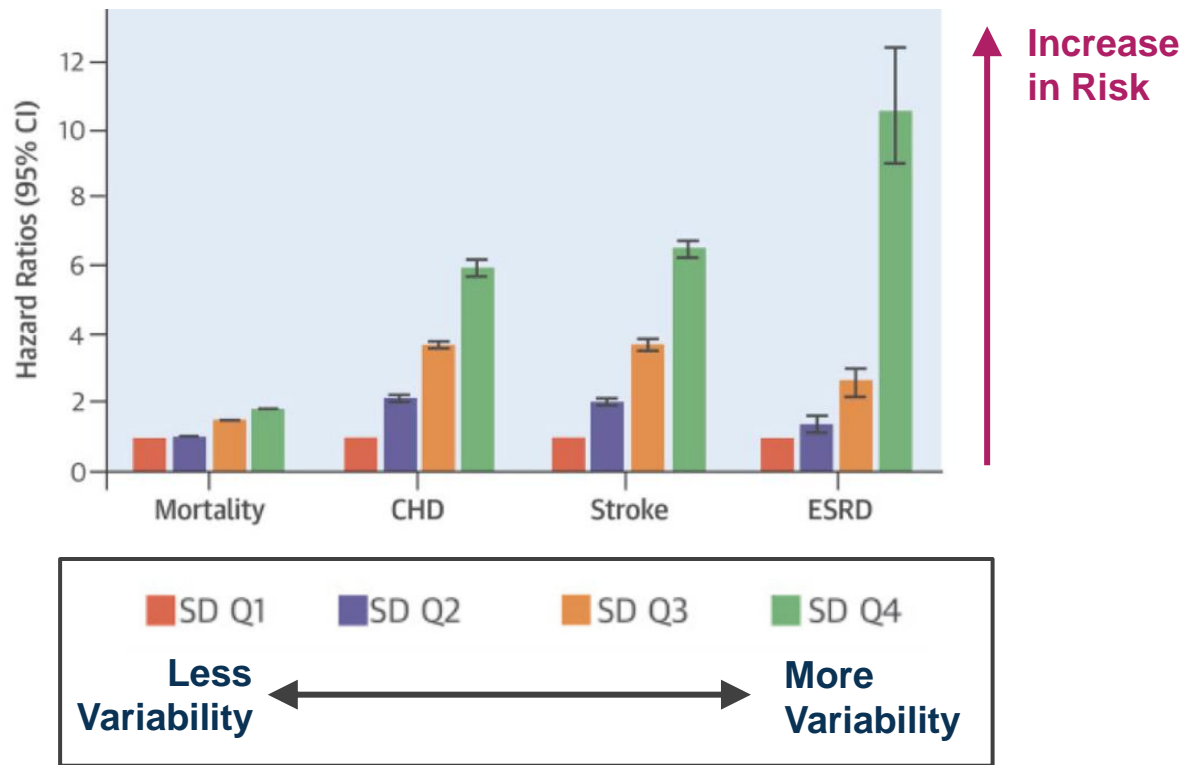
## Uncontrolled HTN with High CV Risk<sup>2, 3</sup>



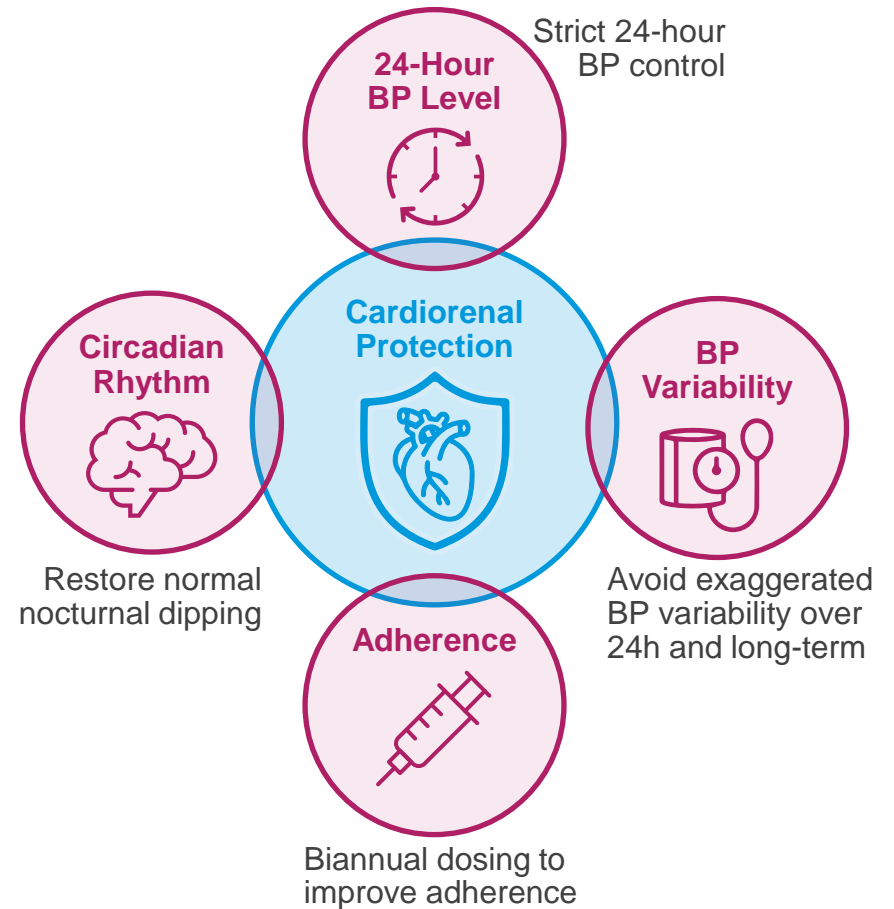
1. Rahimi K, et al. Lancet 2021; 37: 1625–36. 2. Proportions derived from an analysis of a large US administrative claims and EMR database and 3. Muntner et al. Hypertension, 2022 (based BP ≥140/90); Comorbidities are not mutually exclusive. High CV risk patients defined as those with history of ASCVD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

# Targeting Continuous Control of Blood Pressure to Improve Outcomes

**Excessive SBP variability increases Cardiovascular and Renal Risk<sup>1</sup>**



**Zilebesiran: Targeting Continuous Control of BP to Reduce Cardiovascular and Renal Risk<sup>2</sup>**



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

# 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<sup>1</sup>



The NEW ENGLAND  
JOURNAL of MEDICINE

ORIGINAL ARTICLE

Zilebesiran, an RNA Interference  
Therapeutic Agent for Hypertension

Alkshay S. Desai, M.D., M.P.H., David J. Webb, M.D., D.Sc., Jorg Taubel, M.D., Sarah Casey, M.B., Ch.B., Yansong Cheng, Ph.D., Gabriel J. Robbie, Ph.D., Don Foster, M.S., Stephen A. Huang, M.D., Sean Rhyee, M.D., M.P.H., Marianne T. Sweetser, M.D., Ph.D., and George L. Bakris, M.D.

## Phase 2

KARDIA<sub>1</sub> ✓

Zilebesiran monotherapy in pts with mild-to-mod HTN<sup>2</sup>

JAMA | Original Investigation

RNA Interference With Zilebesiran for Mild to Moderate Hypertension  
The KARDIA-1 Randomized Clinical Trial

KARDIA<sub>2</sub> ✓

Zilebesiran in combination with single antihypertensive  
in patients with mild-to-moderate hypertension<sup>3</sup>

Results Presented ACC April 7th, 2024

KARDIA<sub>3</sub>

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

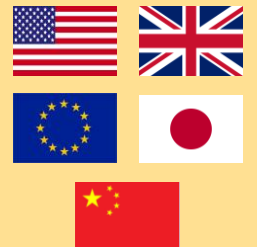
Cardiovascular Outcomes  
Trial (CVOT)

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



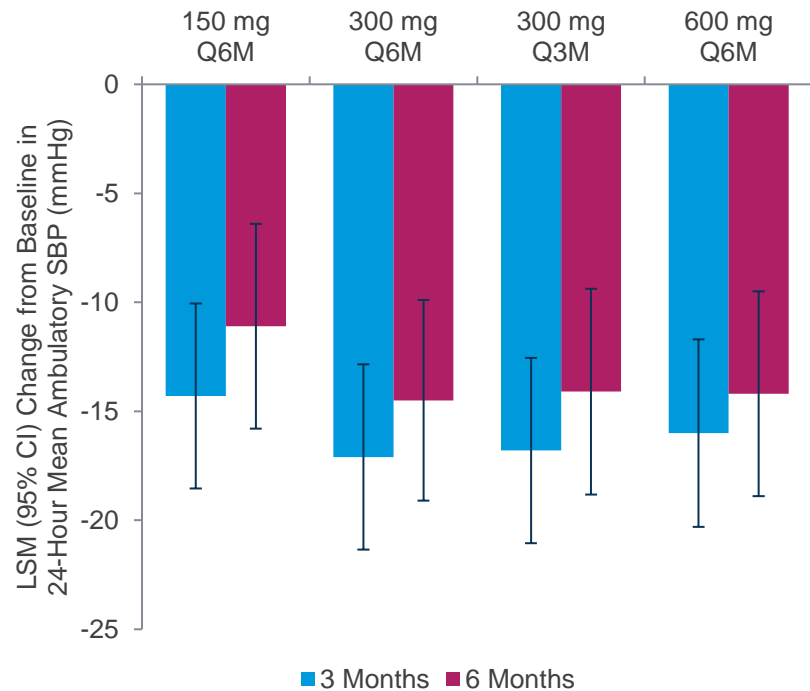
Launch with label  
to reduce  
cardiovascular  
morbidity and  
mortality  
Expected ~2030



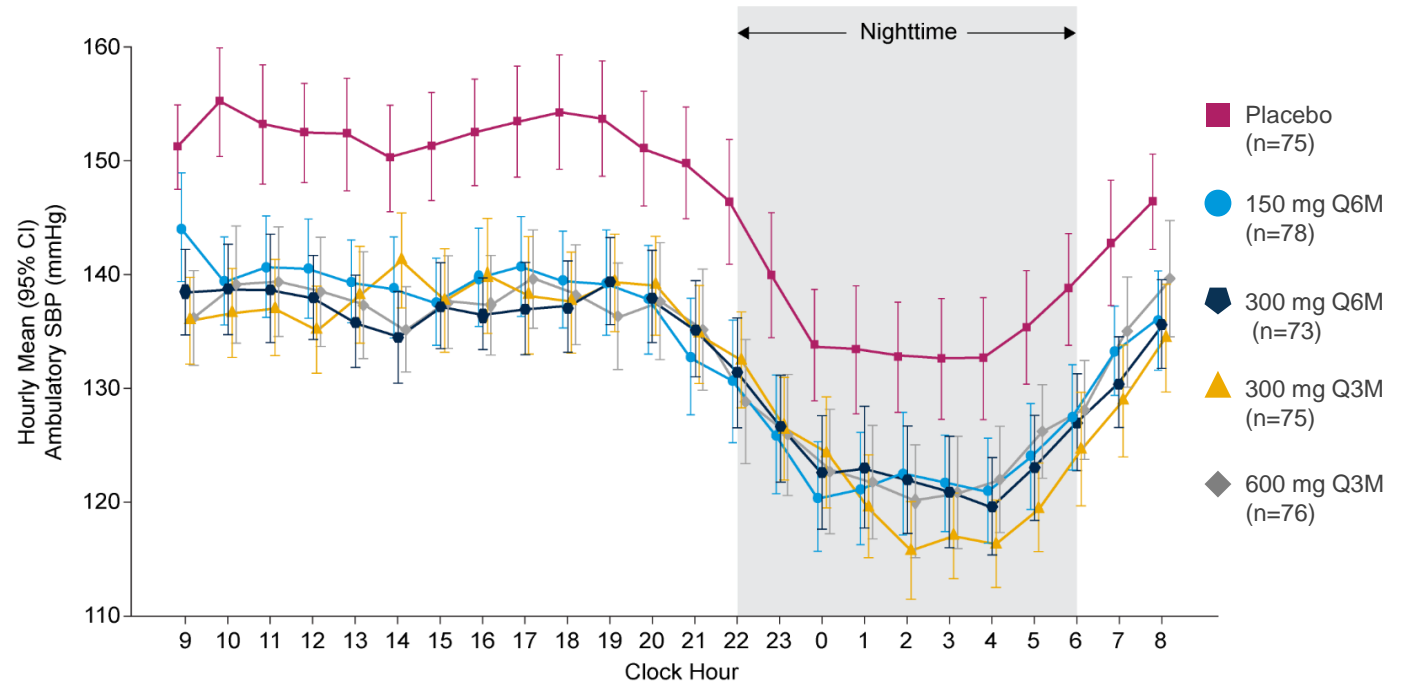
# KARDIA<sub>1</sub> Zilebesiran Monotherapy

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

### Robust 24-hour Mean SBP Reduction<sup>1</sup>



### 24-hour BP Control Maintained Out to Month 6<sup>2</sup>



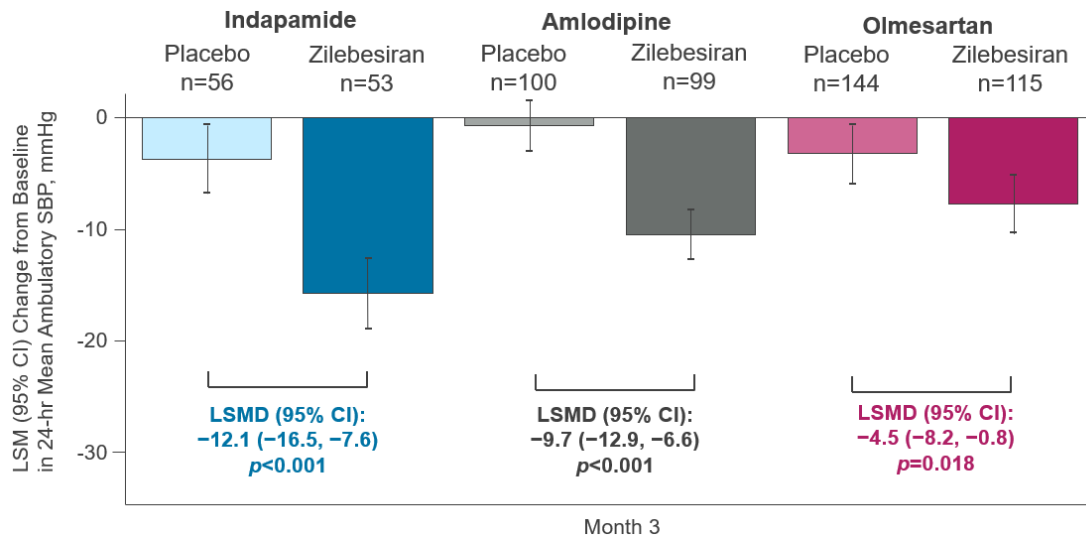
- Generally well tolerated
- Low incidence of AEs of ISR, hyperkalemia, and hypotension, which were mild or moderate in severity and transient; most did not require therapeutic intervention

*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*; <sup>a</sup> 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

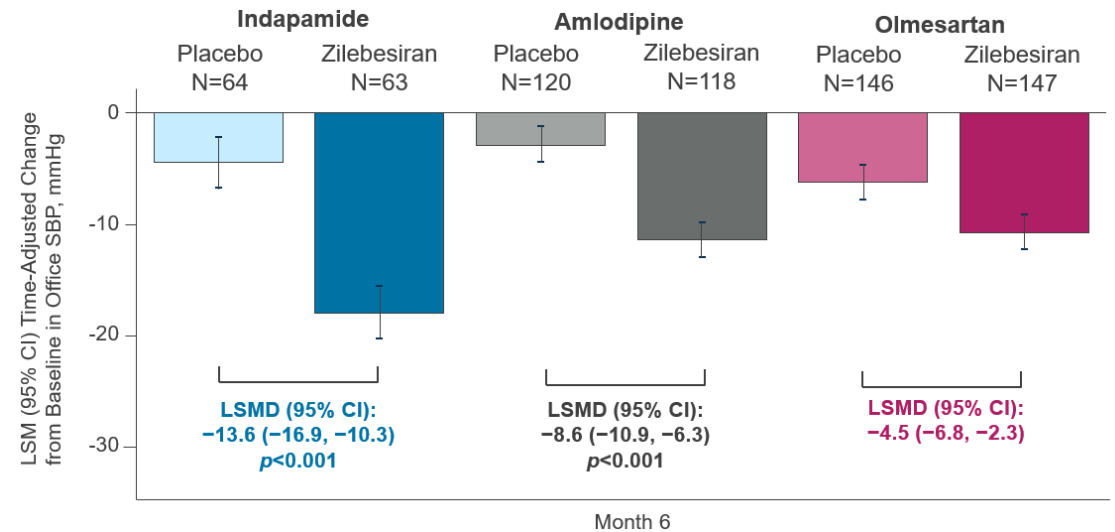
# KARDIA<sub>2</sub> Zilebesiran in Combination with Standard of Care

## 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<sup>1</sup>



### Secondary Endpoint: Time adjusted Office SBP Reduction at Month 6<sup>1</sup>

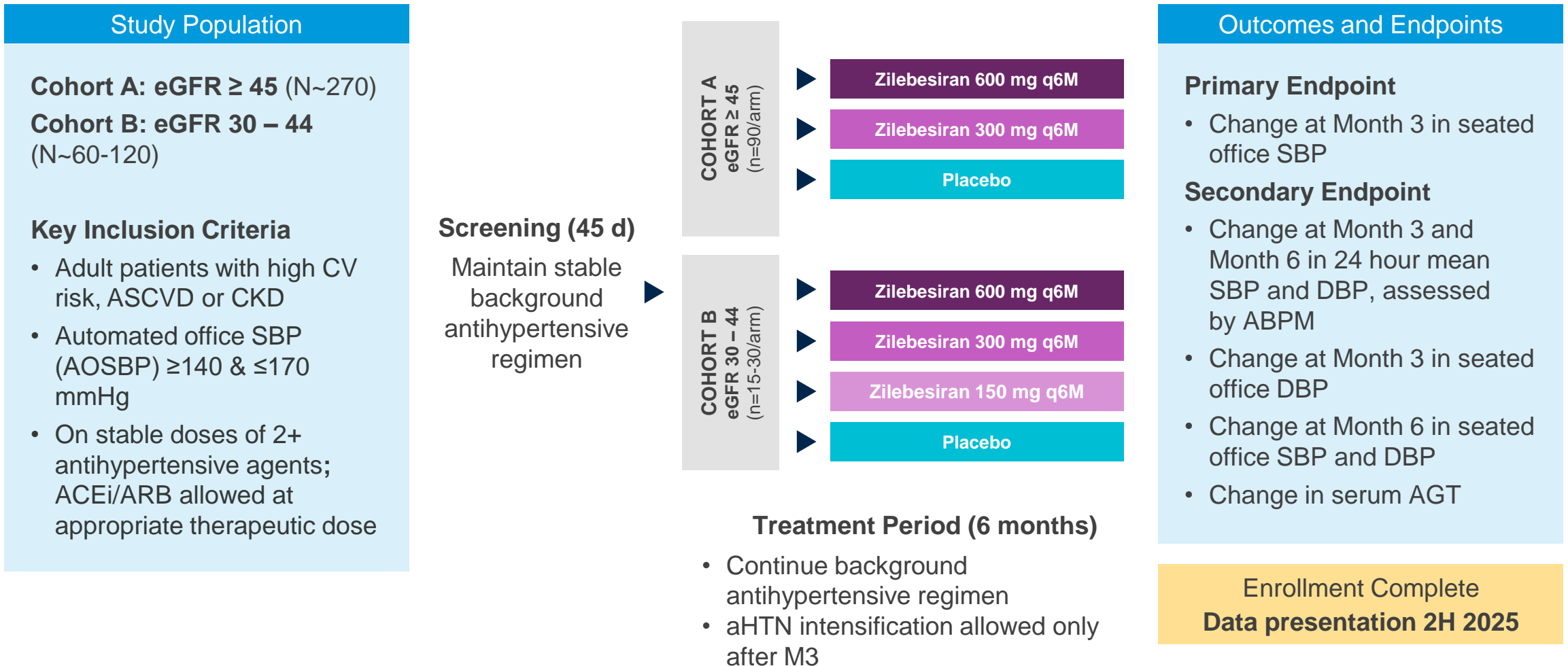


- Zilebesiran was generally well tolerated
- Increased rate of mild hyperkalemia, hypotension, and eGFR decline >30% in those treated with zilebesiran vs placebo
  - Most AEs were non-serious, transient, and resolved without intervention

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.

# KARDIA<sub>3</sub> Phase 2 Combination Study in High CV Risk

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



# KARDIA<sub>3</sub> 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  $\geq 45$  (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)  $\geq 140$  &  $\leq 170$  mmHg
- On stable doses of 2+ antihypertensive agents; ACEi/ARB allowed at appropriate therapeutic dose

## 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

## Informing Phase 3 CVOT

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

### Treatment Period (6 months)

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

Enrollment Complete

Data presentation 2H 2025

# 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



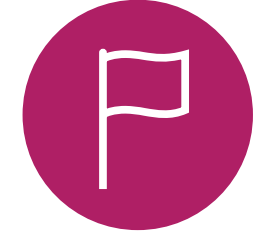
## Patient Population

- $\geq 2$  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

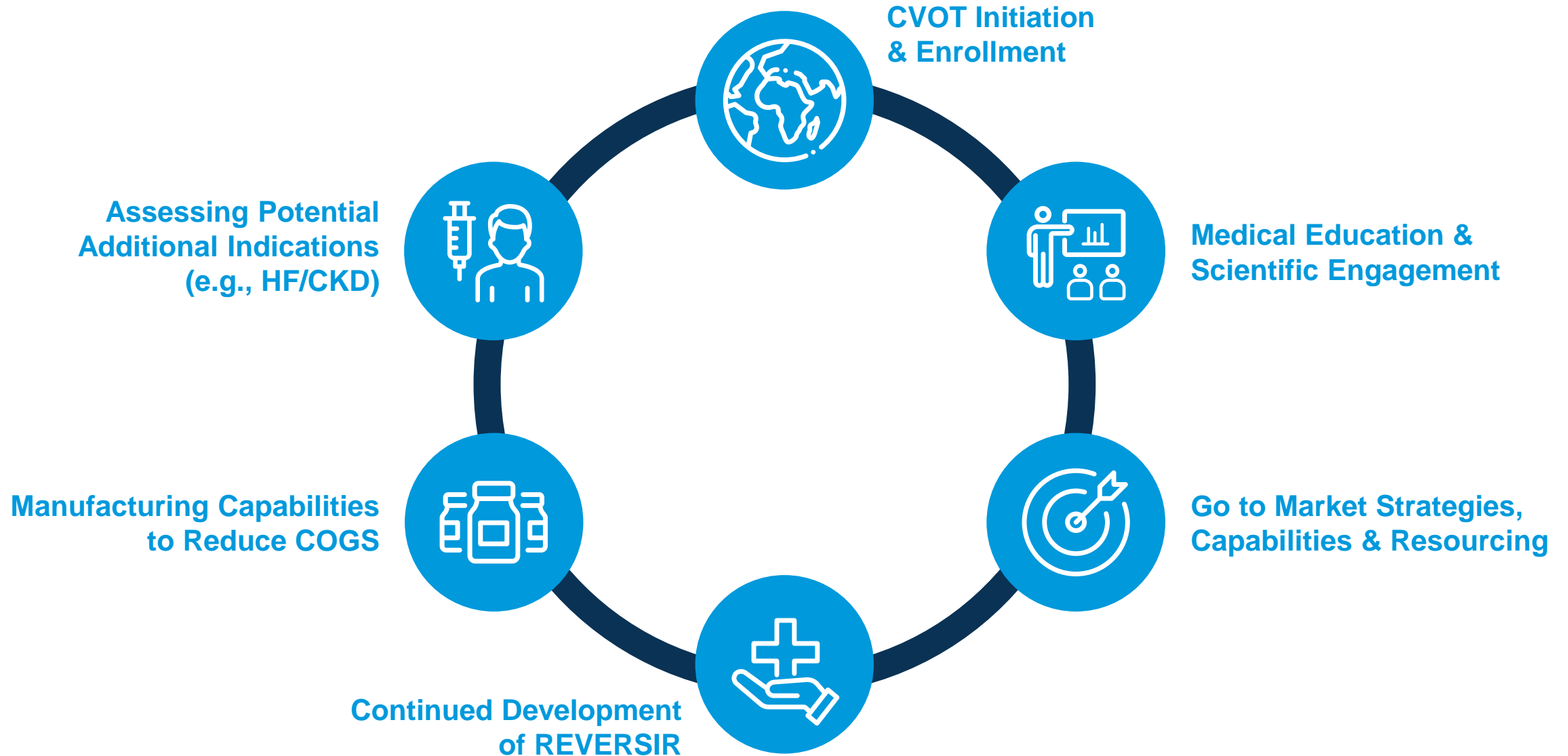


 Duke Clinical Research Institute

*PPD*

**Phase 3 CVOT to initiate in 2H 2025**





# 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



# 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



**ATTR  
Amyloidosis**



**Cardiovascular**



**Neuroscience**

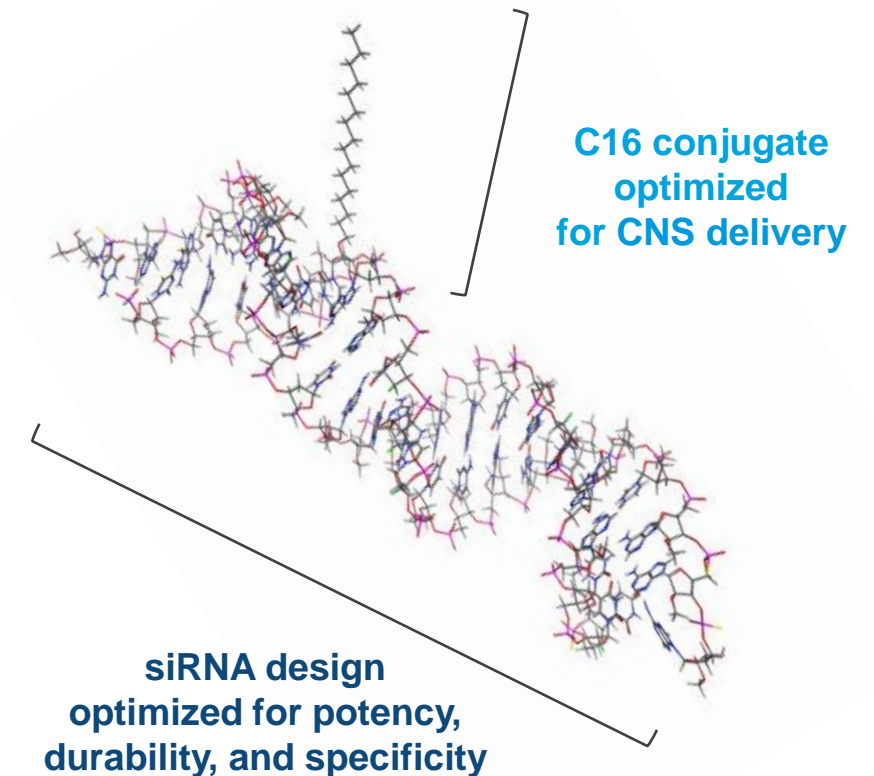
# Alnylam Leads Field in Targeting CNS with RNAi

## 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 |

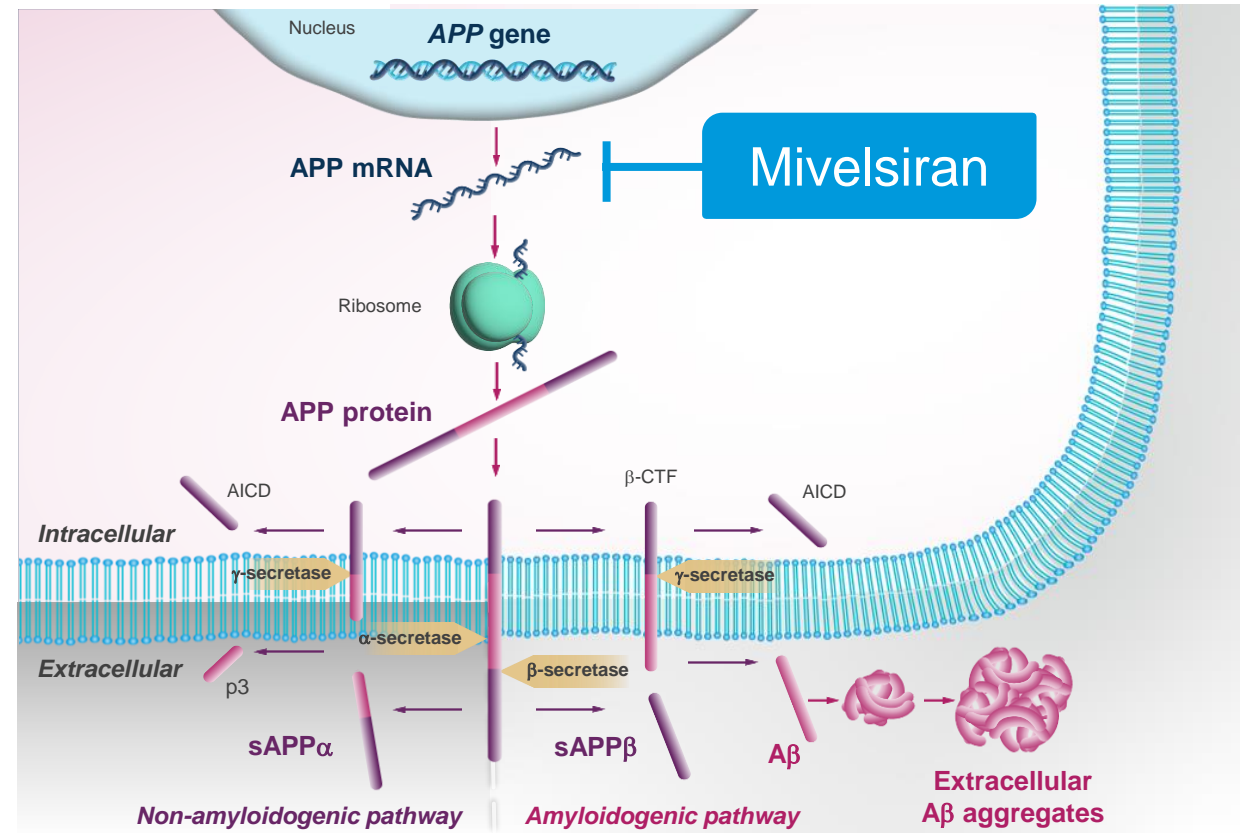
- Other programs rapidly approaching clinic
- Guided by R&D strategic principles
  - Prioritizes high conviction targets
  - Best-in-class opportunities: potency, durability, safety



# 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 A $\beta$  peptides
    - Intracellular and extracellular A $\beta$
- Lowering substrate for amyloid accumulation may enable natural clearance of A $\beta$



# || Amyloid Pathology Contributes to Severe Neurologic Diseases

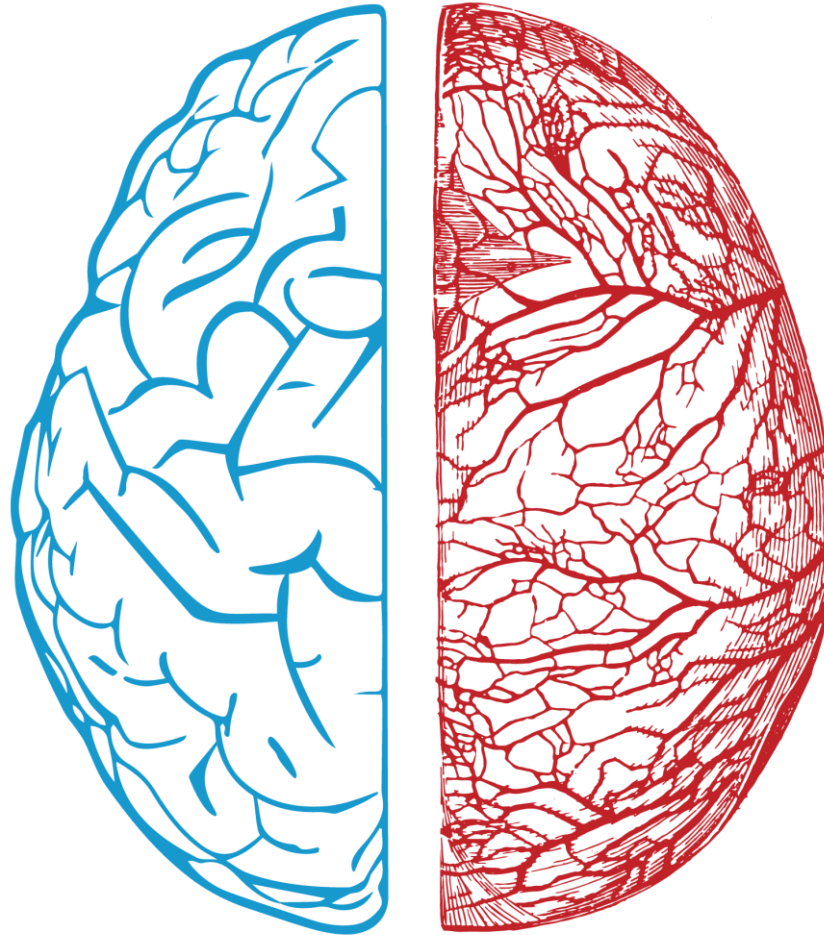
## Mivelsiran May Provide Benefit for AD and CAA

### Alzheimer's Disease<sup>1-3</sup>

A $\beta$  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<sup>4-6</sup>

A $\beta$  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

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

1. [ClinicalTrials.gov. NCT05231785](https://clinicaltrials.gov/study/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](https://clinicaltrials.gov/study/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.



**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<sup>®</sup> 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 sAPP $\alpha$  and sAPP $\beta$

#### 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<br>(Mivelsiran<br>or Pbo) | Single<br>Ascending Dose<br>(SAD, Part A) | Multiple<br>Ascending Dose<br>(MAD, Part B) |
|---------------------------|-------------|-----------------------------|---|---|
| 25 mg                     | 6           | 2:1                         | →   |   |
| 35 mg                     | 8           | 3:1                         | →   |   |
| 50 mg                     | 8           | 3:1                         | →   |   |
| 75 mg                     | 6           | 2:1                         | Pooled<br>analysis [ →<br>→               |   |
| 75 mg                     | 8           | 3:1                         |   |   |
| <b>100 mg</b>             | 9           | 3:1                         | →   |   |
| Additional<br>SAD cohorts | Forthcoming |                             | ⇒   |   |
| <b>50mg MAD</b>           | 10          | NA                          |   | →   |
| Additional<br>MAD cohorts | Forthcoming |                             |   | ⇒   |
| Observation<br>period     |             |                             | Up to 12 months                           | Up to 42 months                             |

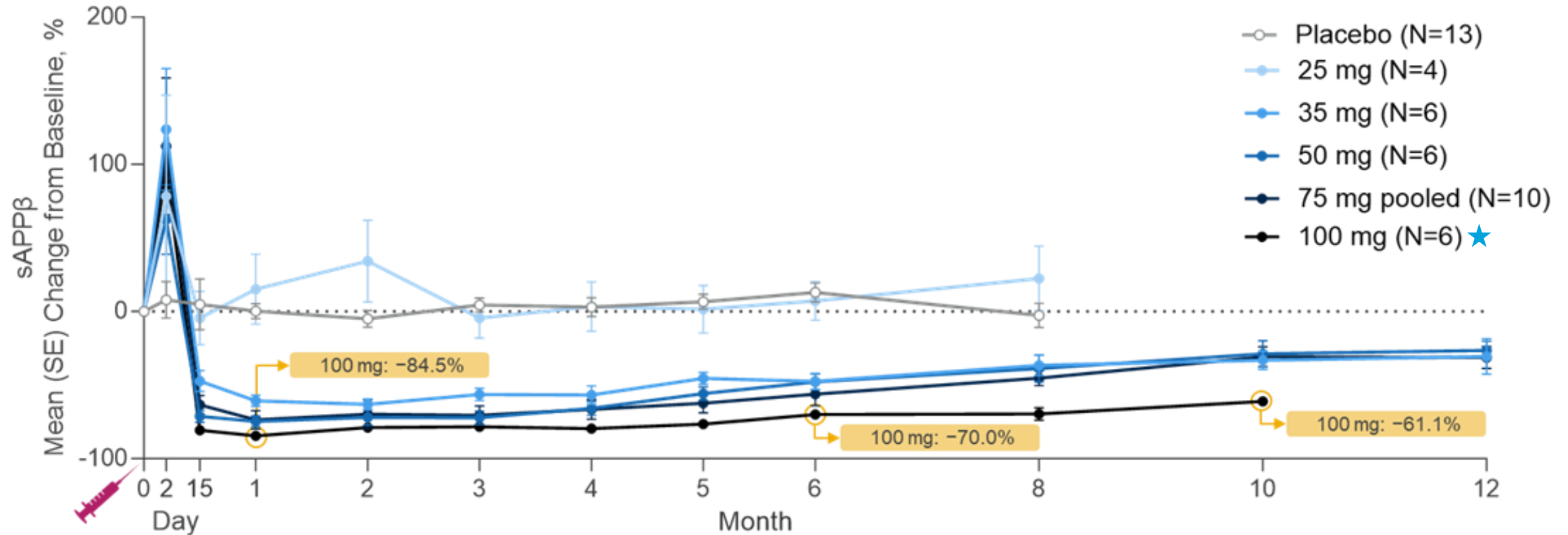
Aβ, amyloid beta; EOAD, Early-onset Alzheimer's disease; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; Pbo, placebo; PET, positron emission tomography; PD, pharmacodynamics; PK, pharmacokinetics; R, randomization; sAPP, soluble amyloid precursor protein;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

# 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 sAPP $\beta$  Levels for Single Ascending Dose Cohorts



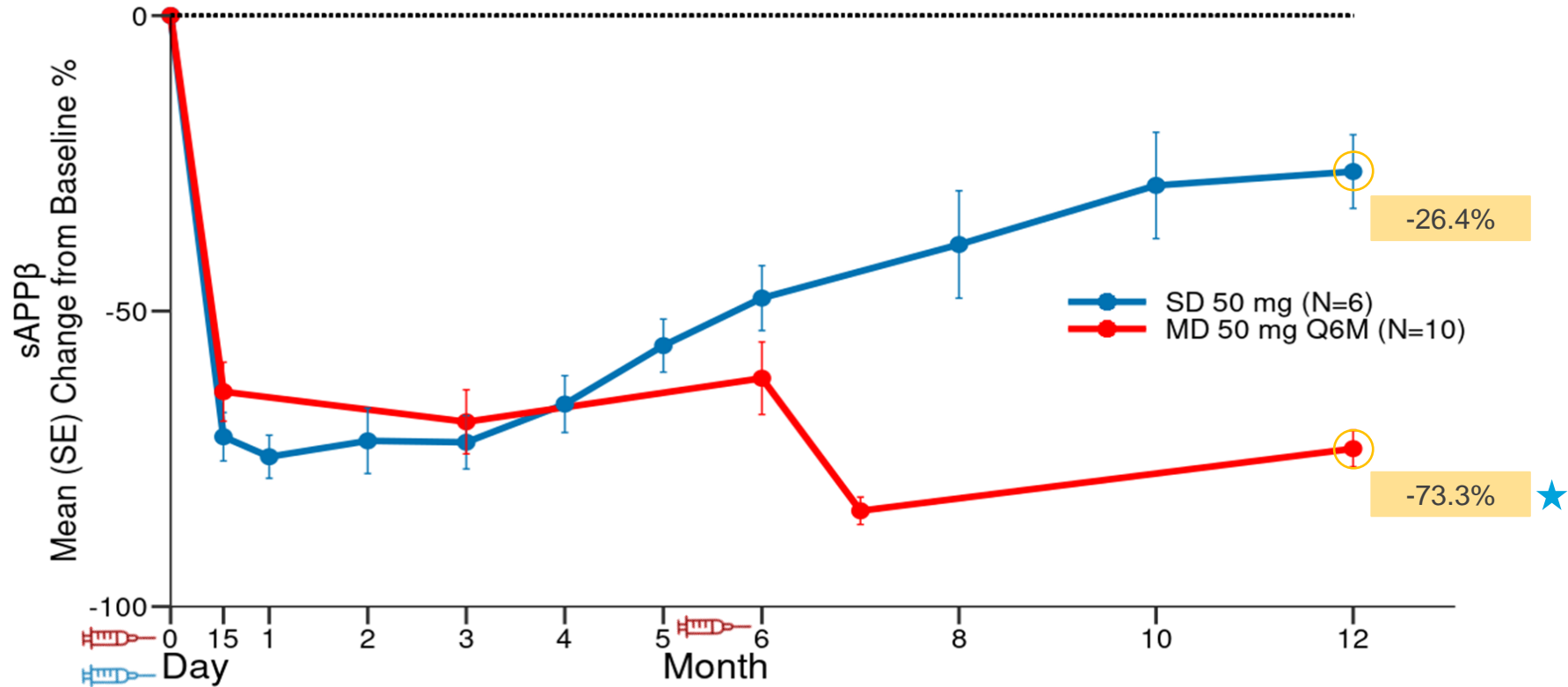
Data shown as of November 20, 2024. Time points with  $n < 3$  patients are not plotted. Placebo:  $n = 13$ , except Day 2 ( $n = 12$ ), Day 15, Months 1–3 and 6 ( $n = 11$ ), Month 4 ( $n = 10$ ), Month 5 ( $n = 9$ ), and Month 8 ( $n = 3$ ); mivelsiran 25 mg:  $n = 4$ , except Month 8 ( $n = 3$ ); 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; sAPP $\beta$ , soluble amyloid-beta precursor protein beta; SE, standard error.

# 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 sAPP $\beta$  Levels for Single Ascending Dose Cohorts

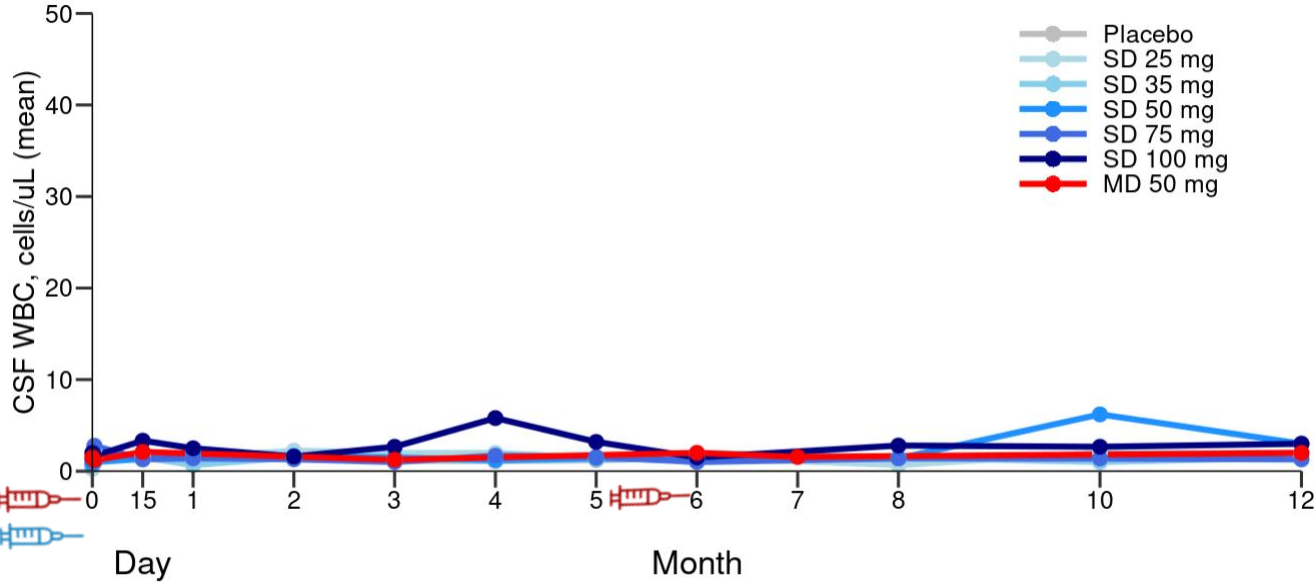


Data shown as of November 20, 2024. Single dose data decreases to n=5 at Month 6. Multidose data decreases to n=9 at Month 7 and n=7 at Month 12.  
SD, single dose; MD, multidose; CSF, cerebrospinal fluid; sAPP $\beta$ , soluble amyloid-beta precursor protein beta; SE, standard error.; M, month

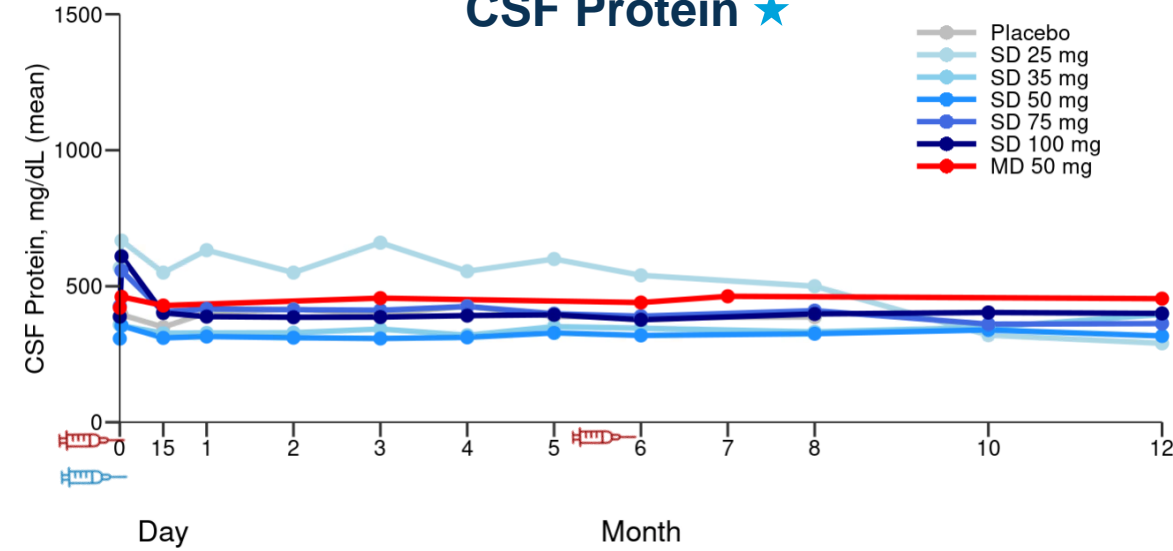
# Favorable Safety Profile Supports Best-in-Class Opportunity

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

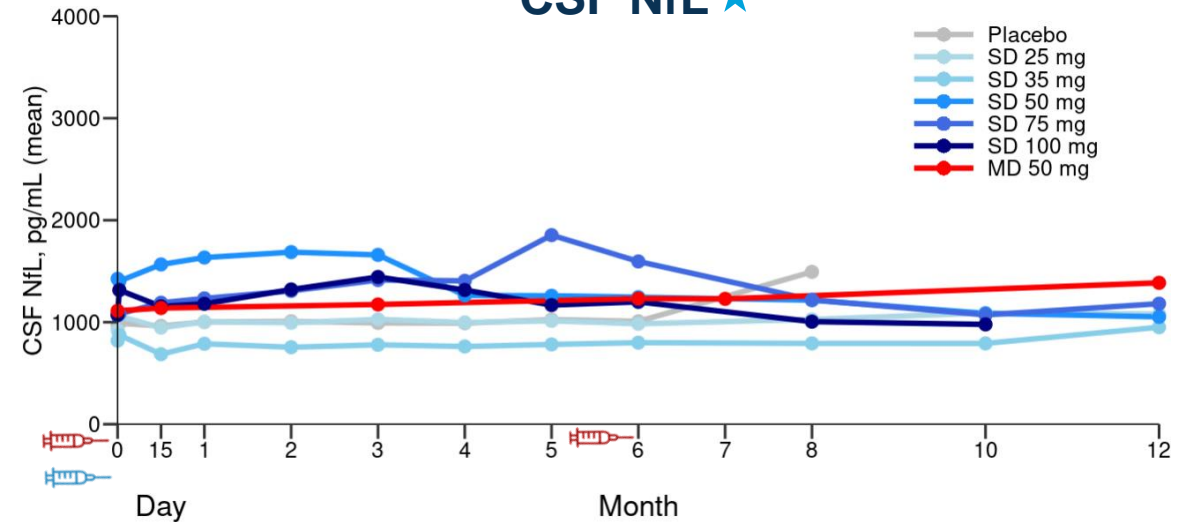
## CSF WBC ★



## CSF Protein ★



## CSF NfL ★



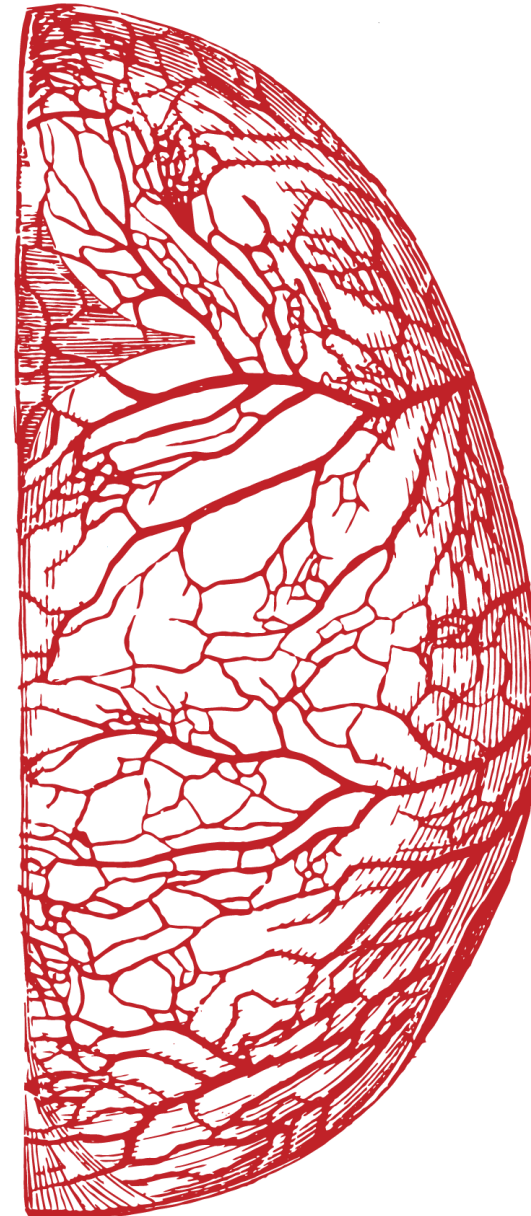
SD, single dose; MD, multidose; CSF, cerebrospinal fluid; WBC, White Blood Cells; NfL, Neurofilament Light chains  
 Data shown as of November 20, 2024. Means are given by cohort through Month 12 visits; WBC values for 3 patients in MD 50mg and 1 SD 100mg patient were excluded due to confirmed laboratory errors

# || 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

**2<sup>nd</sup>** most common cause of ICH<sup>1,2</sup> (after hypertension)

**3x** more likely to recur than other causes of ICH<sup>3</sup>



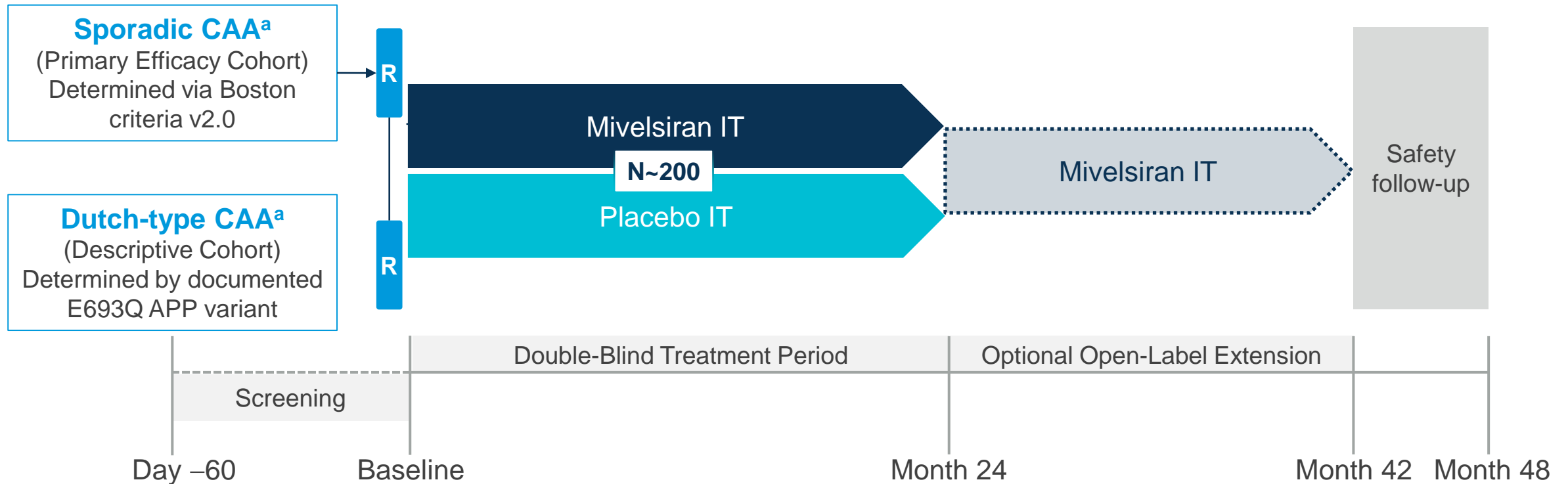
major driver of disability and mortality

### CAA and Cognition

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

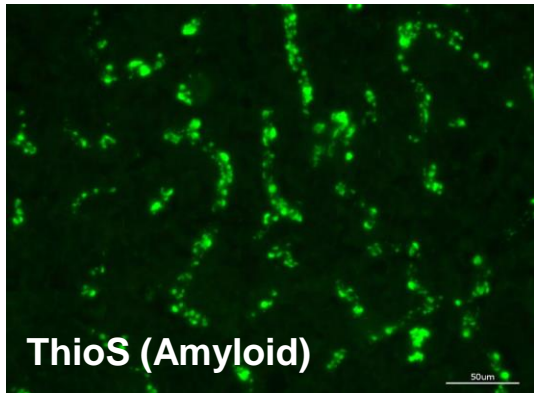
# cAPPricorn-1 is Enrolling in North America, Europe, and Australia

## Endpoints Include Hemorrhagic and Non-hemorrhagic Manifestations of CAA

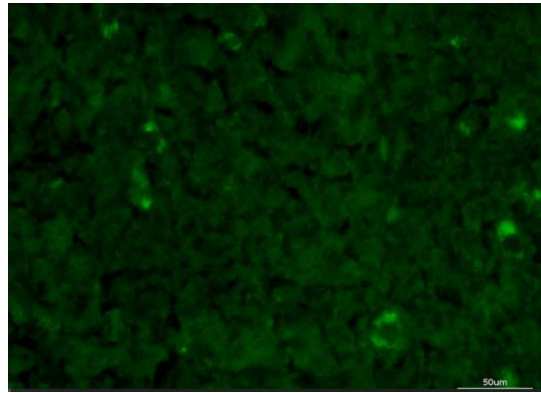


# APP Lowering Reduced Amyloid Deposition in Preclinical Models

Amyloid deposits in vessels  
6 months post-dose

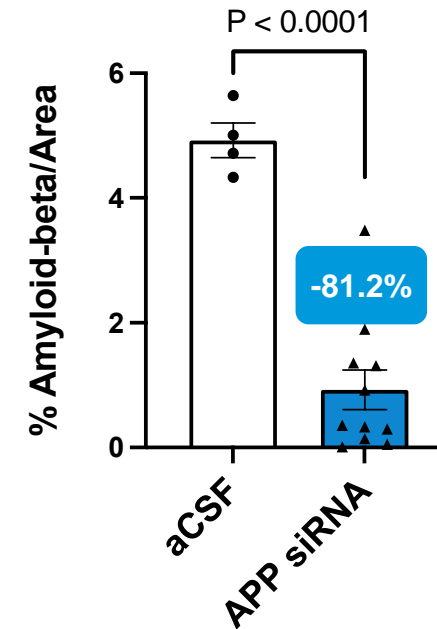


aCSF  
Control



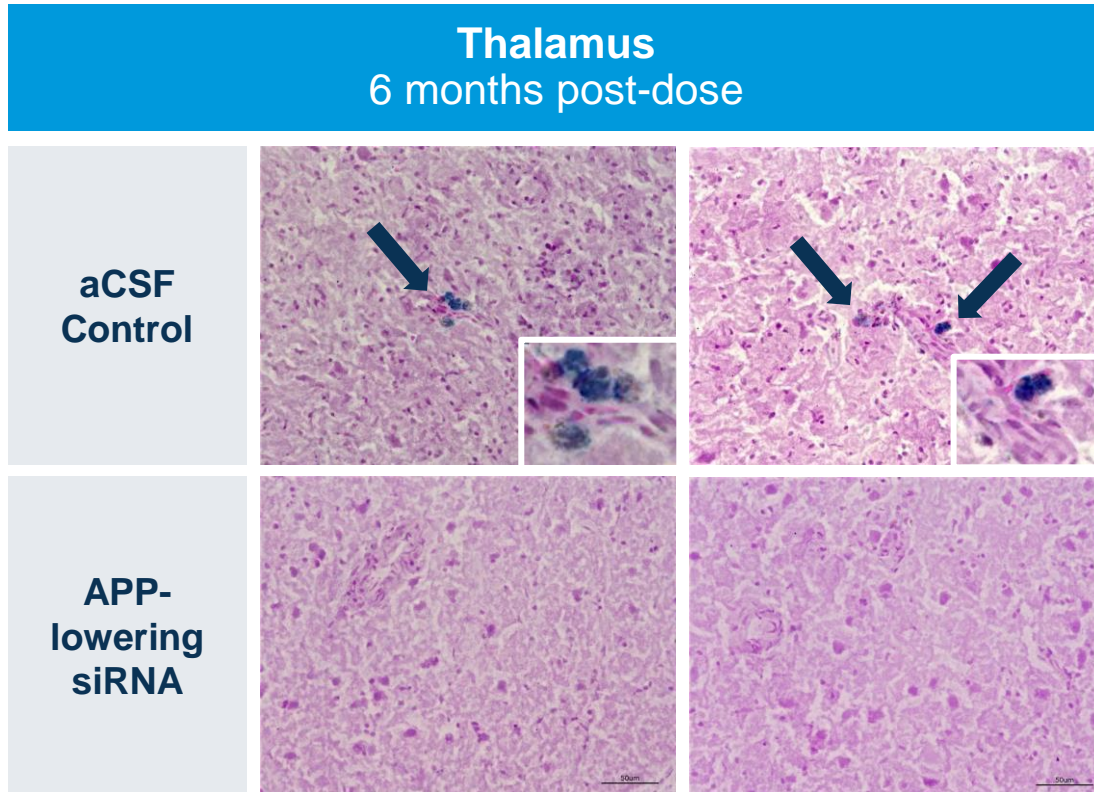
APP-lowering  
siRNA

Vascular area occupied by amyloid  
6 months post-dose



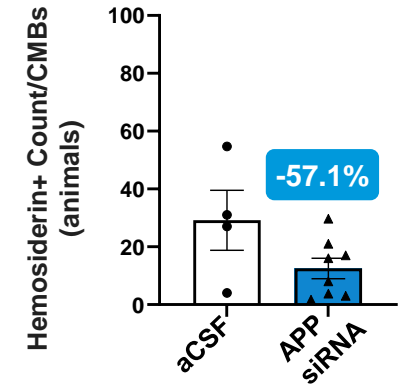
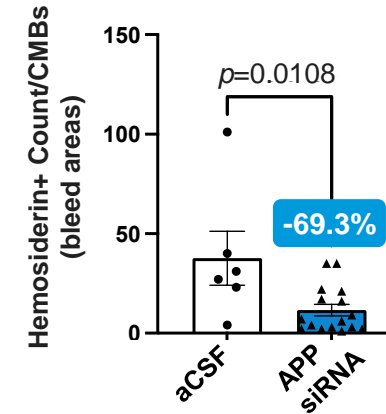
rTg-DI transgenic rats had a significant reduction in A $\beta$  accumulation in the Hippocampus vasculature compared with controls

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

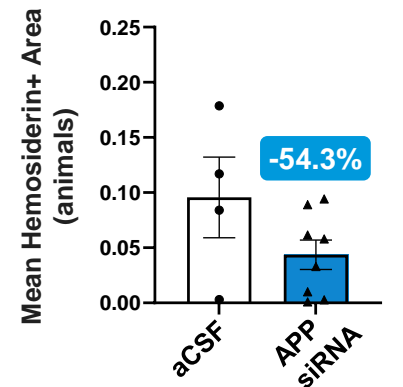
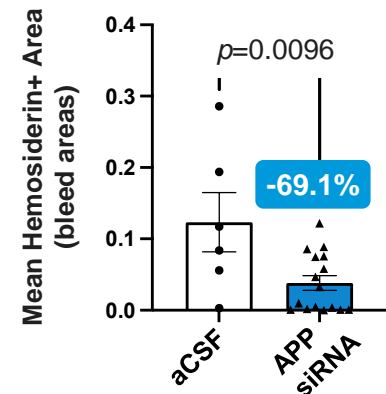


Microhemorrhages (blue) shown with arrows

**Cerebral microbleed occurrence<sup>a</sup>**



**Cerebral microbleed size<sup>a</sup>**

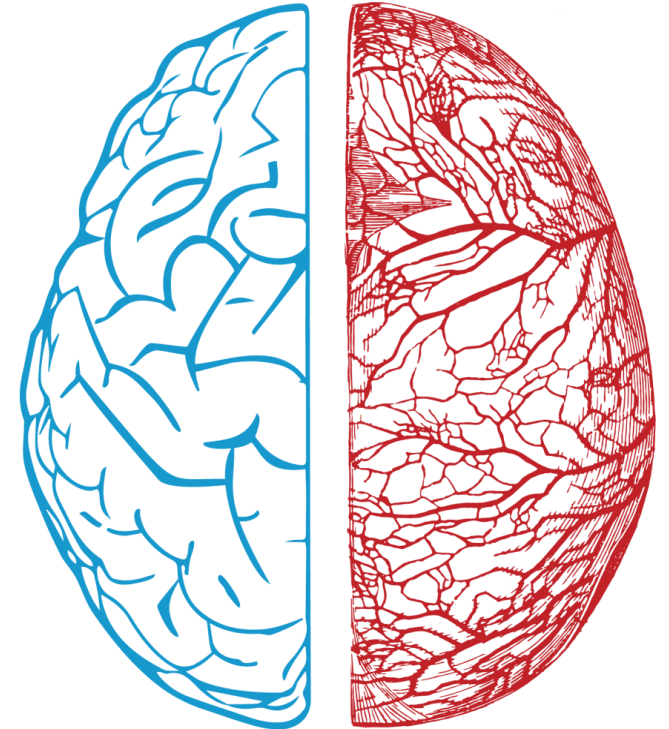


rTg-DI transgenic rats had a **reduction in number of CMBs<sup>b</sup>** and **mean CMB size** 6 months post-dose compared with controls

# || 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





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

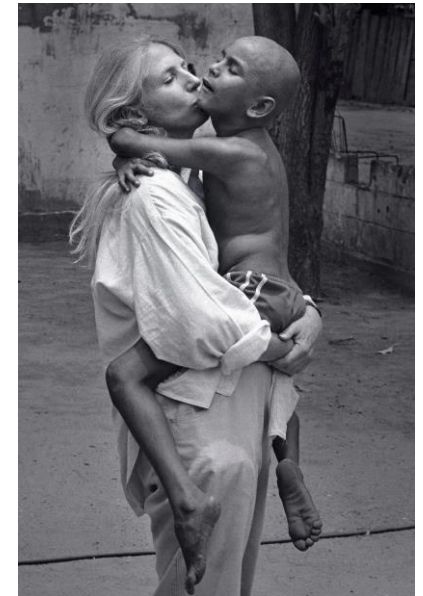
Kevin Sloan, Ph.D.  
Vice President, Early Neuroscience Programs

# || 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*)

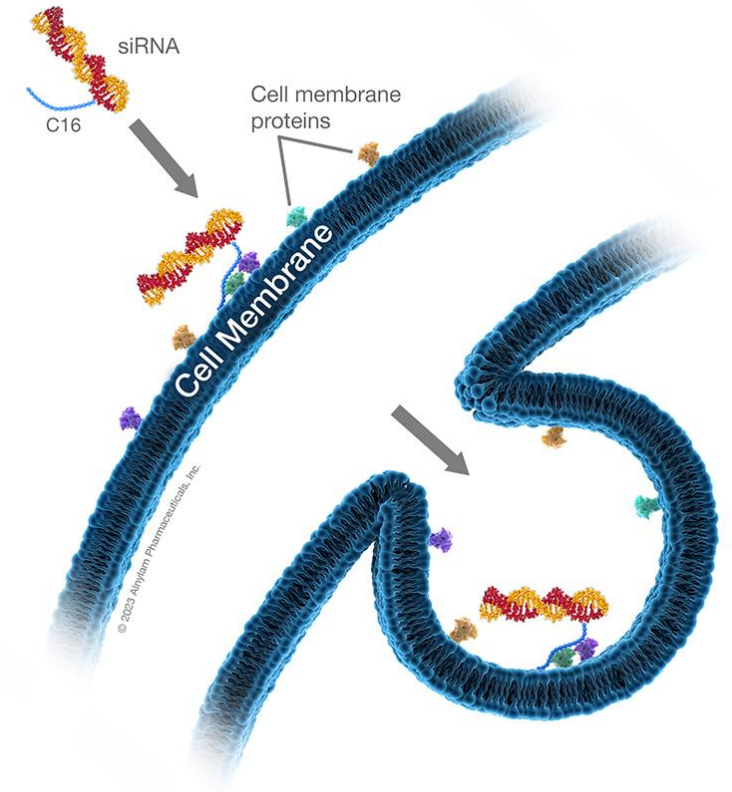


Nancy Wexler & patient  
(*patient & HD research pioneer*)

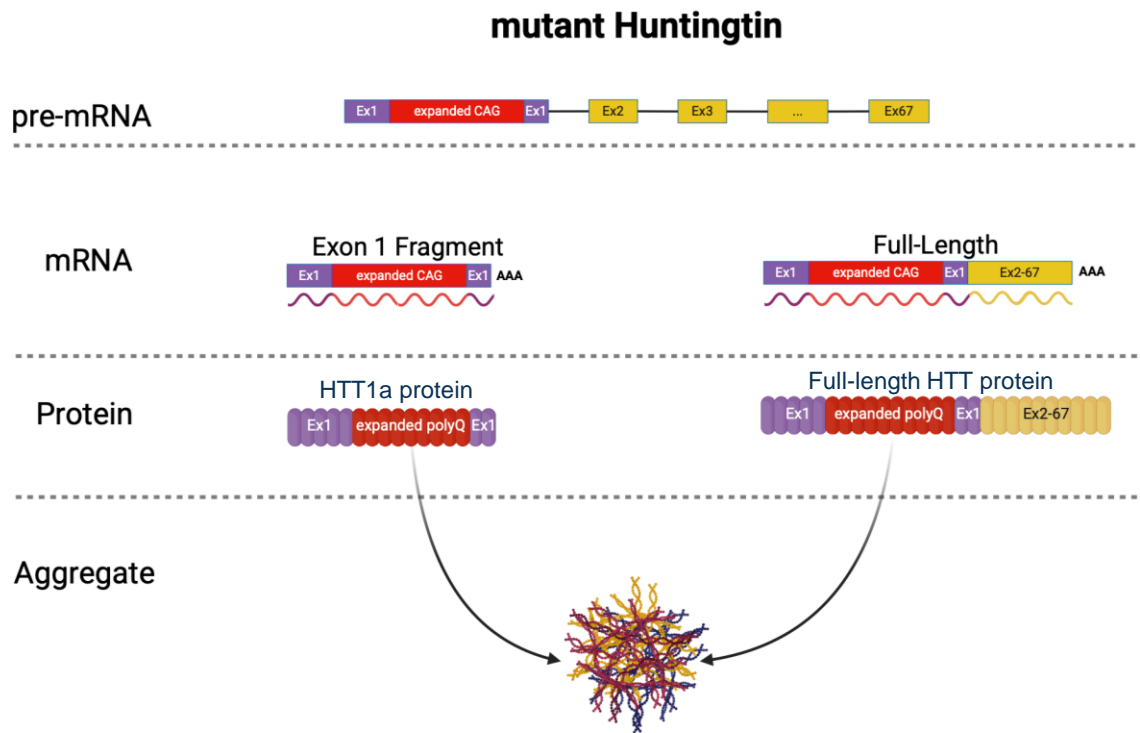
# ALN-HTT02 Program

## 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



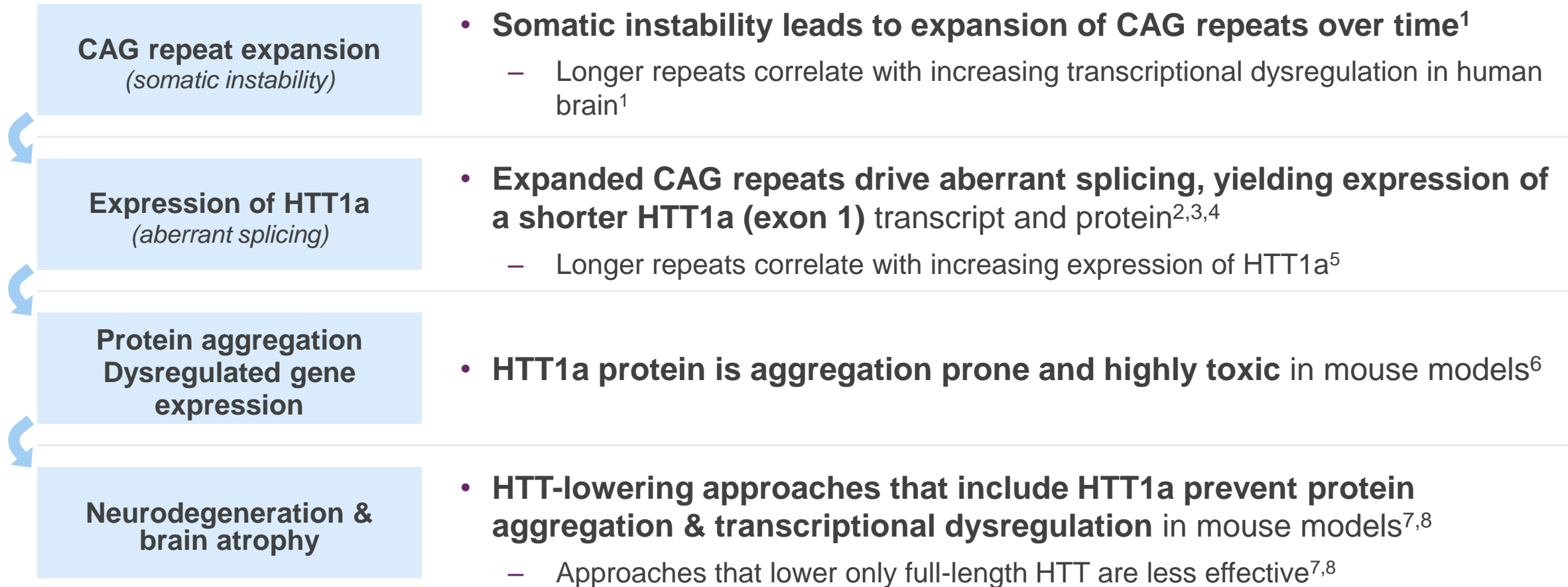
# HTT is a Genetically Validated Target for Huntington's Disease<sup>1</sup>



- **Huntington's disease (HD) is progressive and fatal, driven by mutant huntingtin (HTT)<sup>1,3</sup>**
  - 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<sup>2</sup>**
- **HTT-lowering may alter the course of HD progression<sup>1,4</sup>**
  - Safety and extent of achievable clinical benefit have yet to be elucidated

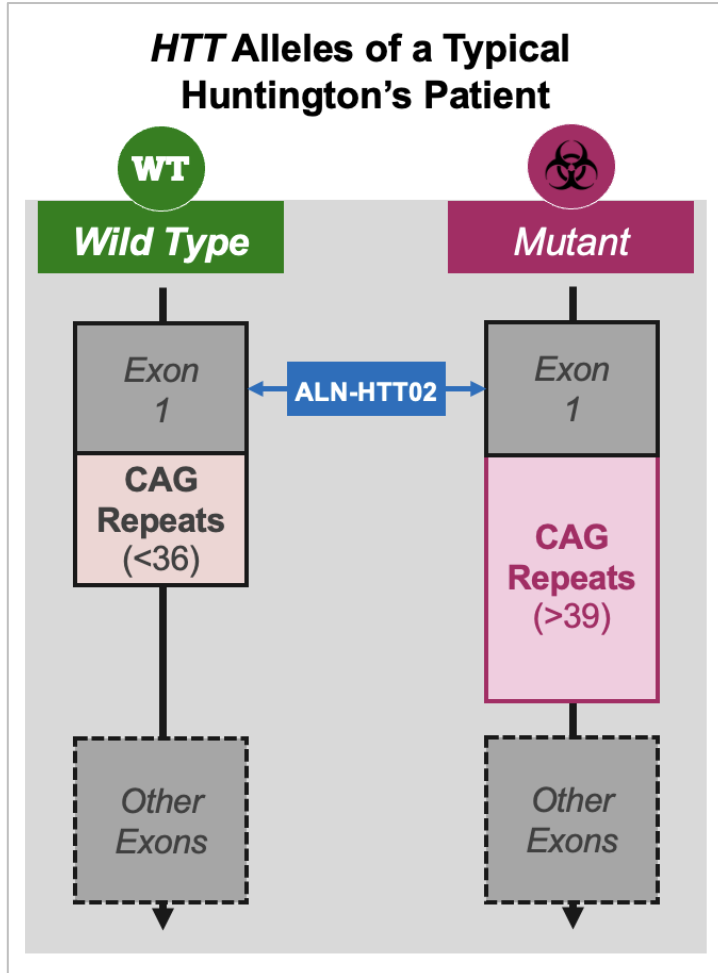
# || The Case for Targeting Exon 1

## HTT1a Isoform Links CAG Repeat Expansion to Disease Pathology



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

# 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

# ***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**

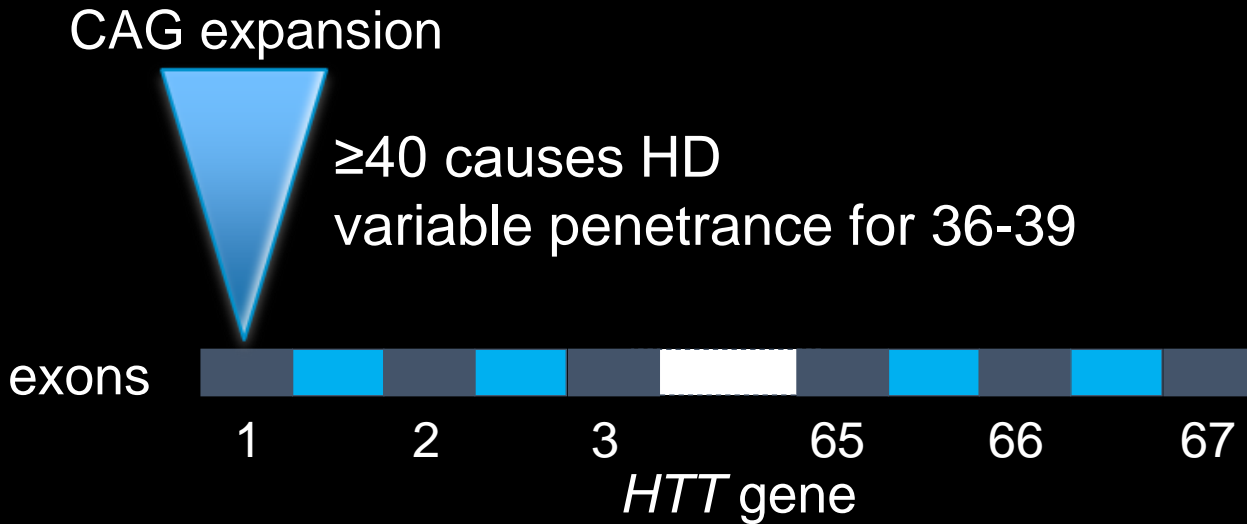


**Alynham R&D Investor Day  
25<sup>th</sup> Feb 2025**



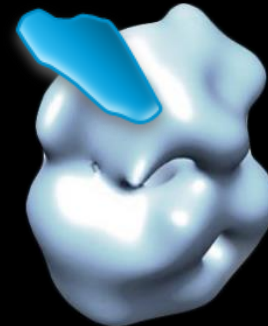
# Huntington's Disease

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



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

Polyglutamine





# Juvenile HD

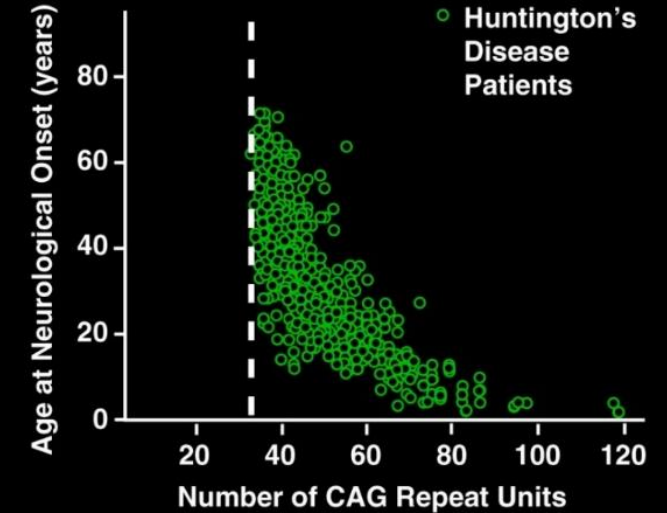


# Huntington's disease – a huge unmet need

- 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

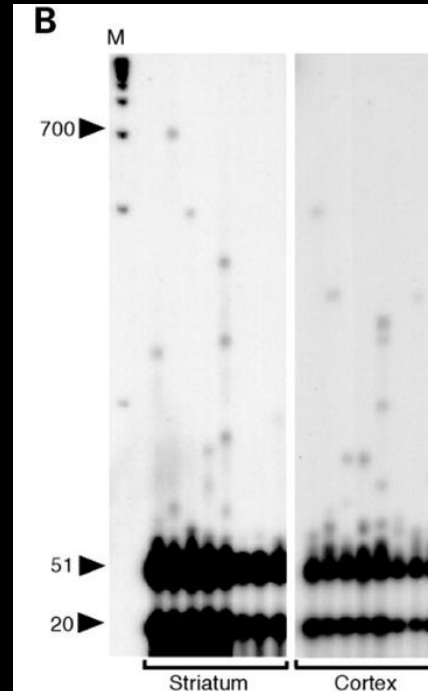
# The molecular basis of Huntington's disease – rate driver

## Step 1



Somatic CAG repeat expansion

Expansions to repeats of several 100 CAGs occur in brain regions

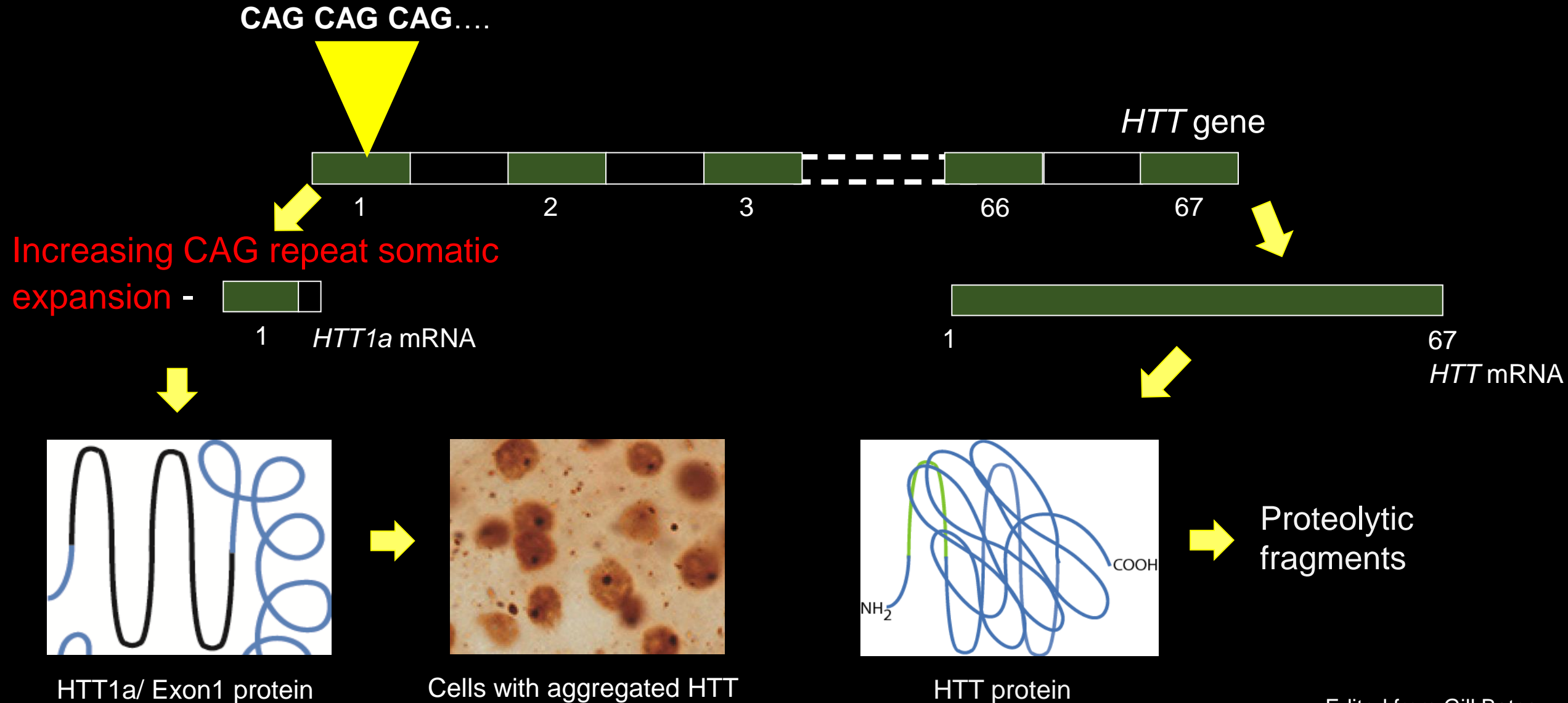


Genetic modifiers in DNA damage repair pathways act on somatic CAG expansion

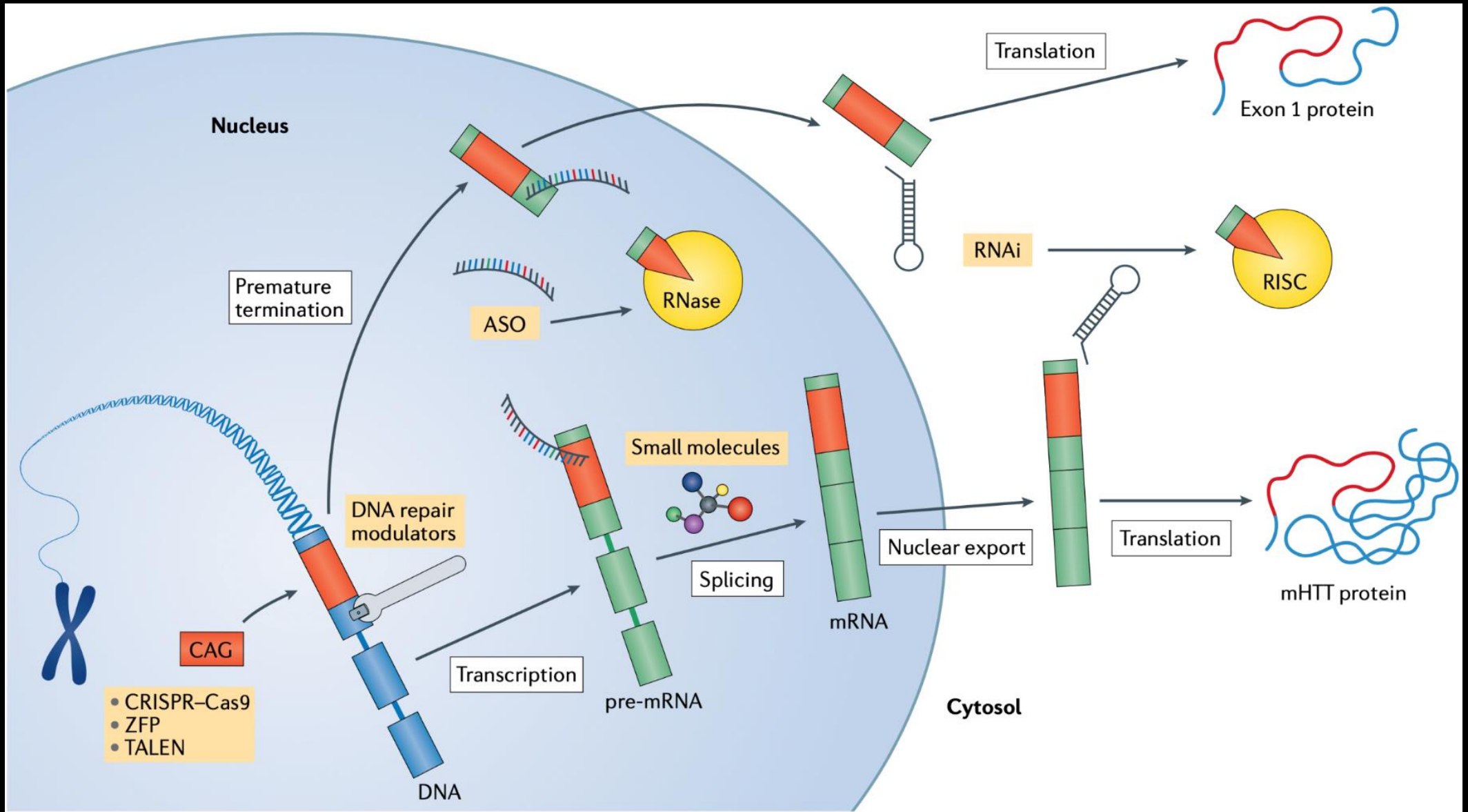
**Somatic CAG repeat expansion drives the age at disease onset and rate of disease progression for Huntington's disease**

# The molecular basis of Huntington's disease

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



# Overview of potential DM therapies in development



# **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<sup>\*†</sup>, Patrick D. Staber<sup>\*†</sup>, Xiaohua He<sup>\*†</sup>, Steven L. Eliaison<sup>\*†</sup>, Inês H. Martins<sup>\*†</sup>, Qinwen Mao<sup>\*†</sup>, Linda Yang<sup>‡</sup>, Robert M. Kotin<sup>‡</sup>, Henry L. Paulson<sup>\*§</sup>, and Beverly L. Davidson<sup>\*†§¶</sup>

## 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,<sup>1,\*</sup> Eileen M. Denovan-Wright,<sup>2</sup> Kevin Nash,<sup>3</sup> Alfred S. Lewin,<sup>3</sup> and Ronald J. Mandel<sup>1,†</sup>

## 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<sup>\*</sup>, M. Sena-Estevés<sup>\*</sup>, K. Chase<sup>†</sup>, E. Sapp<sup>\*</sup>, E. Pfister<sup>†</sup>, M. Sass<sup>†</sup>, J. Yoder<sup>\*</sup>, P. Reeves<sup>\*</sup>, R. K. Pandey<sup>‡</sup>, K. G. Rajeev<sup>‡</sup>, M. Manoharan<sup>‡</sup>, D. W. Y. Sah<sup>‡</sup>, P. D. Zamore<sup>§</sup>, and N. Aronin<sup>¶</sup>

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

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

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

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

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

Lisa M. Stanek<sup>\*†</sup>, Wendy Yang<sup>‡</sup>, Stuart Angus<sup>‡</sup>, Pablo S. Sardi<sup>†</sup>, Michael R. Hayden<sup>‡</sup>, Gene H. Hung<sup>‡</sup>, C. Frank Bennett<sup>‡</sup>, Seng H. Cheng<sup>‡</sup> and Lamya S. Shihabuddin<sup>‡</sup>

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

Ai Yamamoto,<sup>†</sup> José J. Lucas,<sup>†‡</sup> and René Hen<sup>\*</sup>

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

Brett D Dufour<sup>1,2</sup>, Catherine A Smith<sup>2</sup>, Randall L Clark<sup>2</sup>, Timothy R Walker<sup>2</sup> and Jodi L McBride<sup>1,2,3</sup>

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

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

## 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

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

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

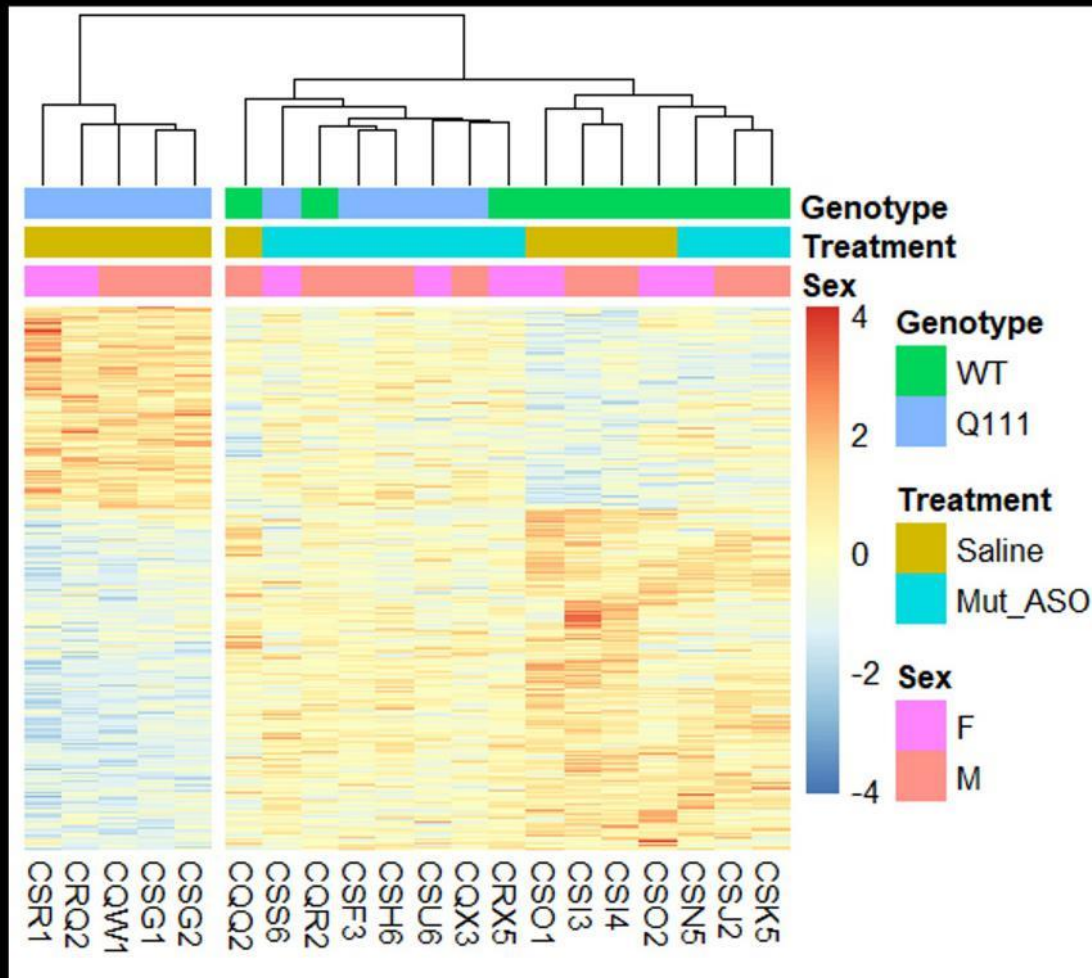
## Huntingtin suppression restores cognitive function in a mouse model of Huntington's disease

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

## 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<sup>1,2,3,†</sup>, Amber L. Southwell<sup>1,2,3,4,†</sup>, Cynthia C. Brouwers<sup>5</sup>, Louisa Dal Cengio<sup>1</sup>, Yuanyun Xie<sup>1,4</sup>, Hailey Findlay Black<sup>1,2,3</sup>, Lisa M. Anderson<sup>1</sup>, Seunghyun Ko<sup>1</sup>, Xiang Zhu<sup>4</sup>, Sander J. van Deventer<sup>5</sup>, Melvin M. Evers<sup>5</sup>, Pavlina Konstantinova<sup>5</sup> and Michael R. Hayden<sup>1,2,3,\*</sup>

# Why targeting toxic HTT Exon 1 is so important?

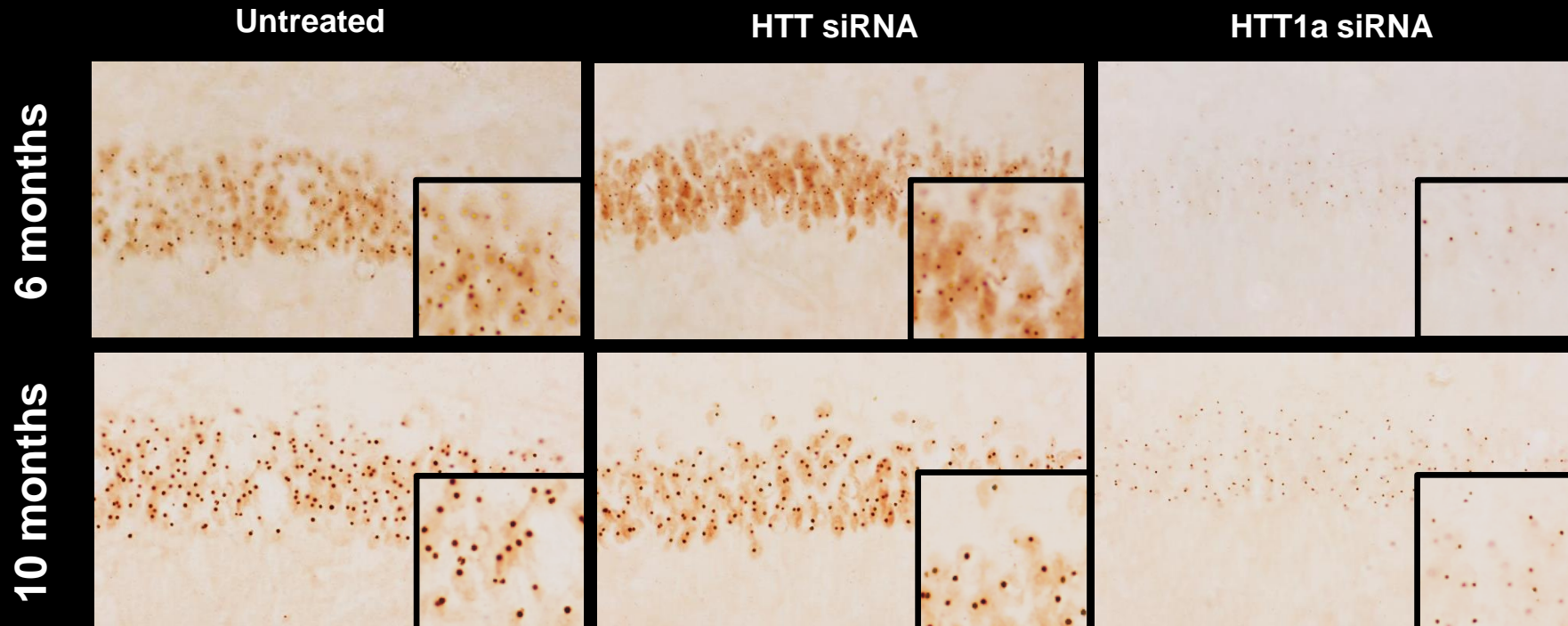


Unsupervised clustering of samples based on expression of HD DEGs splits mice into two distinct groups:

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 Demonstrate Evi

## Fa Cli Hu

June 2

Wave Life Science  
Phase 1b/2a SELE  
Demonstration of  
Lowering in Huntin

June 25, 2024

- FD

- Cor

*Statistically significant, potent, mutant huntingtin (mHTT) protein compared to placebo, preservation of 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*



## 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 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](#)

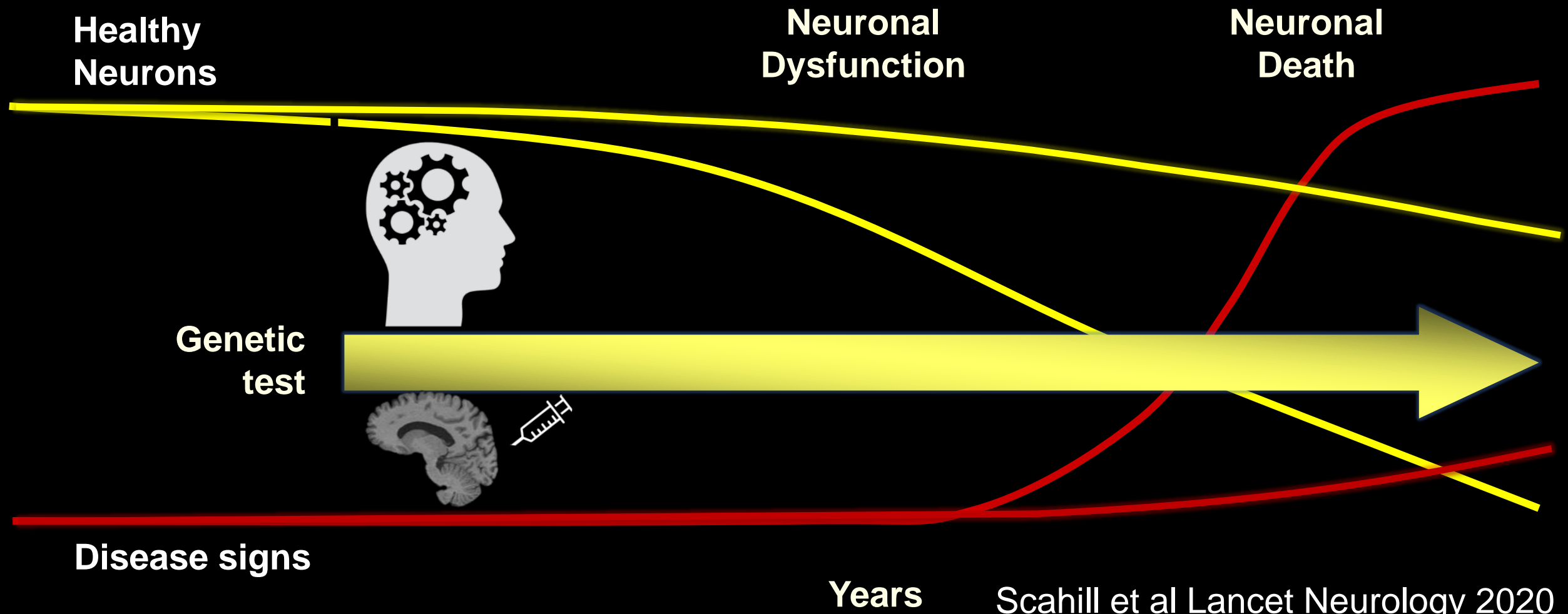
# HTT lowering summary so far

| 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%<br>surgery<br>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



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

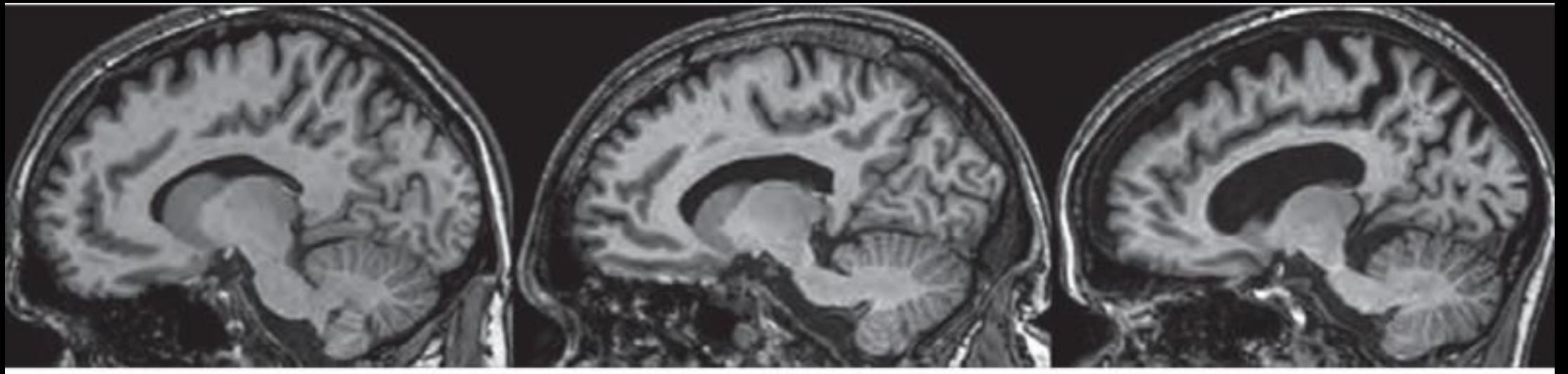
Control

PwHD

PwHD

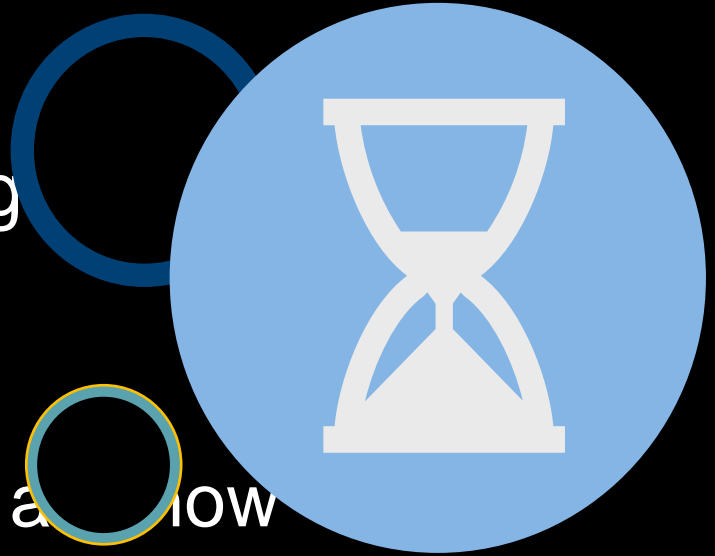
(years before clinical diagnosis)

(clinically diagnosed)



# 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 slow movement in later part of the disease



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

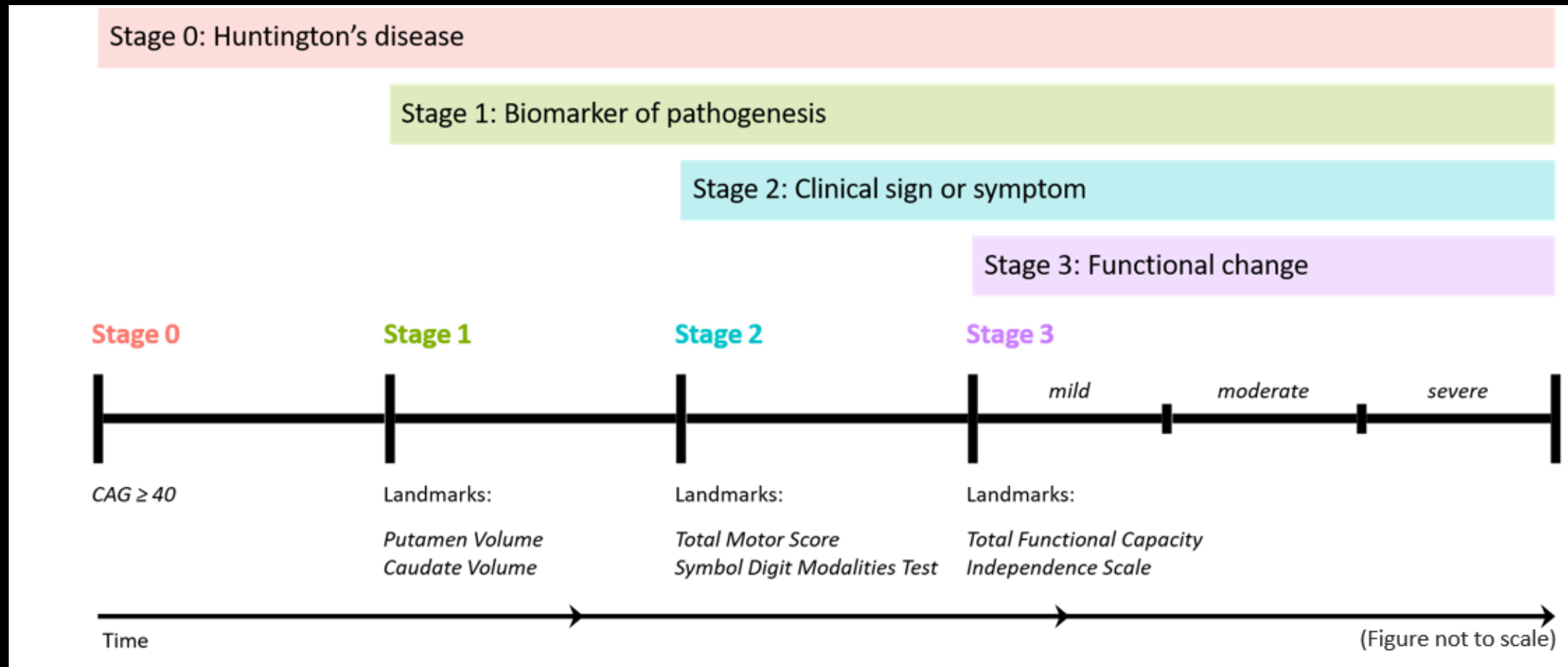


# HD biological research definition

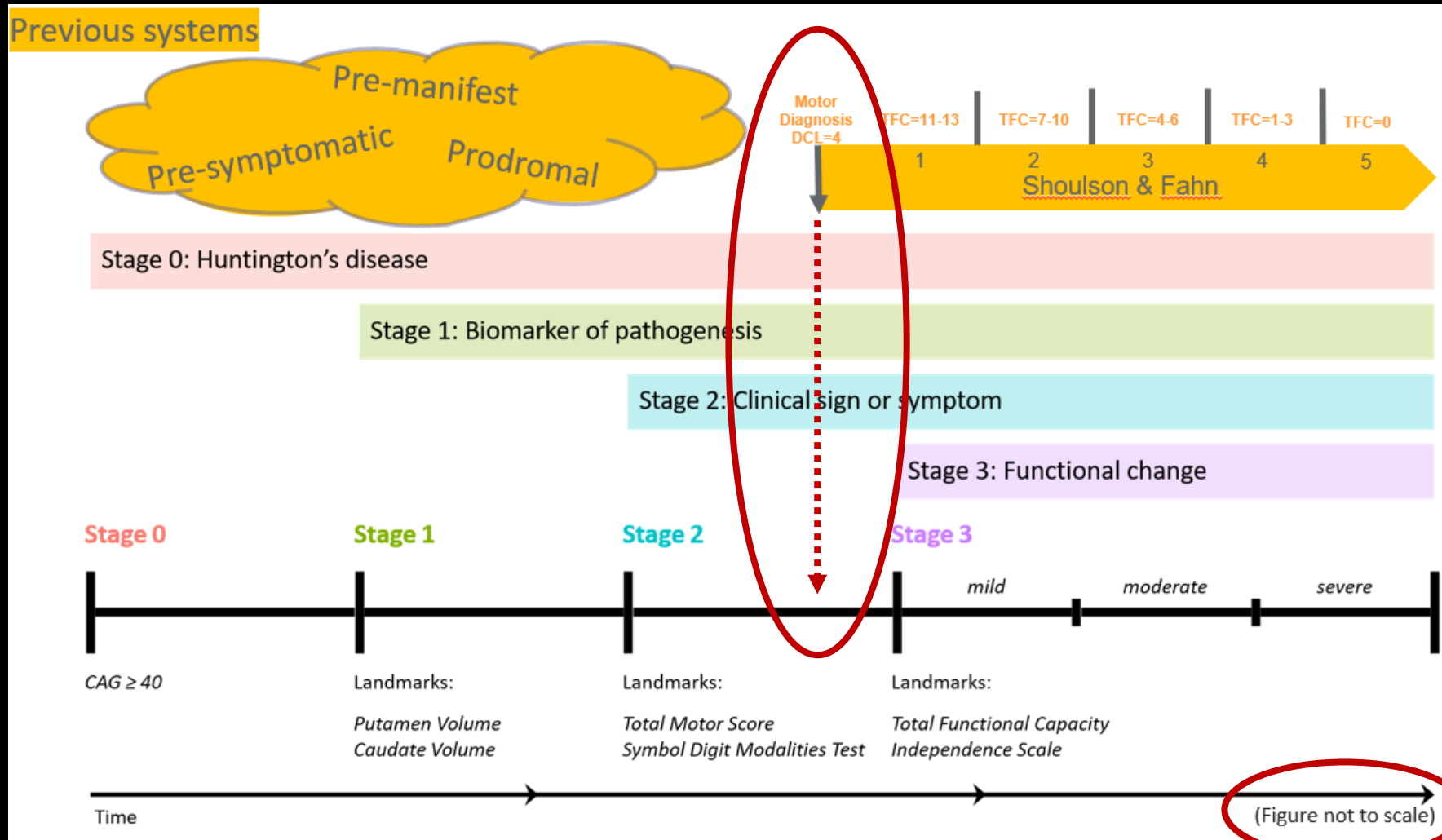
- Huntington's disease is defined as the presence of a CAG expansion in exon 1 of the HTT gene of
  - $\geq 40$  CAG; or
  - $\geq 36$  CAG and the presence of a disease-specific biomarker or disease-specific clinical syndrome.

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  $\geq 40$ .

# HD-ISS represents the entire course of HD

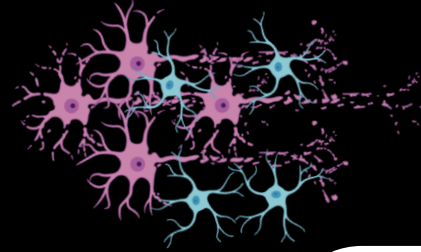
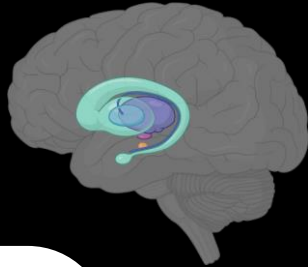


# HD-ISS represents the entire course of HD

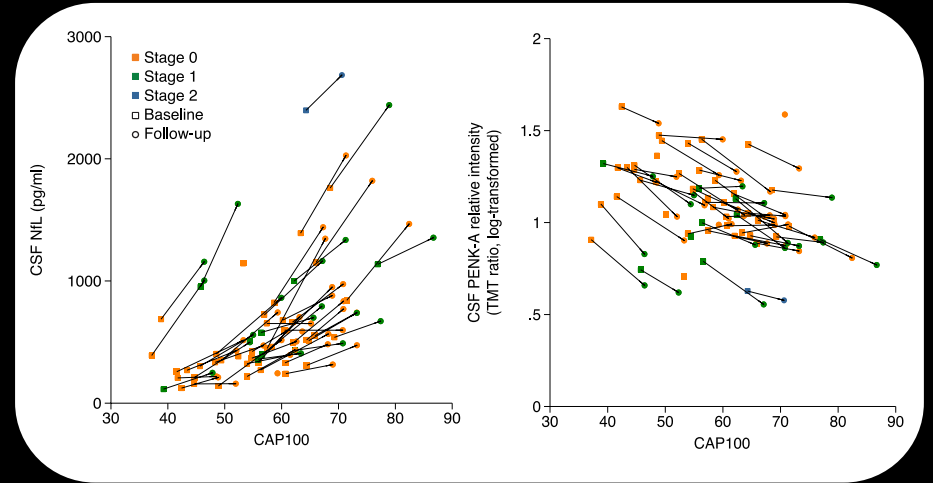
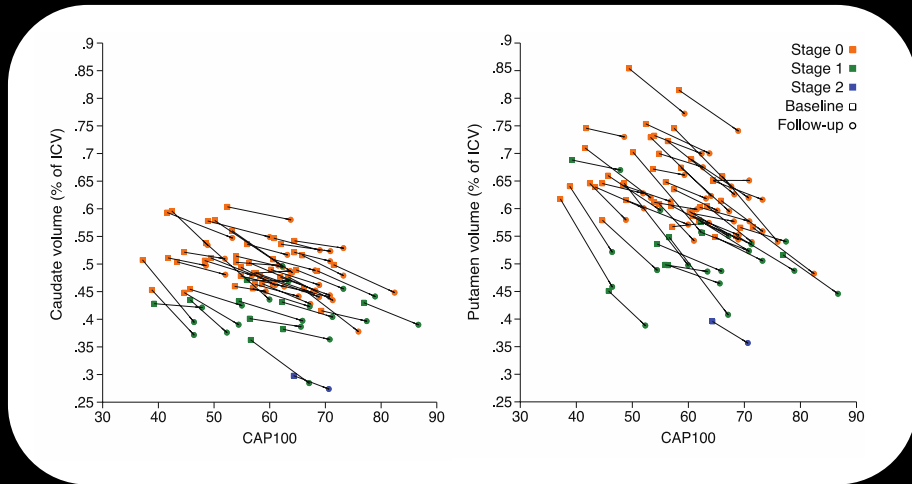


# Biomarkers – Path to Earlier Stage Trials

## Change in caudate and putamen volume



## Change in CSF NfL and PENK levels



Stage 0

Stage 1

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

**n=125**

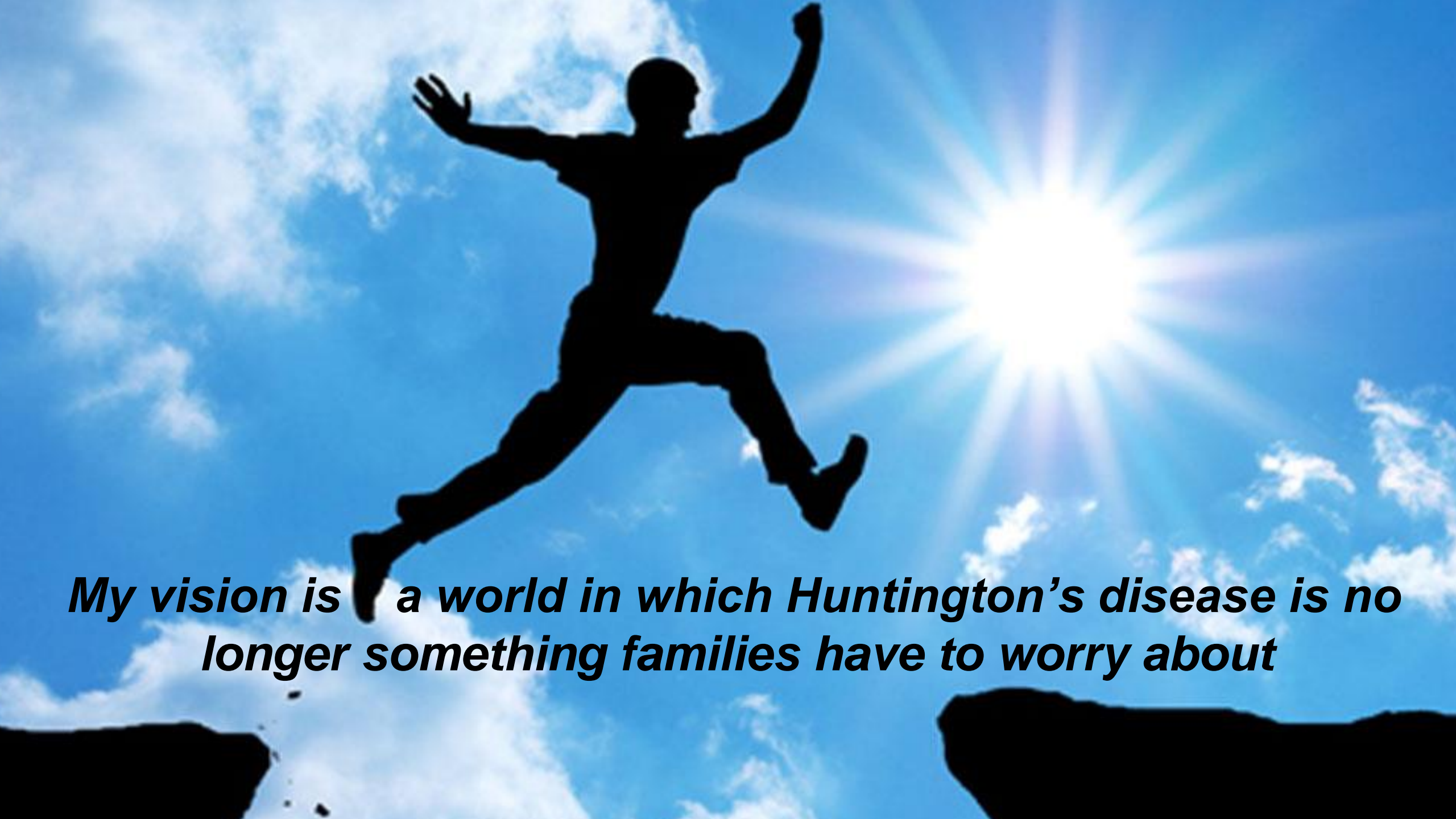
caudate atrophy

**n=146**

putamen atrophy

**n=104**

CSF NfL



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

# Thank You!

## Tabrizi Group

### Wet lab

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Dr Emma Bunting  
Dr Jasmine Donaldson  
Dr Mike Flower  
Dr Marwa Elmasri  
Dr Joseph Hamilton  
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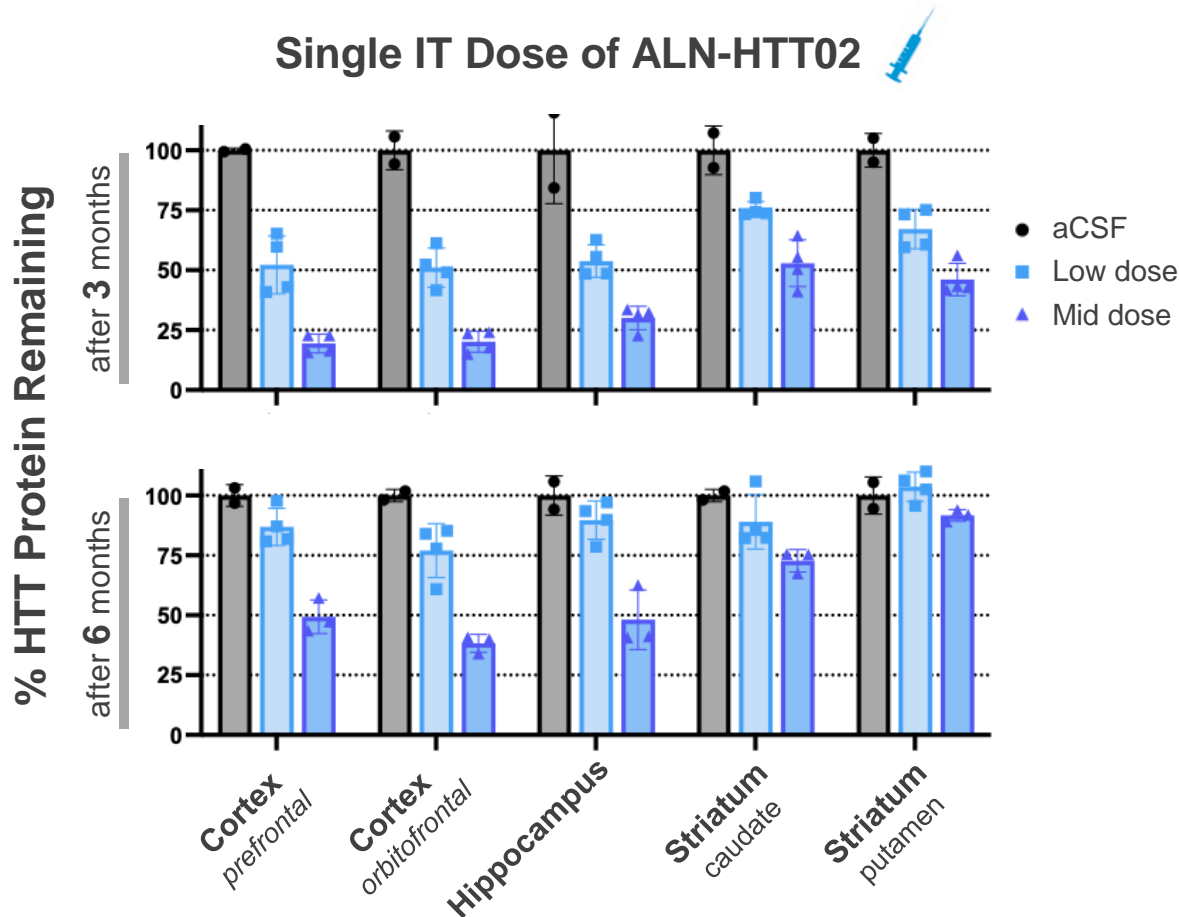
## CHDI

Dr Tom Vogt  
Dr Brinda Prasad  
Dr Michael Finley  
Dr Ramee Lee  
Dr Cristina Sampaio  
Dr Emily Gantmann



# ALN-HTT02 Demonstrates Broad CNS Distribution and Durable HTT-Lowering in NHP<sup>1</sup>

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



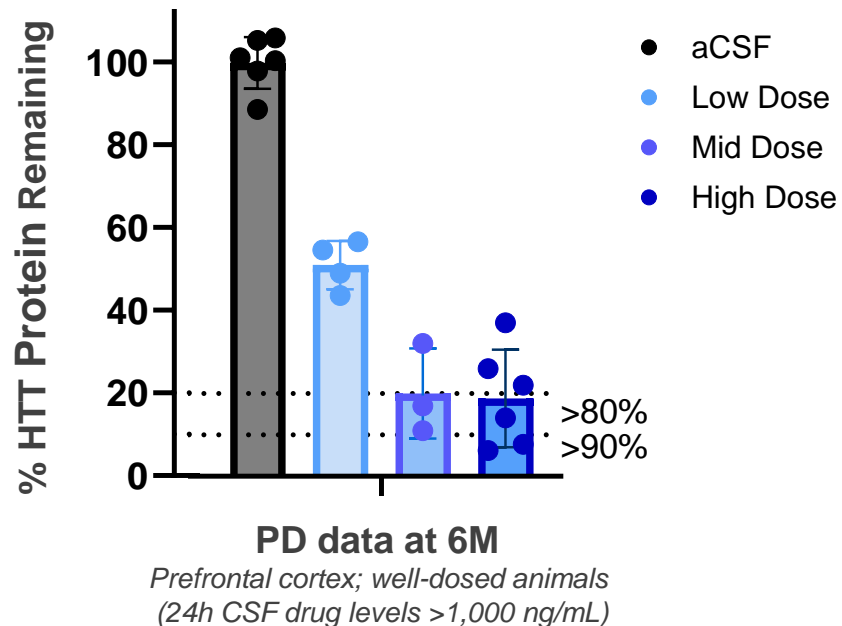
### Observations following a single dose of ALN-HTT02:

- **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

# Multiple Doses of ALN-HTT02 Well Tolerated in NHP<sup>1</sup>

## Safety Profile Supports Continued Development

### Multiple IT Doses of ALN-HTT02



### 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%)**

# Ph1b Study of ALN-HTT02 Underway in Adult Patients with HD<sup>1</sup>

## 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  |
|--|
| <ul style="list-style-type: none"> <li>• Primary endpoint                             <ul style="list-style-type: none"> <li>– Safety and tolerability</li> </ul> </li> <li>• Secondary endpoints                             <ul style="list-style-type: none"> <li>– PK: CSF and plasma profile of ALN-HTT02</li> <li>– PD: Change in mHTT levels in CSF</li> </ul> </li> <li>• Exploratory endpoints                             <ul style="list-style-type: none"> <li>– Clinical, imaging and biomarker measures of disease progression and safety</li> </ul> </li> </ul> |

| Dose<br>(Administered IT) | Randomization              | Single Ascending Dose <sup>a</sup> | Open-label <sup>b</sup><br>(Placebo-treated only) |
|---------------------------|----------------------------|------------------------------------|---|
| Dose 1                    | ALN-HTT02<br>or<br>Placebo | →                                  | ⇒ ...   |
| Dose 2                    |                            | →                                  |   |
| Dose 3                    |                            | →                                  |   |
| Additional cohort(s)      |                            | → ...                              |   |
| Observation period        |                            | Up to 12 months                    | Up to 12 months                                   |

- 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

# 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<sup>1</sup>
  - 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](https://RNAiScience.com). Non-US HCPs should contact [medinfo@alnylam.com](mailto: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).*

# 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**<sup>1</sup> – Huntington's
  - **ALN-SOD**<sup>2</sup> – ALS
- **Additional molecules in CTA-enabling development**, rapidly approaching clinic
  - **MAPT**<sup>1</sup> – tauopathies, including Alzheimer's
  - **SNCA**<sup>3</sup> – 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**

The logo consists of a stylized white symbol on the left, resembling a lowercase 'a' with a dot above it and a sharp tail extending downwards and to the left. To the right of this symbol is the word 'Alylam' in a white, clean, sans-serif typeface, followed by a registered trademark symbol (®).

Alylam®

# 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 | Julia Shirvan, M.D., Ph.D., Senior Director, Mivelsiran Clinical Lead |
|  | Overview of Huntington’s Disease Unmet Need   | Professor Sarah Tabrizi, M.D., Ph.D. FMedSci FRS, UCL                 |
|  | ALN-HTT02: Hope for Huntington’s Disease Patients   | Kevin Sloan, Ph.D., VP, Early Neuroscience Programs                   |

The logo consists of a stylized white symbol on the left, resembling a lowercase 'a' with a dot above it and a sharp tail extending downwards and to the left. To the right of this symbol is the word 'Alylam' in a white, clean, sans-serif typeface, followed by a registered trademark symbol (®).

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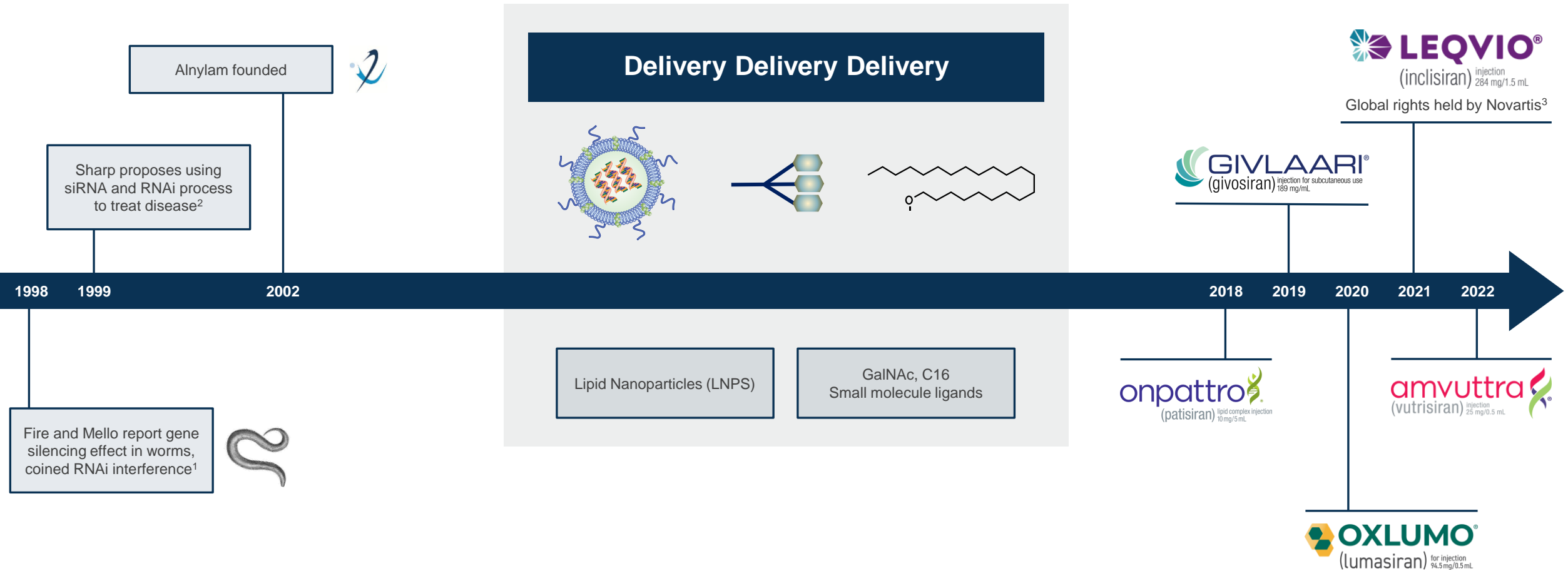


# Durable Leadership in RNAi Therapeutics

**Kevin Fitzgerald, Ph.D.**  
**Chief Scientific Officer**

# || Anylam Drove the First Phase of the RNAi Revolution

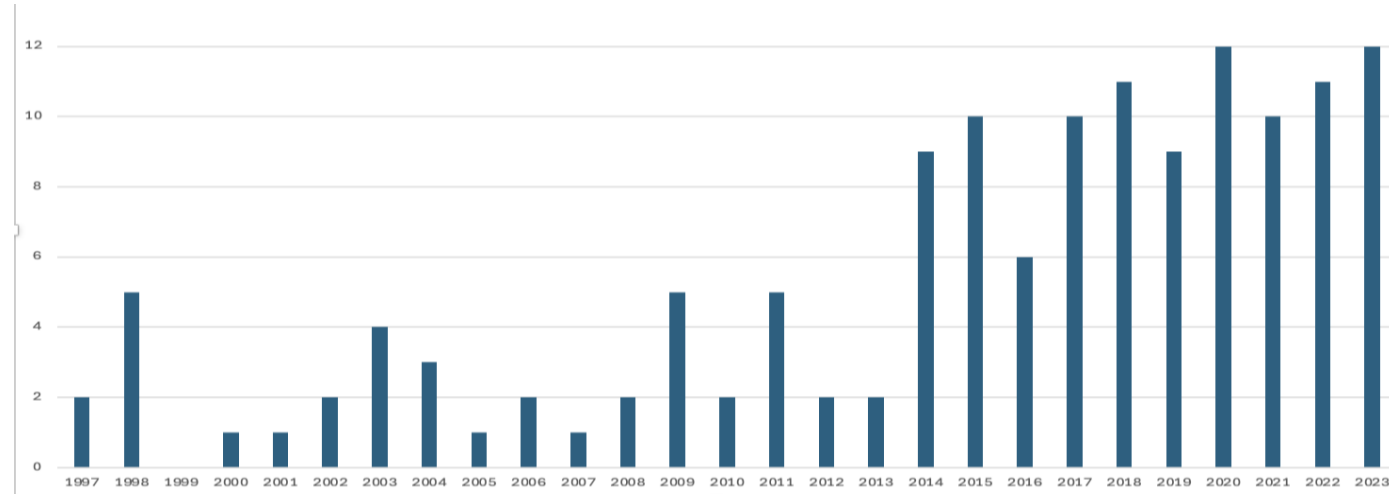
We Conquered Delivery to the Liver and Discovered the World's First Five RNAi Therapeutics



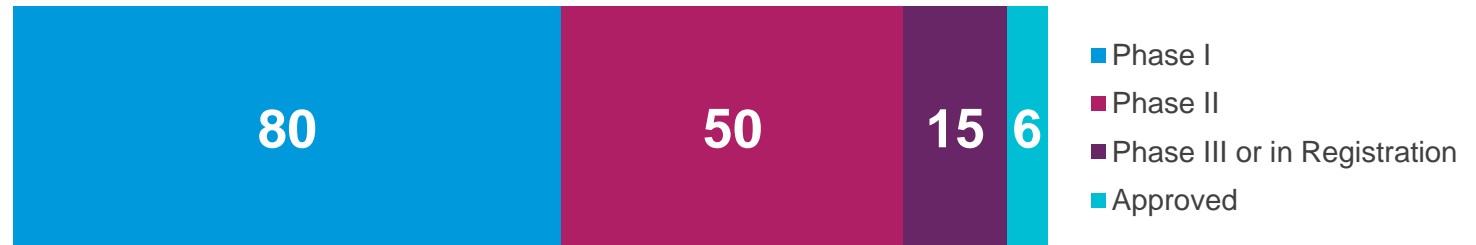
# RNAi Therapeutics – A Generational Technology

Following the Trajectory of Another Generational Technology

Antibody-Based Biologics Approved by FDA<sup>1</sup>



145 siRNA Programs in Development Across the Industry<sup>2</sup>



95 distinct assets in development across 85 indications

# || Anylam is Positioned to Continue Leading the Field Into the Future

Unmatched Depth of Expertise, Experience and Innovation in RNAi



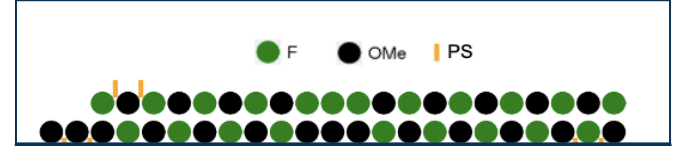
**Largest database of active siRNAs**  
interrogated with AI;  
**Proven innovation in delivery**

+



**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**

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

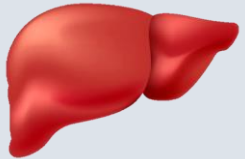
15 New Programs in Clinic (2024-2025) Across Wholly-owned and Partner-led Programs



**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)**

# 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

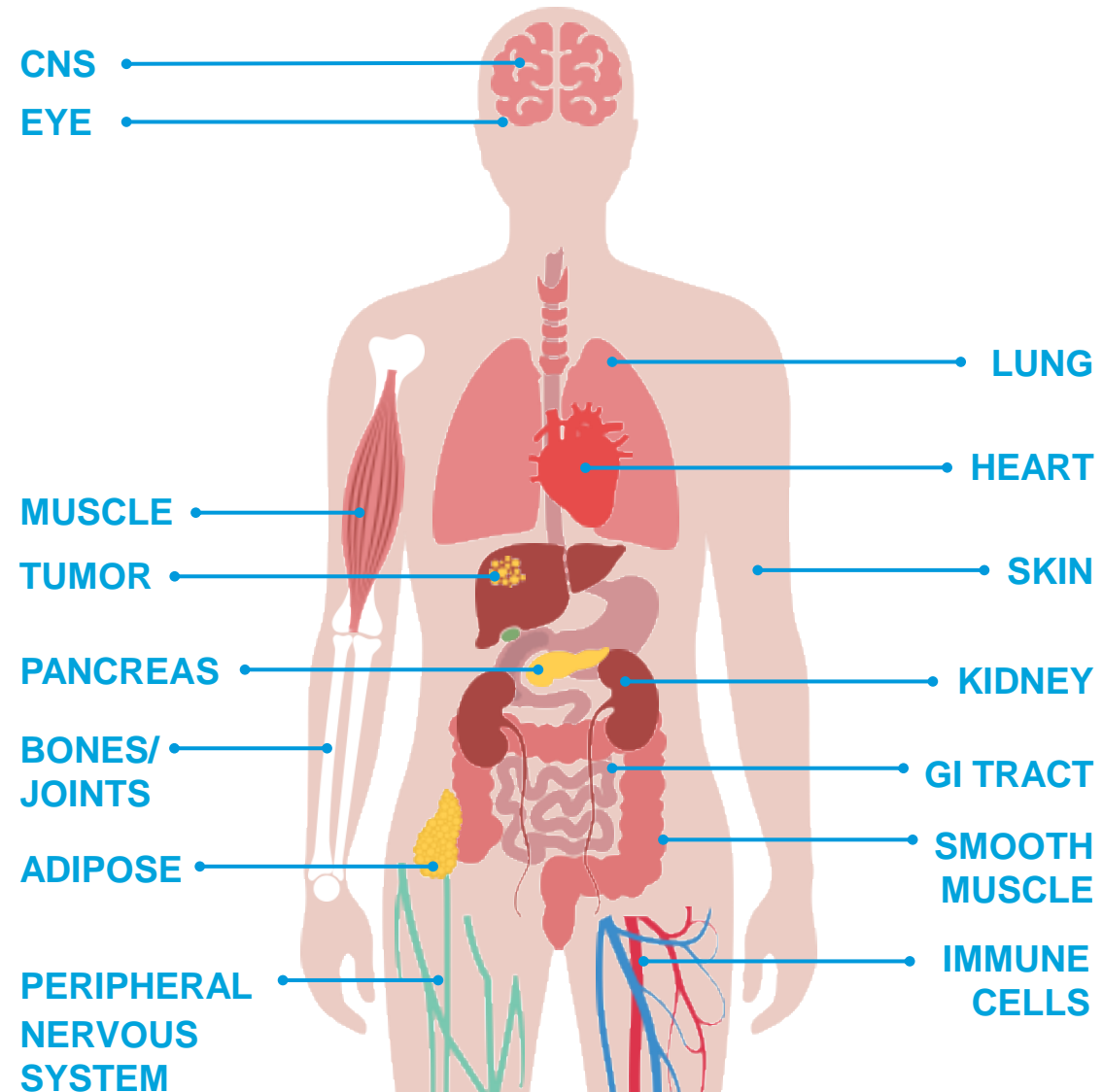
## Achieving Best-in-Class Delivery - Differentiated Profile

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:

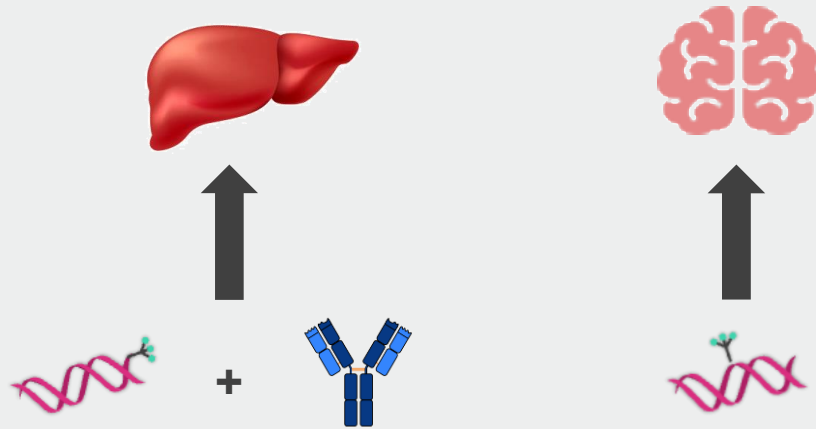
- Cardiovascular disease
- Metabolic disease
- Neurodegenerative disease

**1 in 4 people**  
in the world has metabolic syndrome<sup>1</sup>

# Exponentially Expanding Patient Impact with Combinations

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

2024

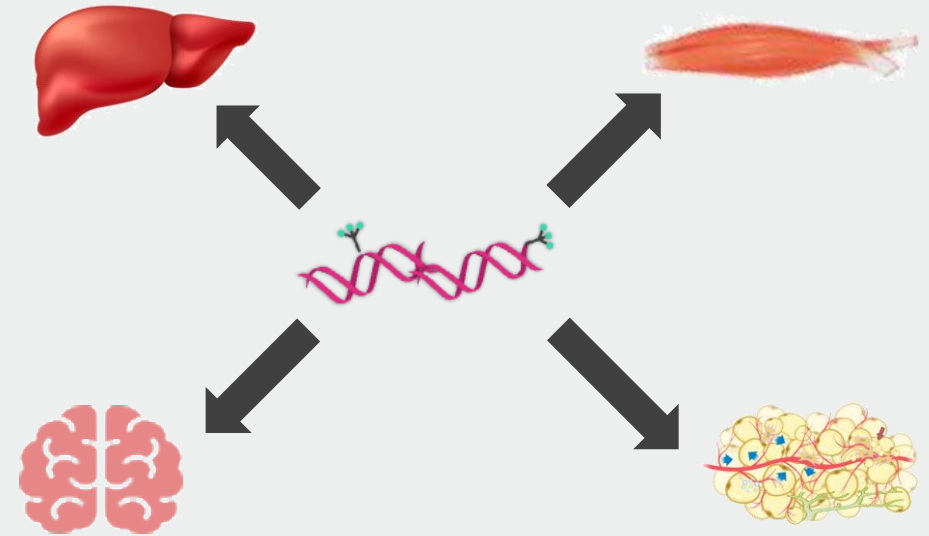


**Basic Combos** with other agents

Example: cemdisiran + pozelimab<sup>1</sup>

Combos of existing RNAi Tx also possible

2025 Forward



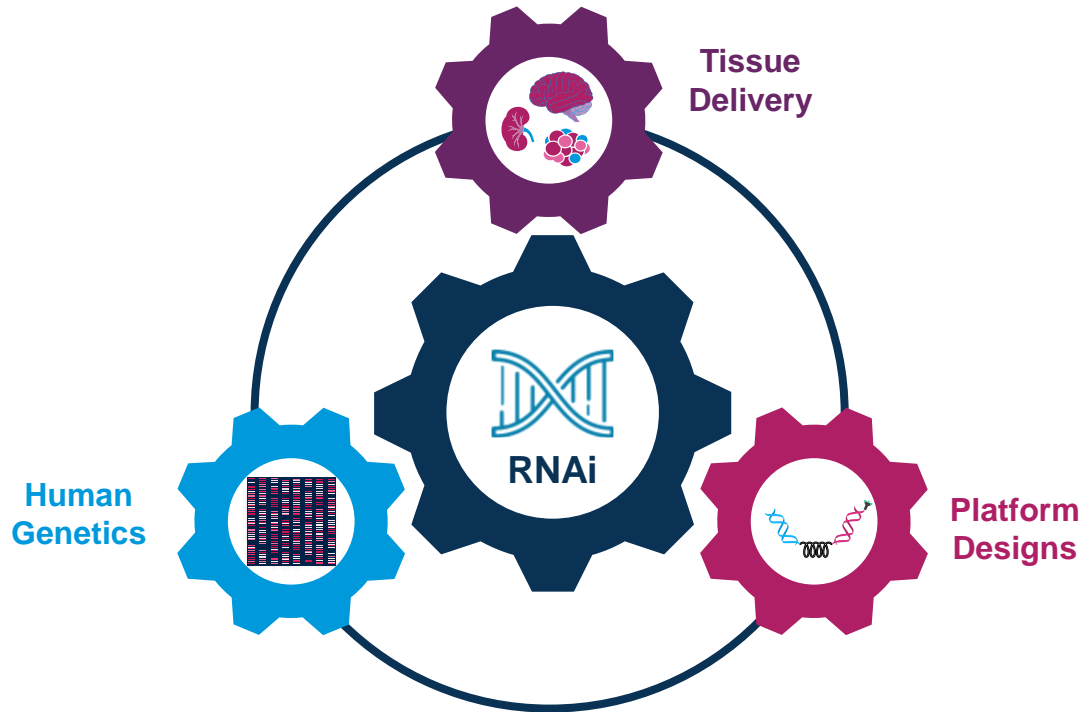
**Accelerating Progress** with multiple siRNAs delivered to one organ, or multiple organs simultaneously. May be combined with antisense, small molecule, antibody and peptide drugs.

Example: Delivery to Target A and Target B in liver

*Preclinical data on knockdown will be presented today*

# 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**



# Next Wave of Innovation in Metabolic Diseases

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

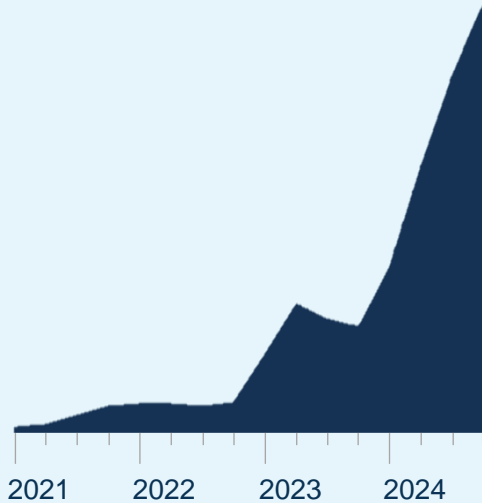
# Aligning Alnylam's Strategic R&D Principles to Metabolic Strategy

| 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<br>INHBE<br>GPR75*<br>“Gene X”<br>Novel siRNA combinations | GRB14<br>Novel siRNA combinations  |

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

## First Wave of Innovation

GLP-1 Treatment Rate Since Approval<sup>1</sup>



- 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**

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



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

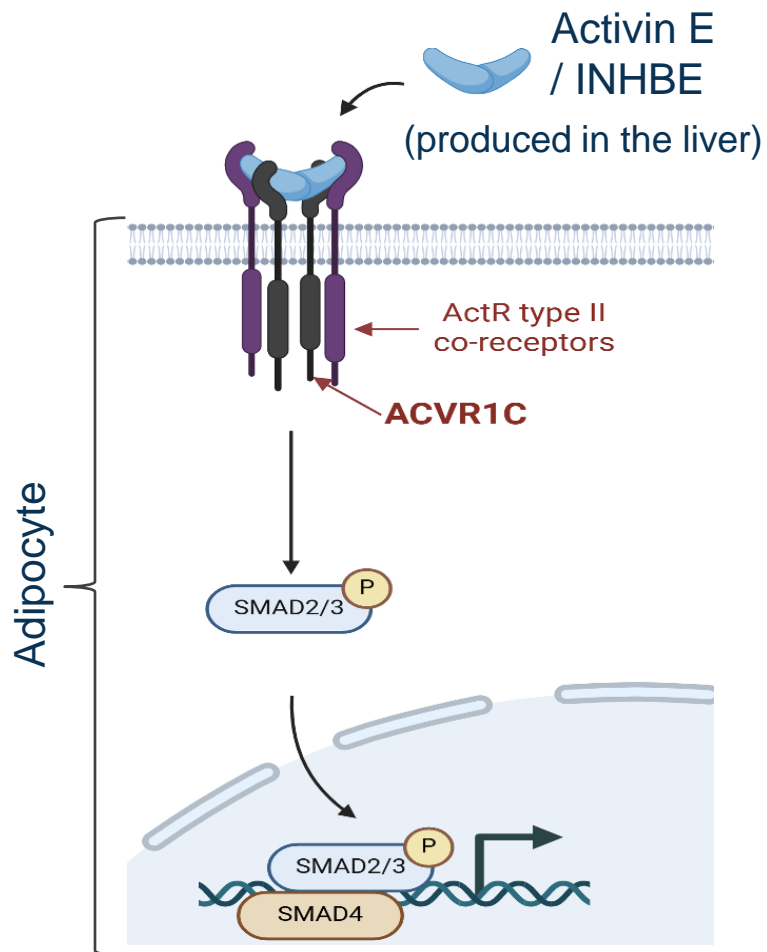
- Strong genetics
- Exquisite tissue selectivity
- Long acting (biannual / annual dosing)
- Strong pre-clinical data
  - Monotherapy
  - Combinations with novel siRNAs
    - Multiple tissue
    - Multiple targets
  - Combinations with low dose incretin



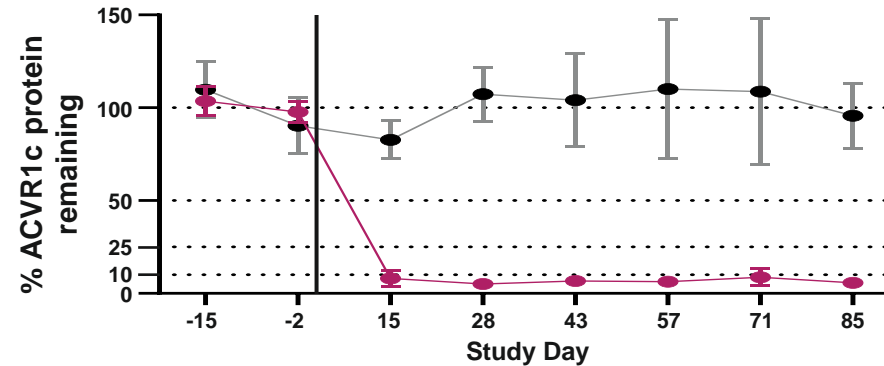
- **Durable** weight loss
- Improve **quality of weight loss**
  - Prevent muscle loss
  - Improved body composition
- **Improve tolerability**
- **Reduce discontinuation rate**

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

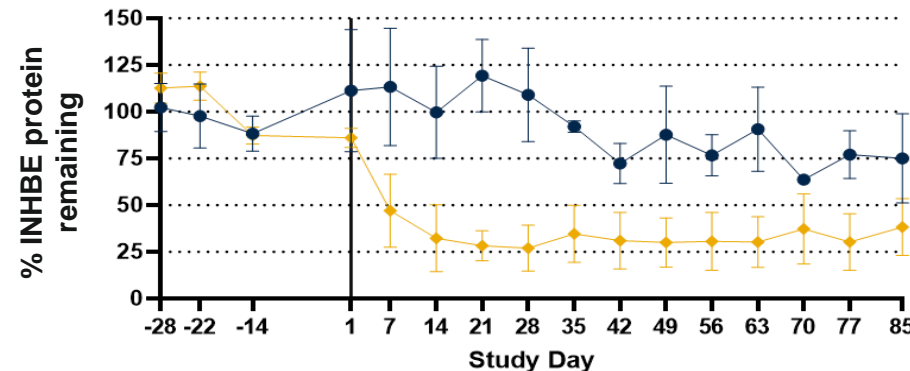
Ligand/Receptor Inhibin/Activin Pathway: INHBE (in liver) and ACVR1c (in adipose)



## 95% ACVR1c Knockdown in NHP Adipose



## INHBE Knockdown in NHP Liver

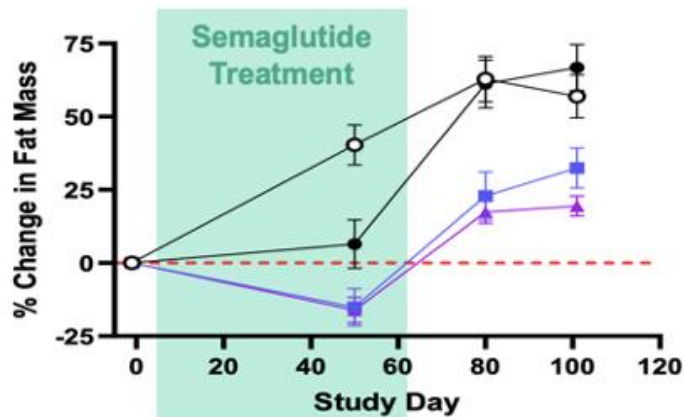


- Deep and durable knockdown with single dose
- Highly potent with exquisite tissue specificity
- Infrequent, sub-cutaneous dosing
- Fat loss, lean mass preservation & weight regain attenuation

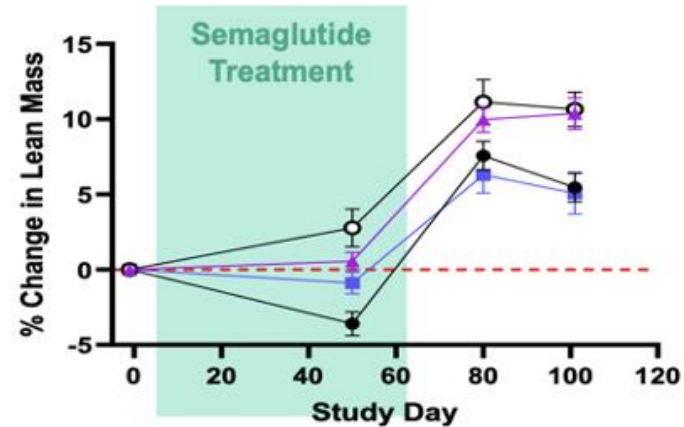
# Combining Long-acting siRNAs with Low Dose Semaglutide Gives Greater Fat Loss, Lean Mass Preservation and Attenuated Weight Regain

Rodent models

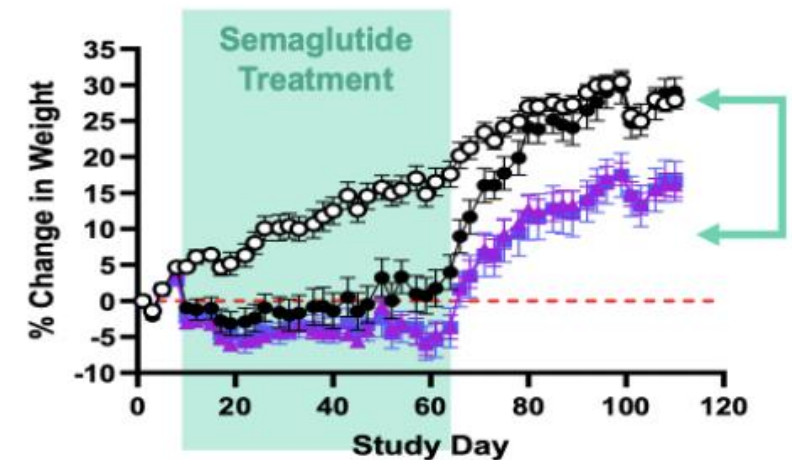
Greater Fat Loss



Lean Mass Preservation



Attenuated Weight Regain

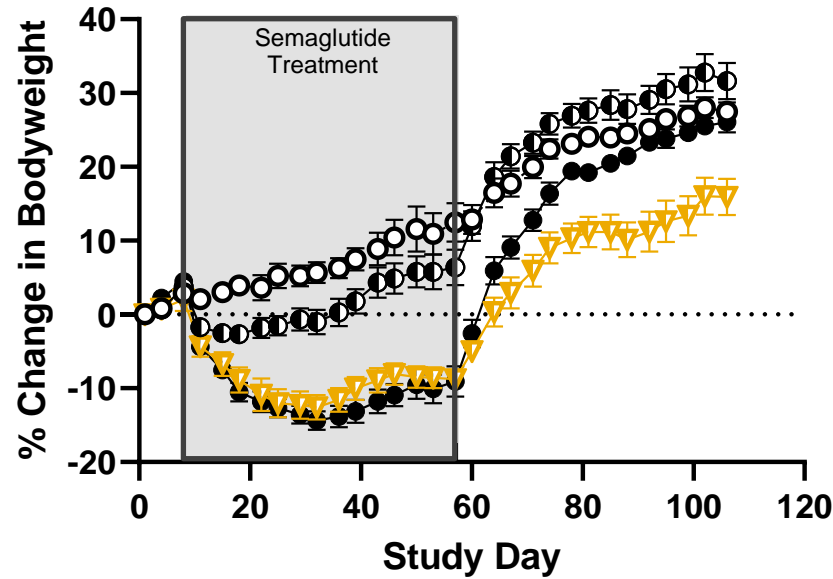


○ PBS + Vehicle    ● PBS + Semaglutide    ■ si-INHBE + Semaglutide    ▲ si-ACVR1C + Semaglutide

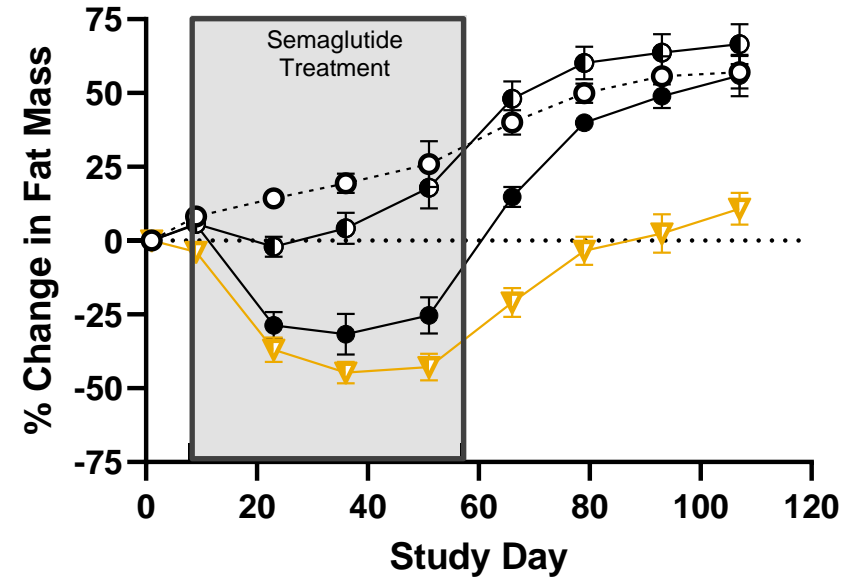
# Novel siRNA Combinations Enhances Fat Loss with Sustained Weight Loss

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

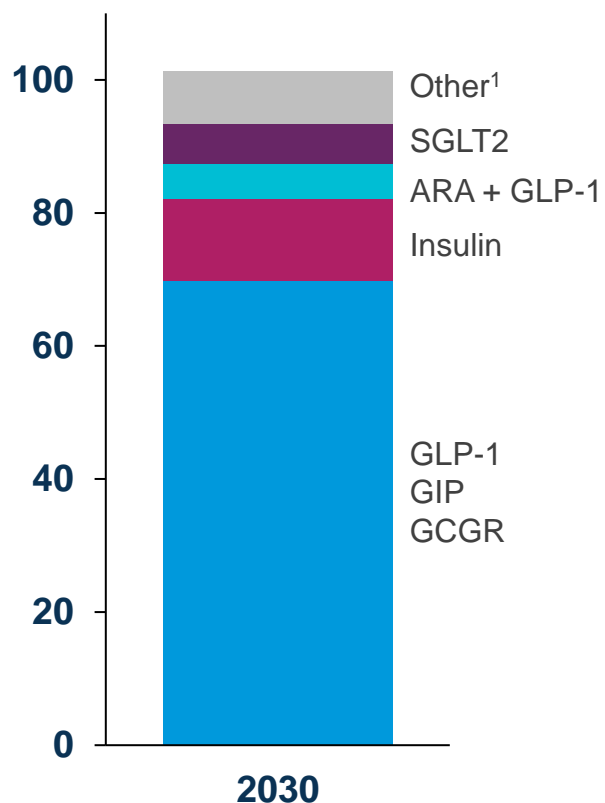
Plan to progress ALN-2232 (ACVR1c), the first Alnylam adipose tissue program, into the clinic in 2025

# Type 2 Diabetes Represents Significant Opportunity

**Anylam Portfolio Provides Optionality for Both Monotherapy and Combination Approaches**

## Large Market Opportunity

Estimated Annual WW Sales (\$B)



## 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

## Anylam 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 Health; 2023; Person-Stuttard. Lancet. 2022; Puneet. Diabetes and Endocrinology. 2023; Cowen Reports; Evaluate Pharma; ClearView Analysis.

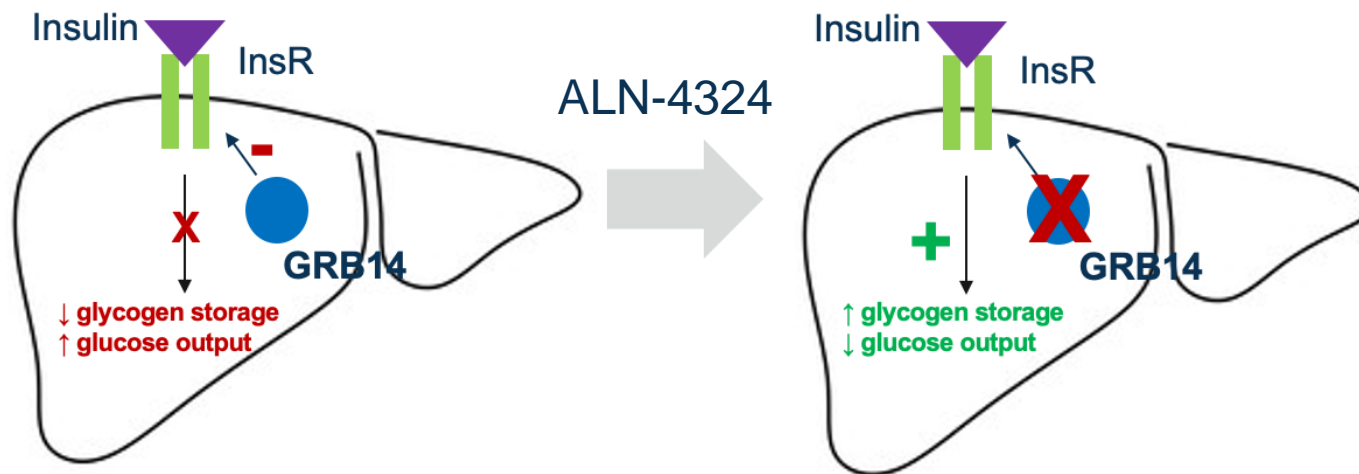
# ALN-4324: Aiming to Deliver the First Long-Acting and Safe Novel Insulin Sensitizer in 30 years

## 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

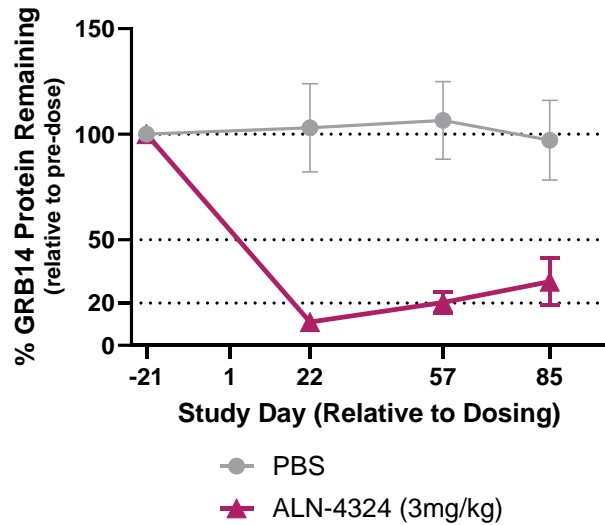


### Emerging Potential Profile

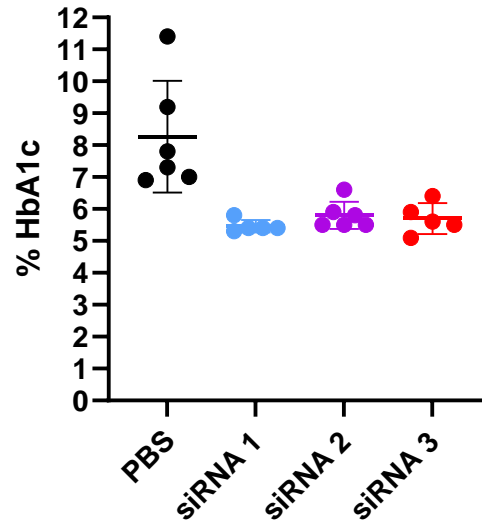
- Liver targeted insulin sensitizer with strong human genetics
- Preclinical validation showing impressive HbA1C lowering without liver fat accumulation
- Weight Neutral
- Long acting
  - Q3M to Q6M dosing
- Potential for insulin sensitization in muscle

# ALN-4324 Demonstrates Desired Potency, Specificity, and Durability

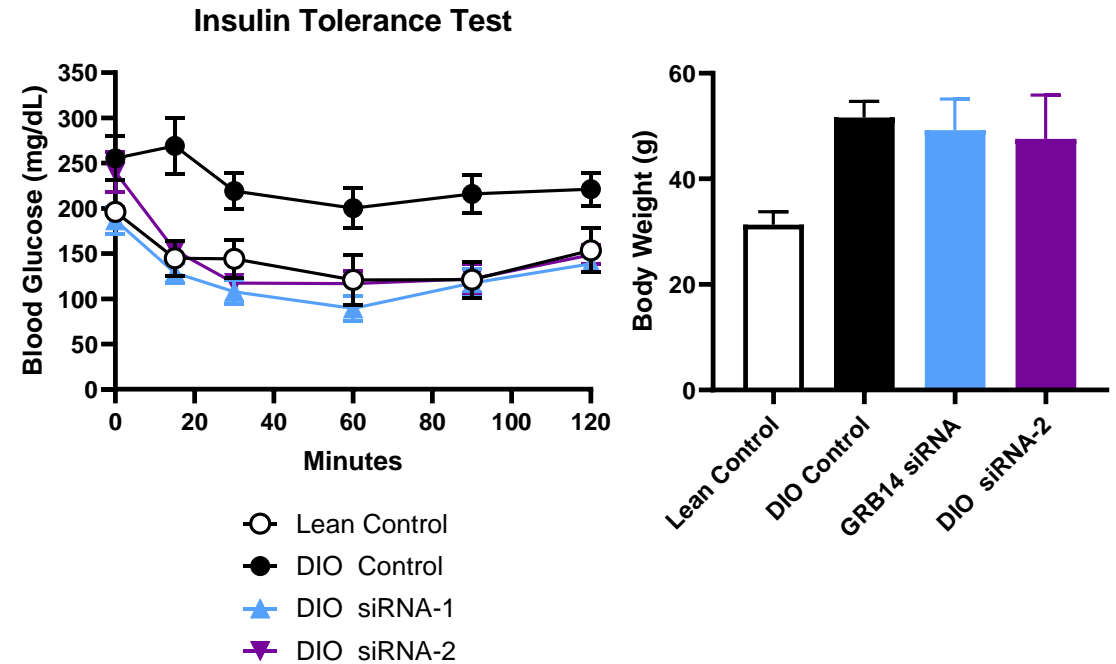
**Achieves ~90% GRB14 Knockdown at Day 22 (NHP)**



**Normalizes HbA1c (Ob/Ob mice)**



**Improves Insulin Sensitivity Without Weight Gain (DIO mice)**



# ALN-4324 Phase 1 Study Overview

## Healthy Overweight or Obese Subjects

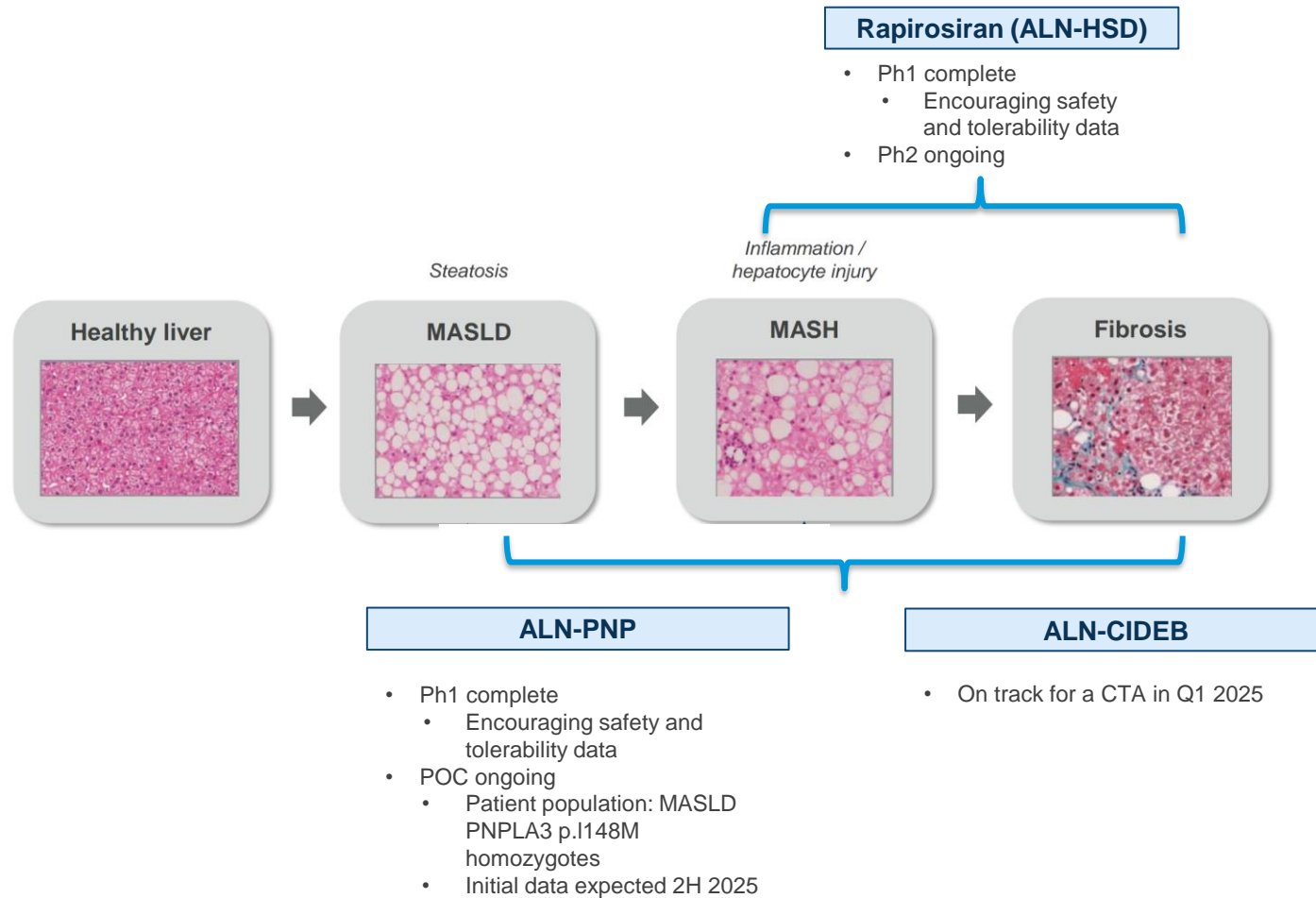
- **Primary Objective:** Safety & Tolerability
- **Exploratory Objective:** PD effect assessed by insulin sensitivity and biomarkers
- **Population:**
  - HbA1c <6.5%
  - 18 to 65 yrs., BMI 27 to 40
  - 5 dose cohorts (N=40; 8/Cohort)
- **First Patient First Dose expected Q1 2025**

## 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

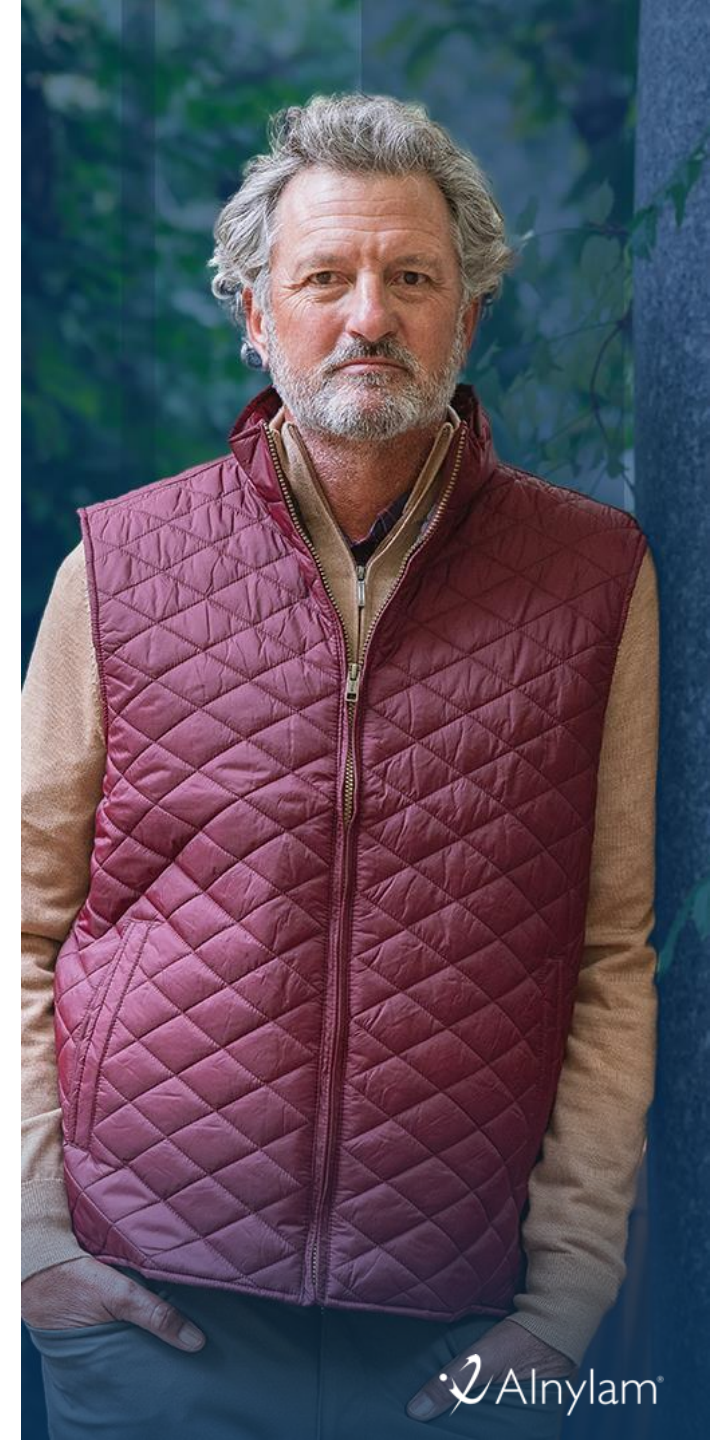
# Succeeding in MASH with RNAi Therapeutics

## Genetically Validated Targets Offer Multiple Therapeutic Strategies



# 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



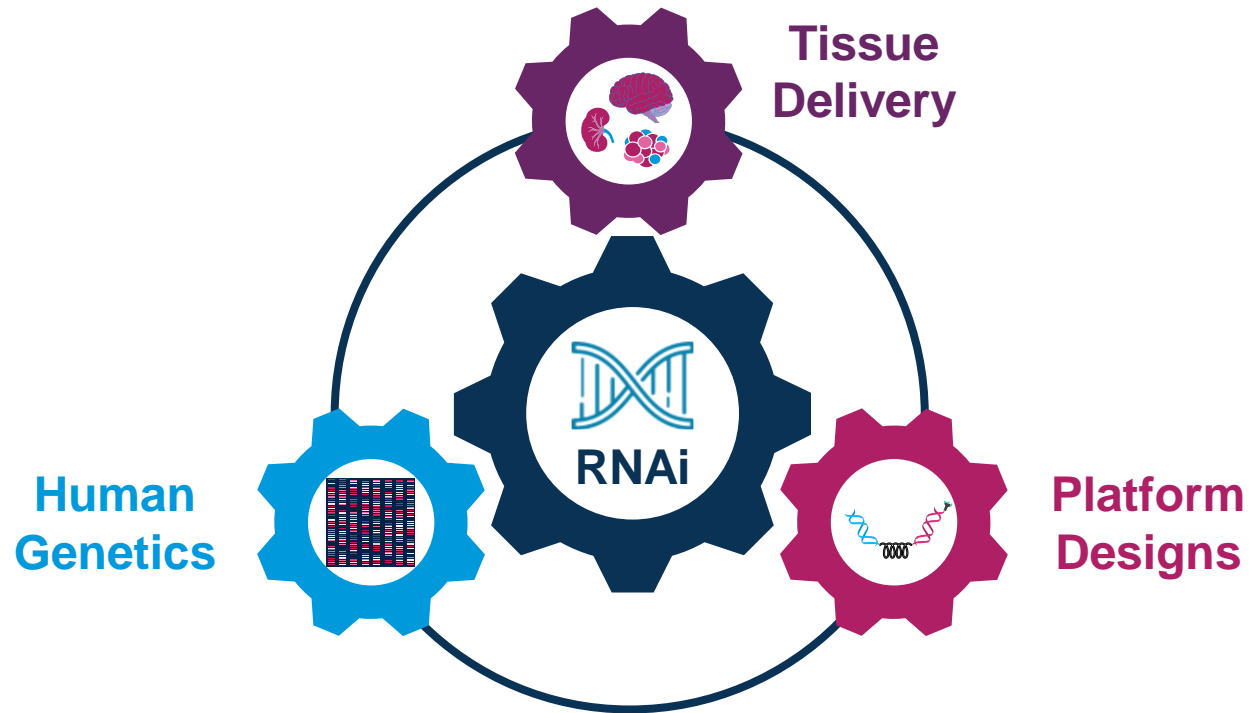


# Next Wave of RNAi Therapeutics to Fuel a Robust Clinical Pipeline

**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

# Genetic Insights from > 1M People Fuel Our Differentiated Pipeline

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

## Data Access

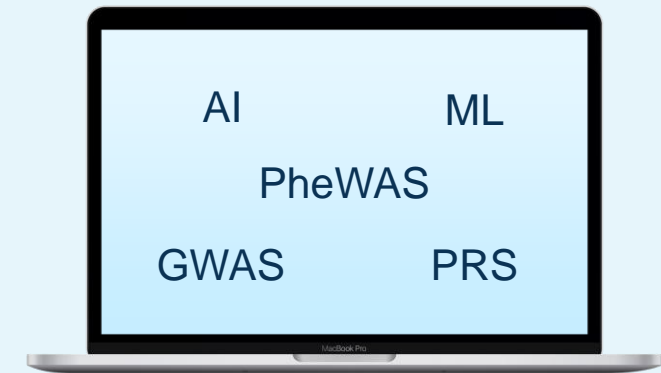


biobank<sup>uk</sup>



1M Individuals scaling to > 6M by 2030

## Analytical Expertise



High Probability of Success Targets

# || 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

| || **ALN-6400**  
**An Investigational Drug For**  
**Bleeding Disorders**

# Majority of Bleeding Disorders Lack Treatment

## ALN-6400 is a Potential Universal Hemostatic Agent

Bleeding disorder patients experience:

Anemia

ER Visits

Anxiety & Depression

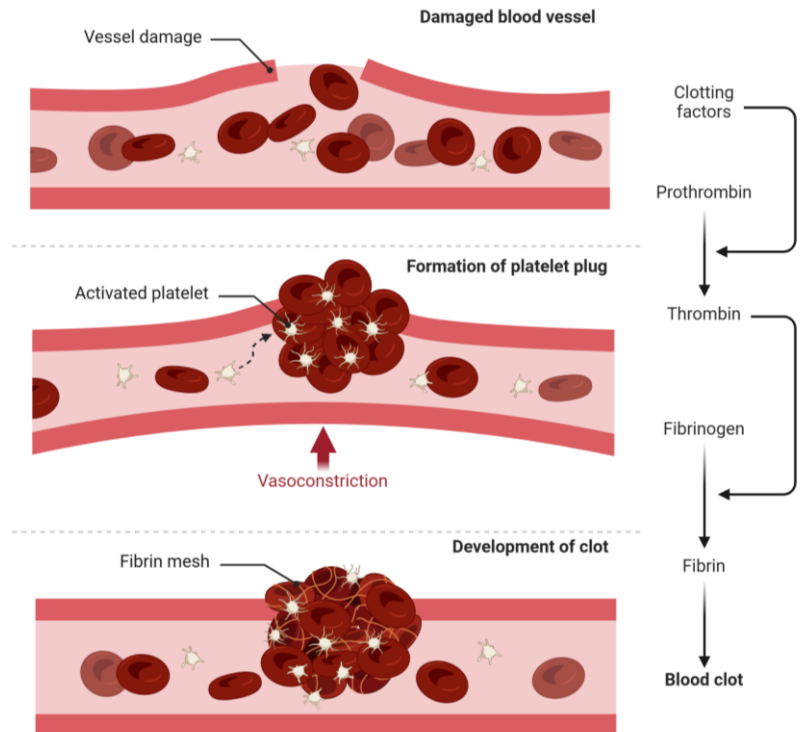
Major Bleeding Events

Hospitalization

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

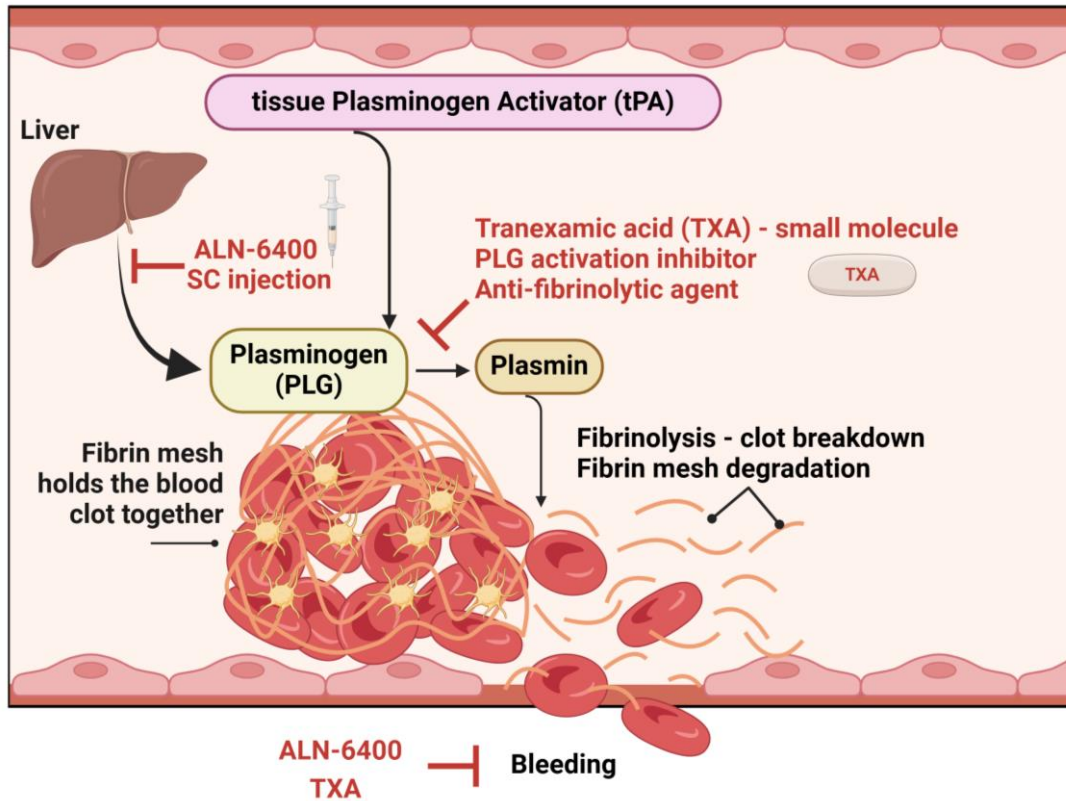
*Existing treatments are burdensome and can increase risk of thrombosis*

### Hemostasis



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

# 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

# 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**

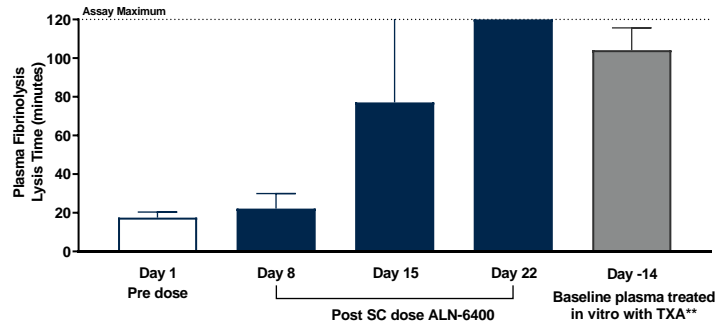
| Protein measured | Risk of thrombosis (OR per SD decrease in plasma level) | p value     |
|------------------|---|-------------|
| Protein S        | 1.23  | 2e-24       |
| Protein C        | 1.11  | 1e-06       |
| Antithrombin     | 1.08  | 6e-05       |
| <b>PLG</b>       | <b>1.00</b>   | <b>0.91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

*In house proteomics analyses*

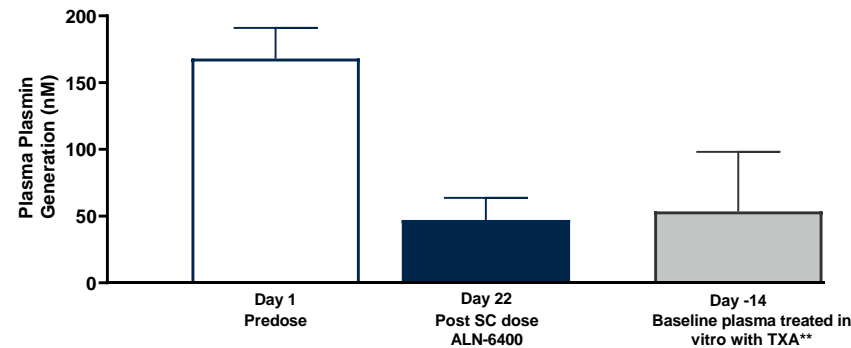
# Treatment of NHPs With ALN-6400 Reduces Plasmin Generation, Fibrinolysis and Mucosal Bleeding

- 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)

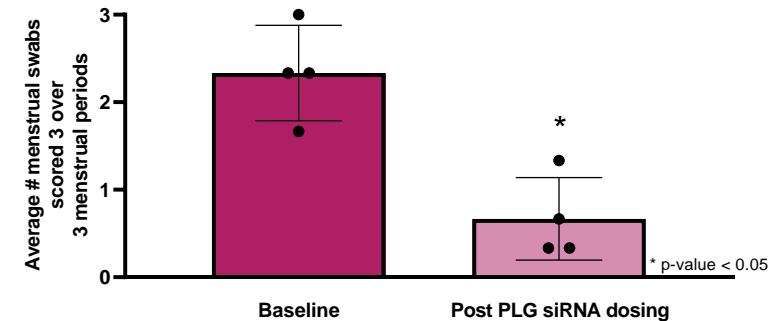


## Reduced Plasmin Generation (NHP plasma)



Plasmin is an activation product of PLG

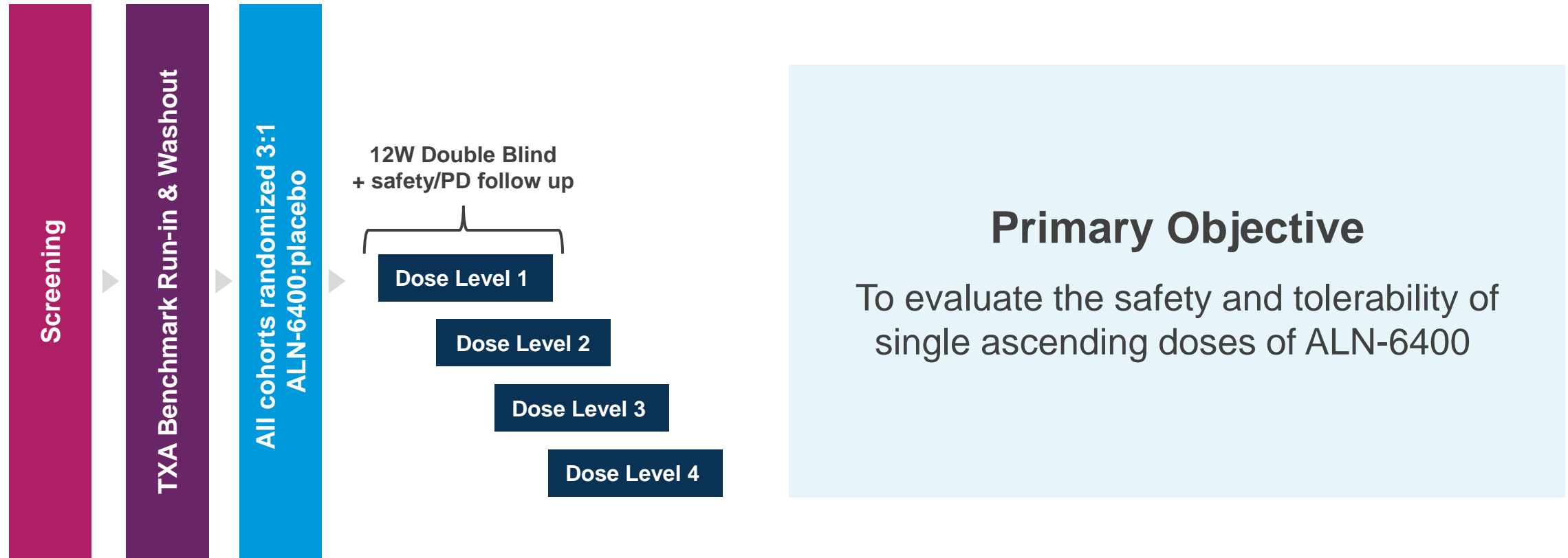
## Reduced Menstrual Bleeding



Daily monitoring of menstrual bleeding scored 0-3

# ALN-6400 Phase 1 Study in Healthy Volunteers

With Proof of Mechanism for Fibrinolysis Inhibition (Currently Enrolling)

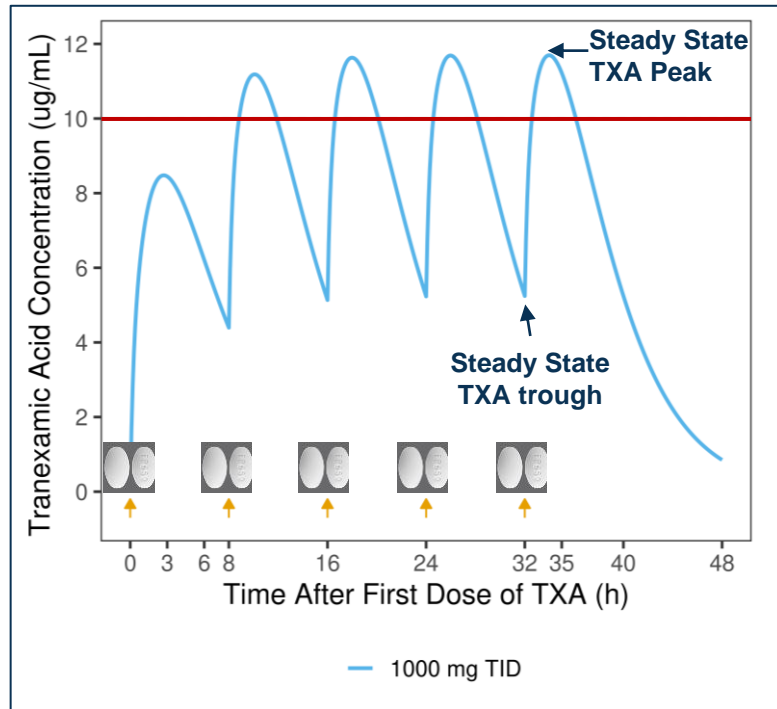


Includes SOC oral TXA dosing prior to SC ALN-6400/Placebo to evaluate impact on ROTEM (antifibrinolytic effect) and benchmark the antifibrinolytic response of TXA to ALN-6400

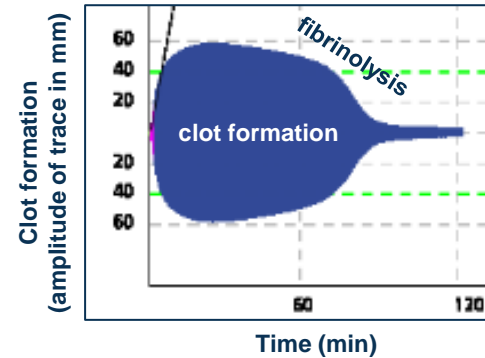
# Evaluation of Fibrinolysis Using Ex-Vivo ROTEM Assay

## Clinical Whole Blood Assay of Clot Formation and Fibrinolysis

Predicted PK Profile of TXA



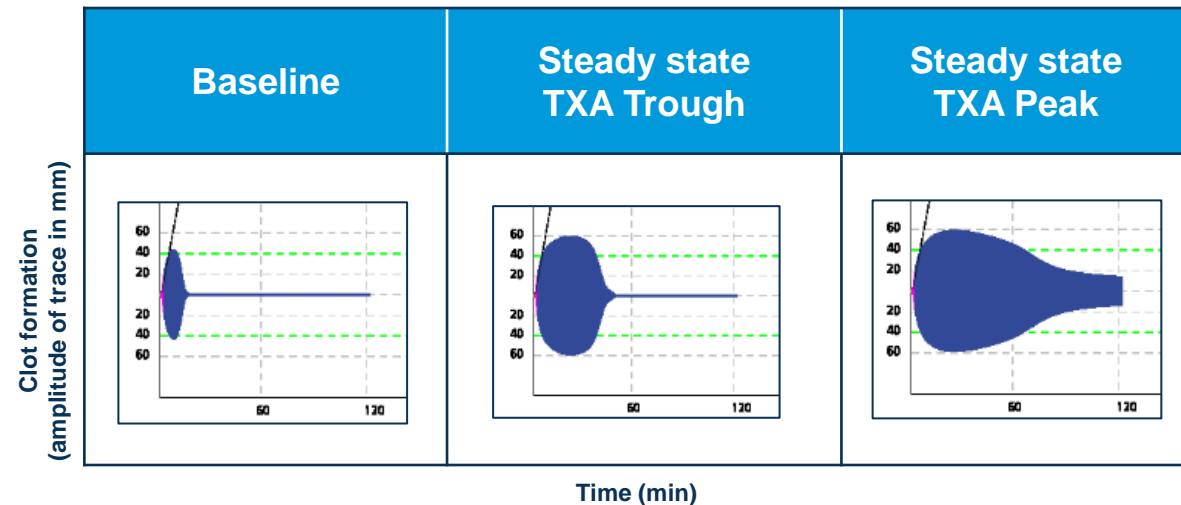
High pill burden and variable PK



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\*

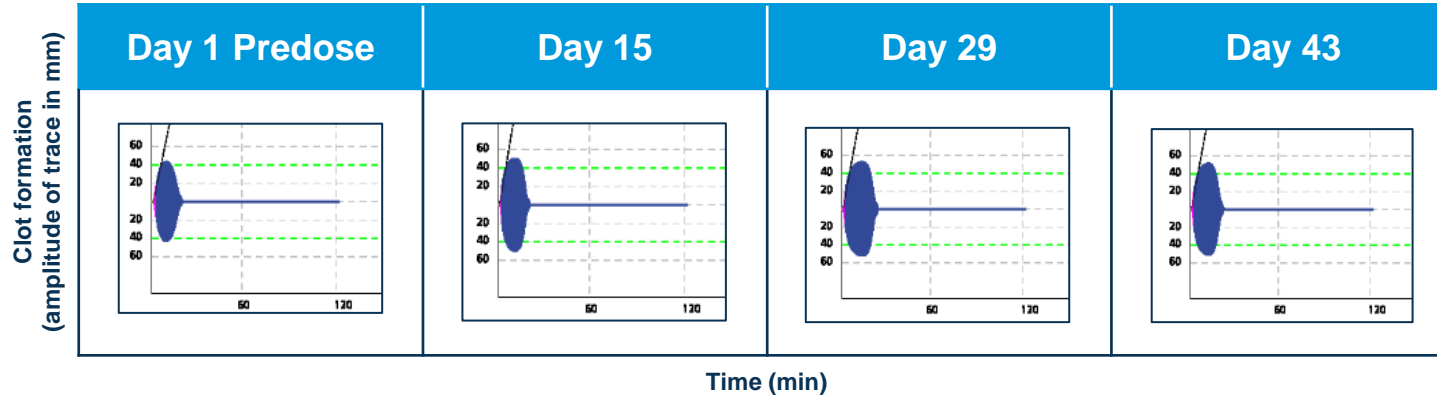


Clot formation is not affected, clot breakdown (fibrinolysis) is delayed

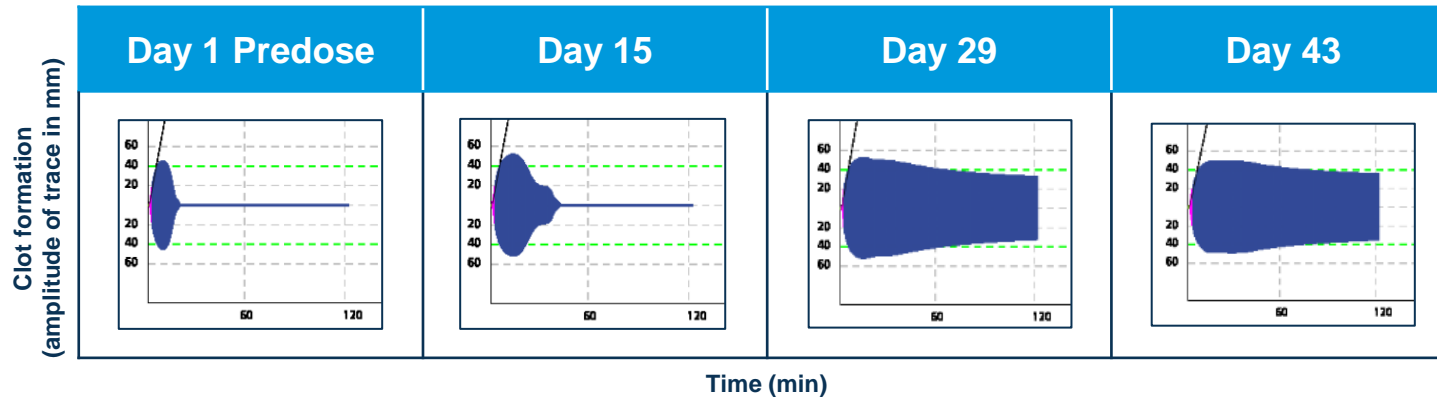
# Initial Clinical POM: Inhibition of Fibrinolysis with ALN-6400

## Four Months From CTA Filing to Clinical POM Data

Healthy Volunteer dosed with placebo



Healthy Volunteer dosed with ALN-6400



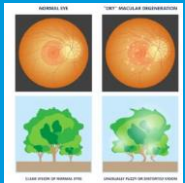
Plan to initiate a Phase 2 study in a bleeding disorder in the second half of 2025

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

# || 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

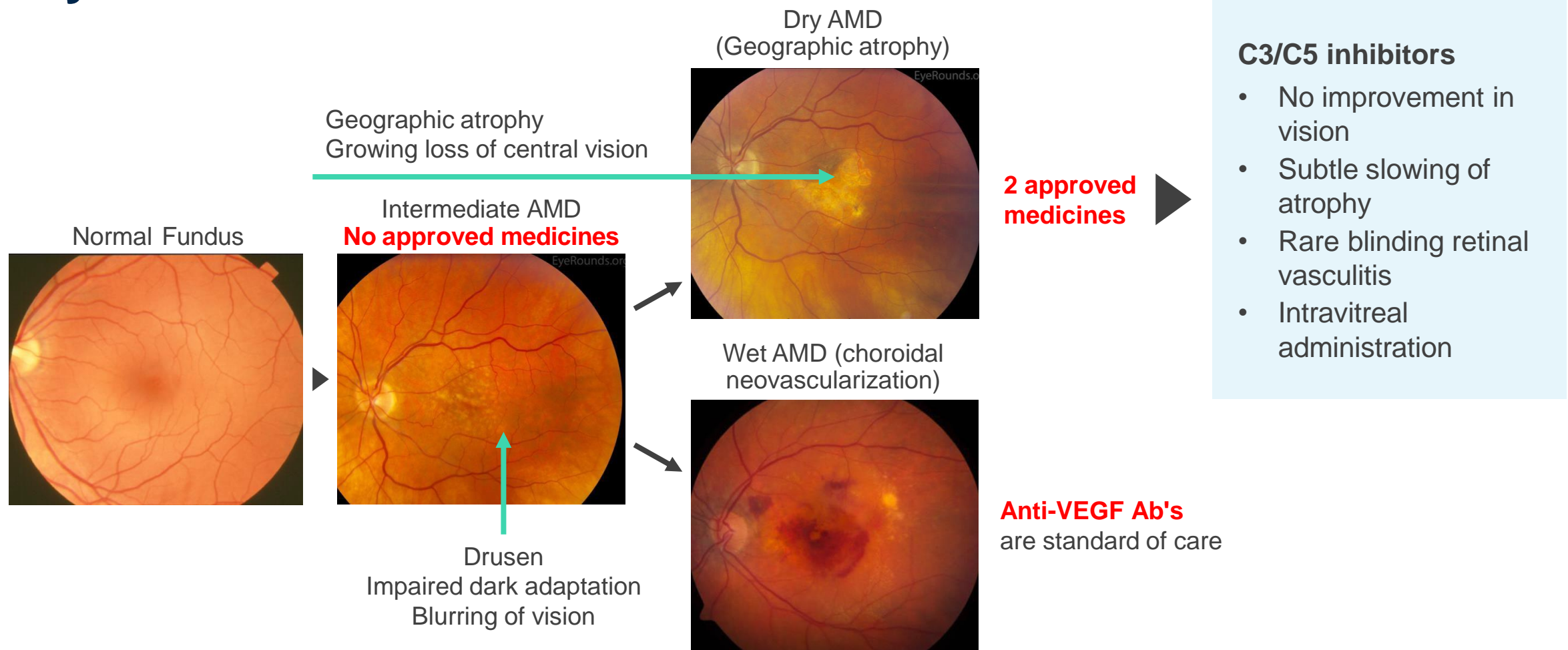


Risk factors include genetics, heart disease, obesity



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

# Significant Unmet Need Exists for Intermediate and Dry AMD Patients



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

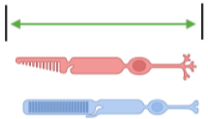
# Gene G: A Differentiated Genetically Validated Target for AMD

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

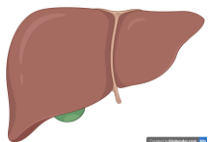
| Disease/Trait       | Effect of Gene G LOF | Pvalue |
|---------------------|----------------------|--------|
| AMD (dry or wet)    | OR = 0.50            | 7E-45  |
| Dry AMD             | OR = 0.49            | 1E-34  |
| Wet AMD             | OR = 0.49            | 2E-28  |
| Photoreceptor IS/OS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

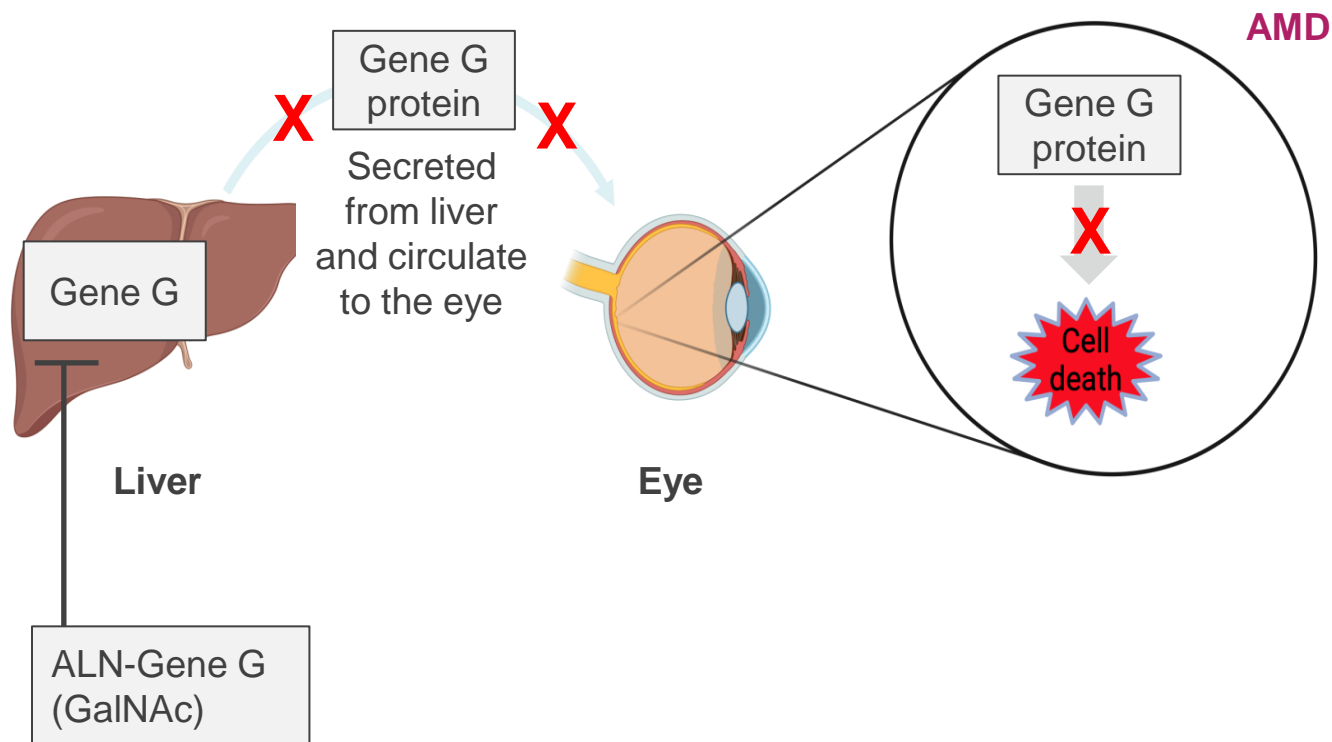


Exclusively liver expressed = targetable with GalNAc platform with infrequent subcutaneous dosing

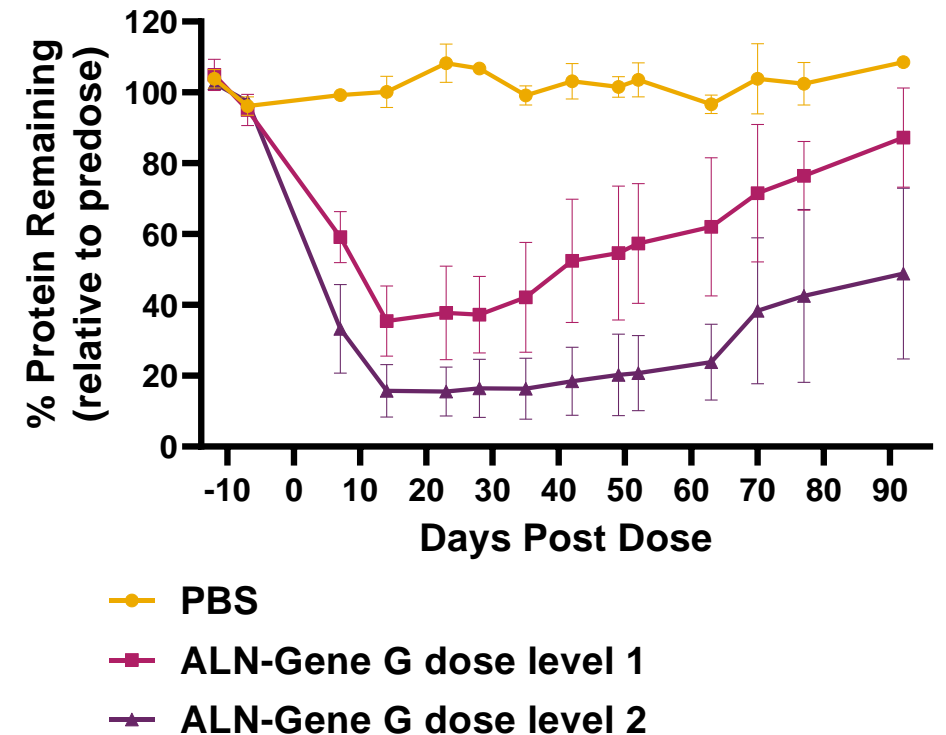
# ALN-Gene G Effectively Knocks Down Gene G in the Liver

Profile Supports Q3-Q6M Subcutaneous Dosing

## Therapeutic Hypothesis



## Circulating Gene G Protein Levels in NHP



ALN-Gene G IND on track for '25 filing

# | || **Coming Attractions**

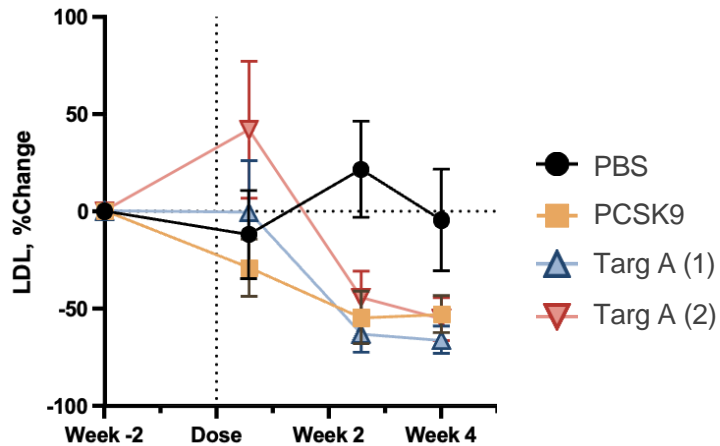
# Genetic Discoveries Fuel Preclinical Pipeline Across Tissues

## Liver

Target A – loss of function

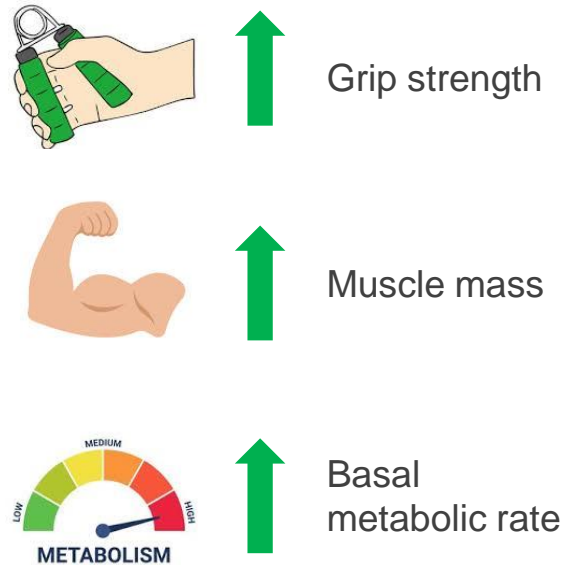


PCSK9-independent LDL lowering in NHP



## Skeletal Muscle

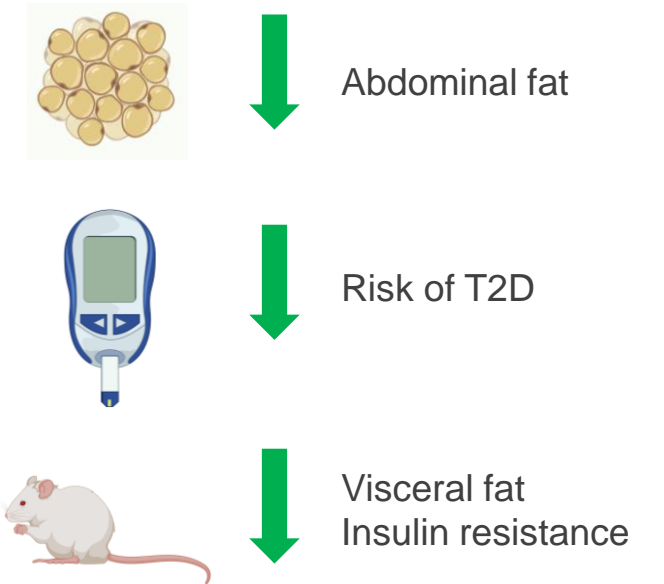
Target B – loss of function

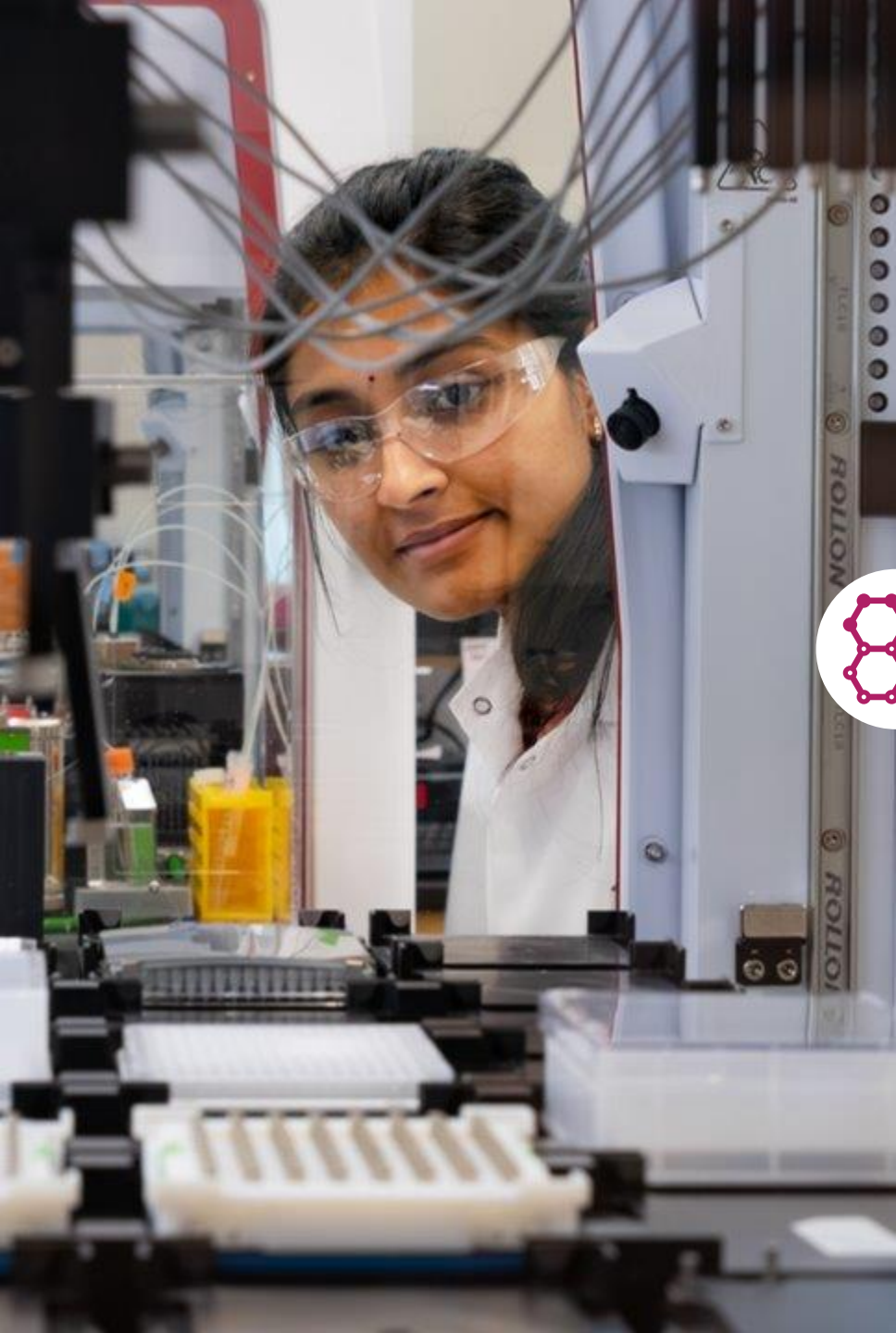


Distinct mechanism from myostatin

## Adipose

Target C – loss of function





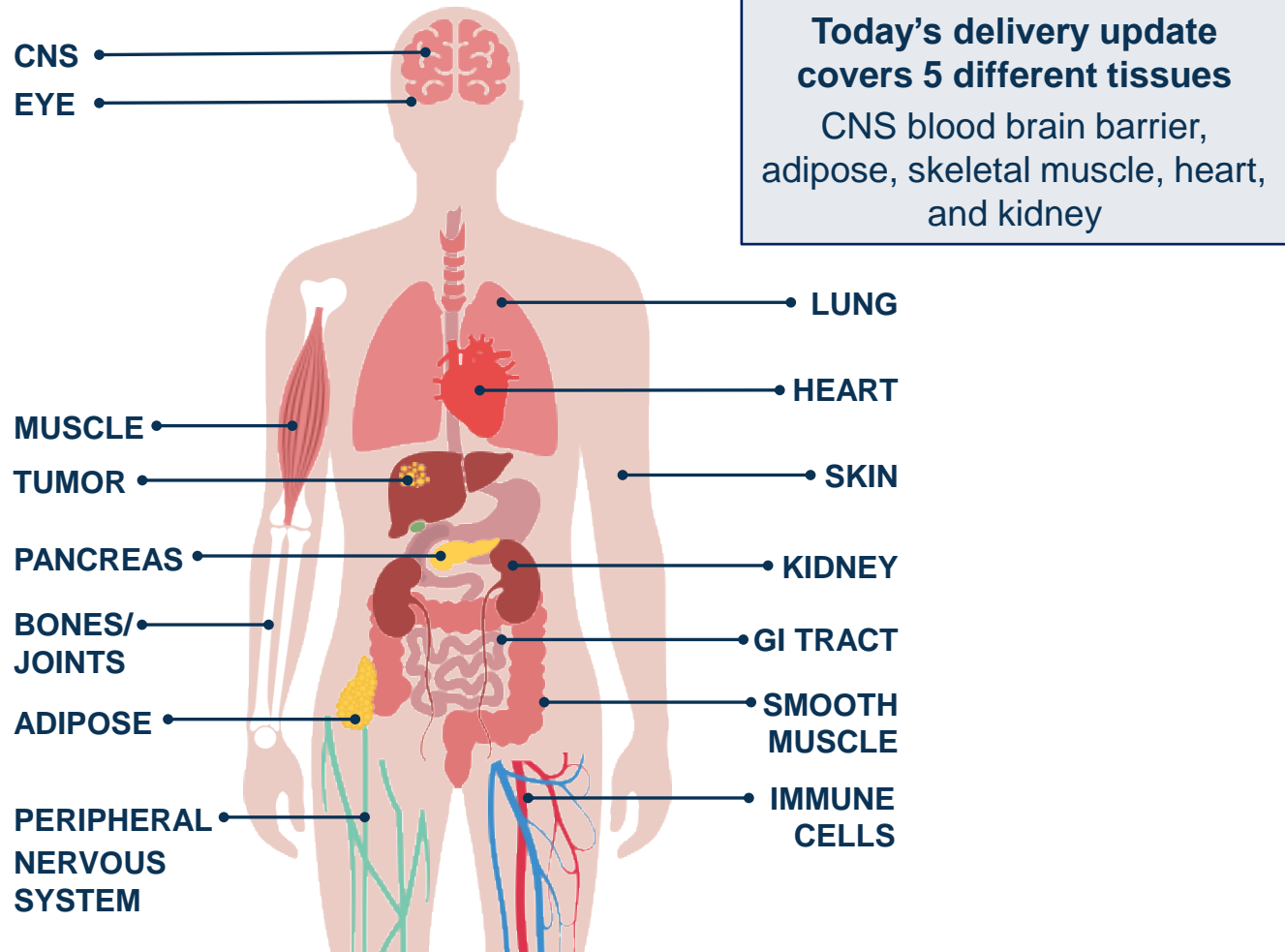
# Unlocking Opportunities: Platform Innovation

**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



### Best-in-Class Delivery Solutions

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

### Continued Innovation

siRNA design and manufacturing

- Fine-tuning siRNA
- Revolutionize manufacturing

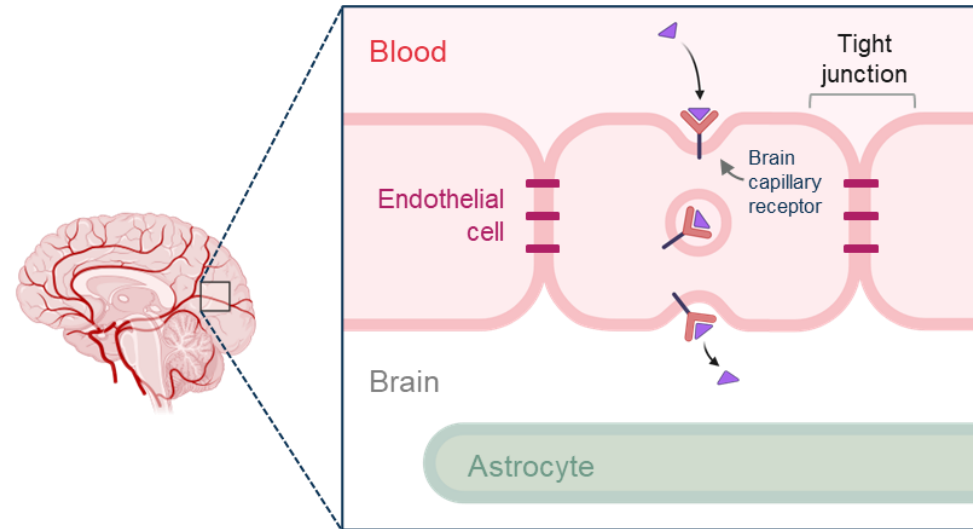
# Overcoming Blood Brain Barrier (BBB): Expand CNS Opportunities via Systemic Dosing



## Overcoming BBB Allows:

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

## BBB restricts direct access to brain cells



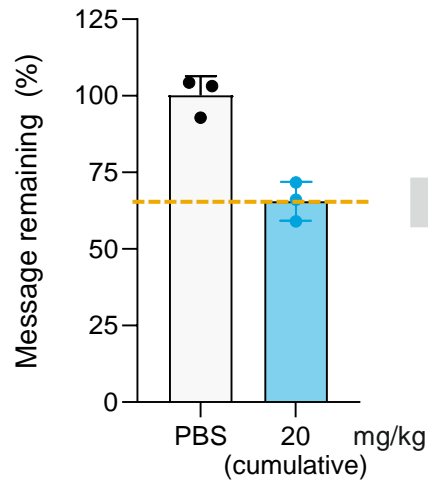
# Overcoming BBB: Robust Activity After Systemic Dosing



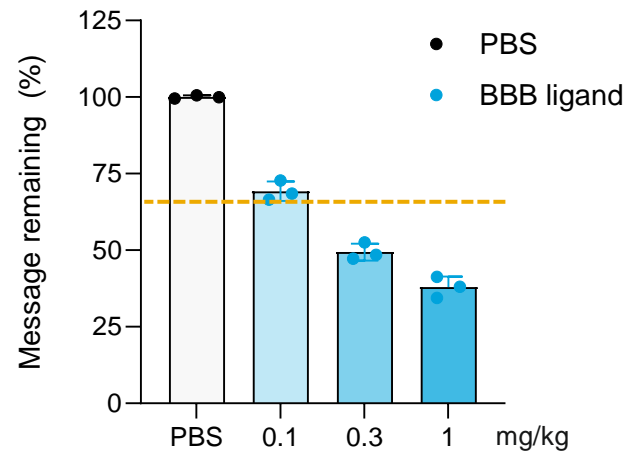
## Multi-log improvement in rodent activity through systematic optimization

2023 R&D Day presentation

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

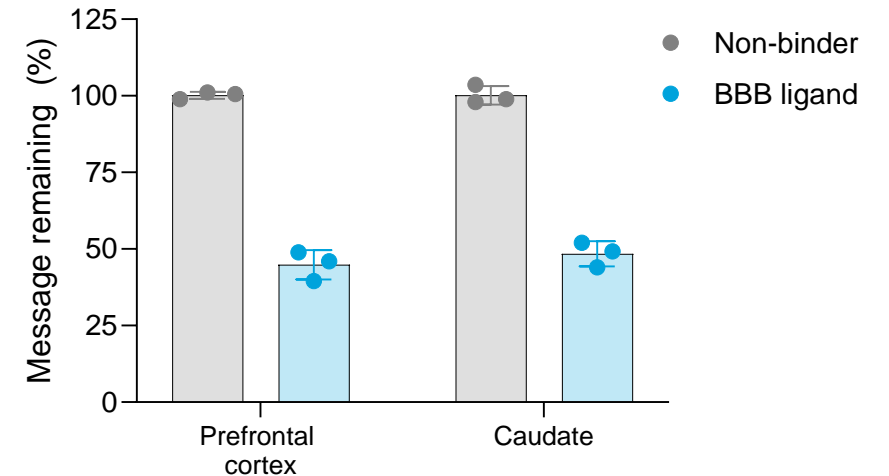


**Mouse Right Hemisphere**  
Single dose · IV · D14



## Homogeneous activity across brain structures in non-human primates

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

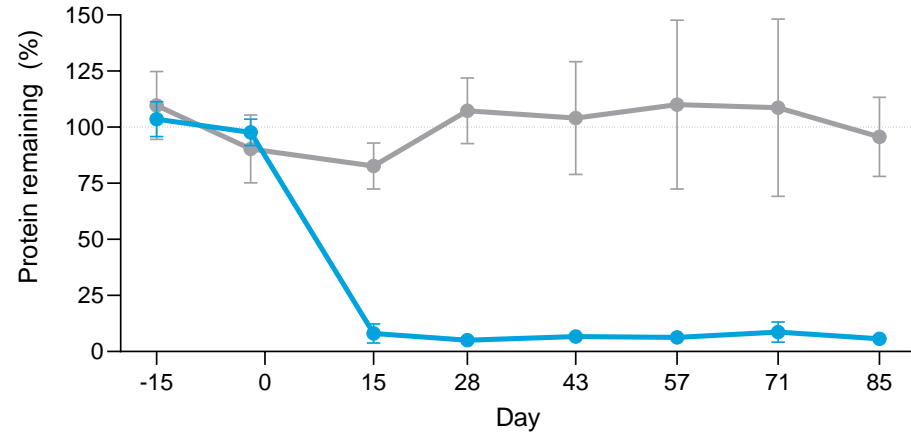


# Adipose: Small Molecule Conjugate Elicits Robust Knockdown in NHP After SC Injection

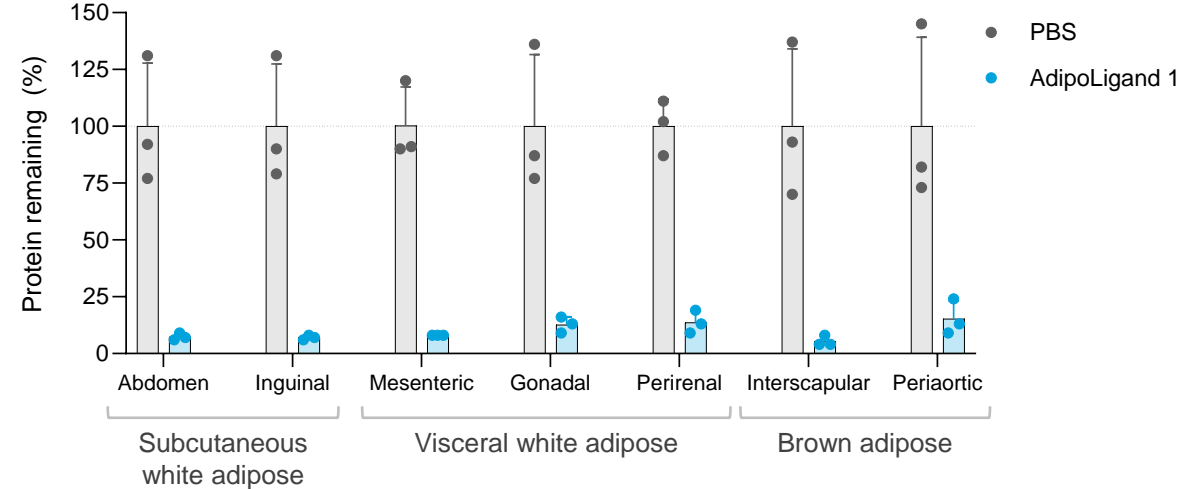


**NHP Data from ACVR1C**  
Single dose · SC · 3 mg/kg

*Deep and durable knockdown*



*Consistent activity across adipose depots at D85*



**AdipoLigand 1**



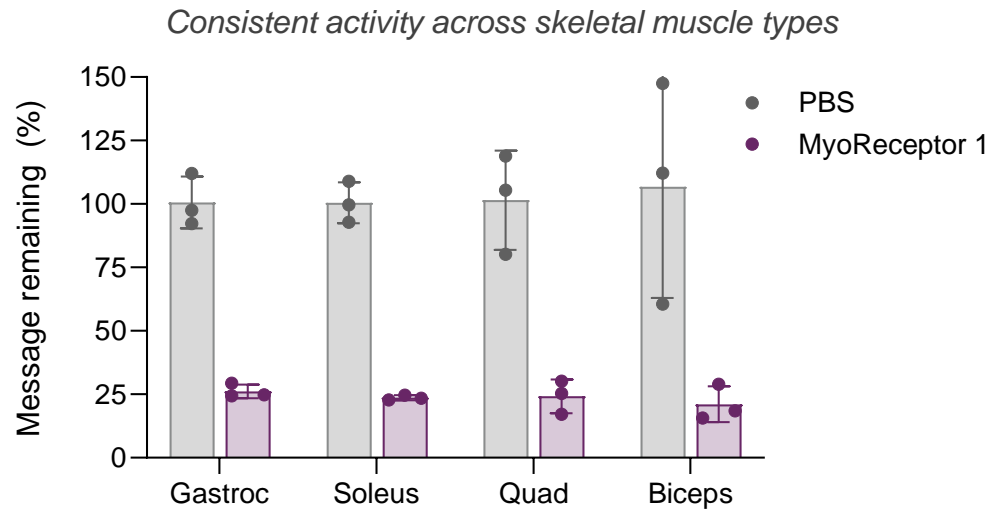
- SC dosing ✓
- ≤ 3 mg/kg dose ✓
- Efficient manufacturing ✓

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

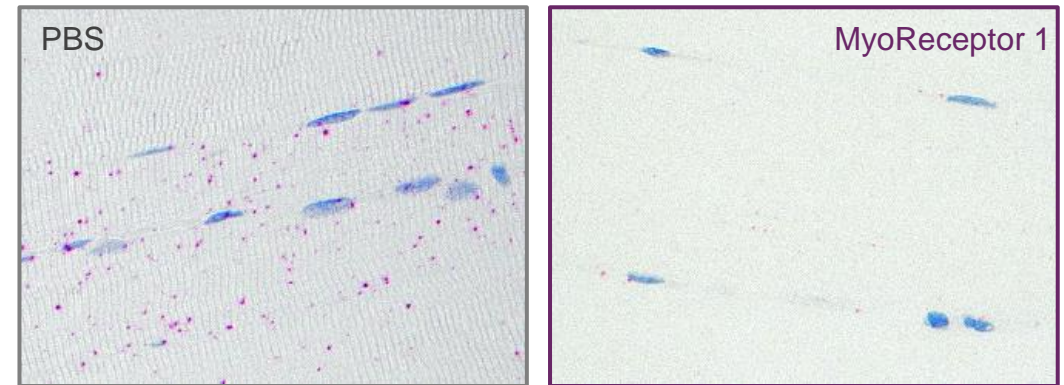


Overcomes Requirements for IV Infusions and High Doses of Antibody With TfR1 Based Approaches

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



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

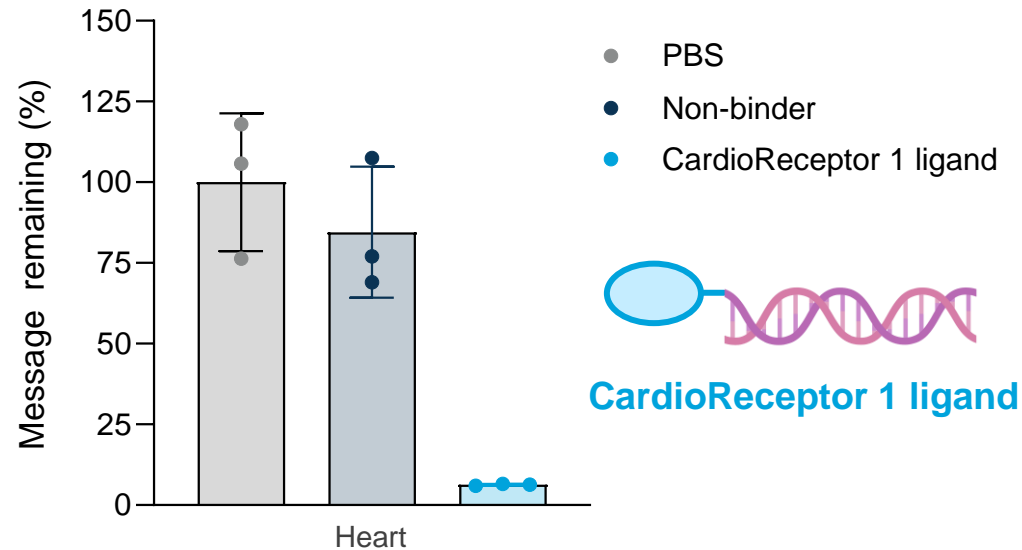
# Heart: Ligands Targeting CardioReceptor 1 Demonstrate Potent and Selective Knockdown in Mice



Mouse

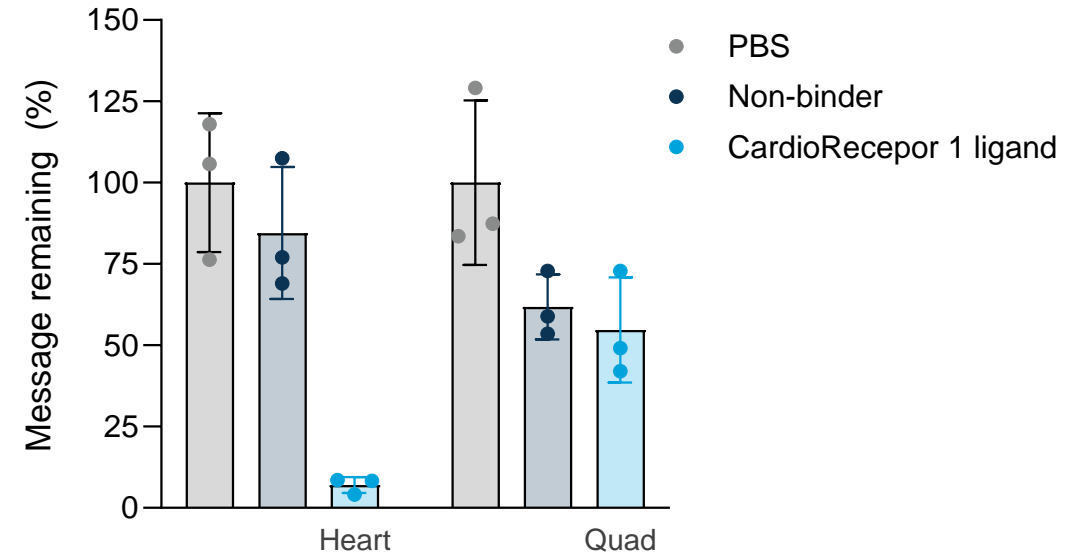
## Heart Activity

Single dose · 2 mg/kg · SC · D21



## Heart Specificity

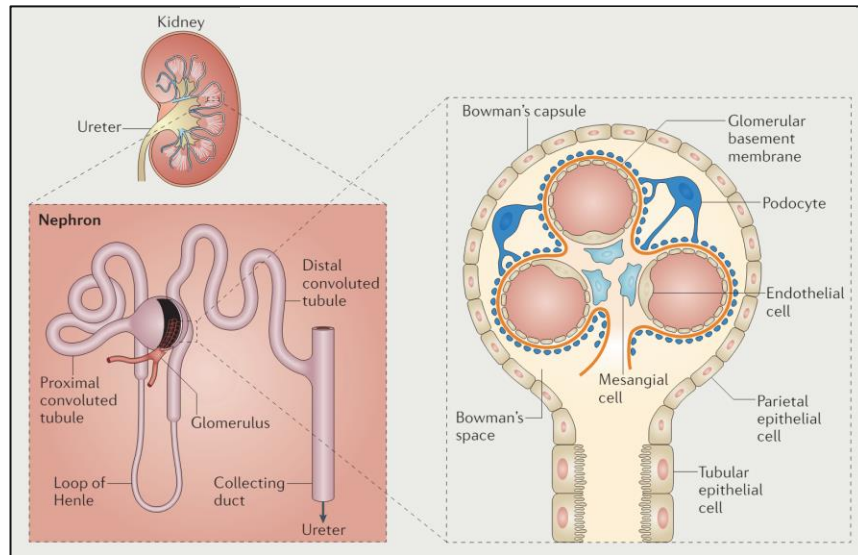
Single dose · 2 mg/kg · SC · D21



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



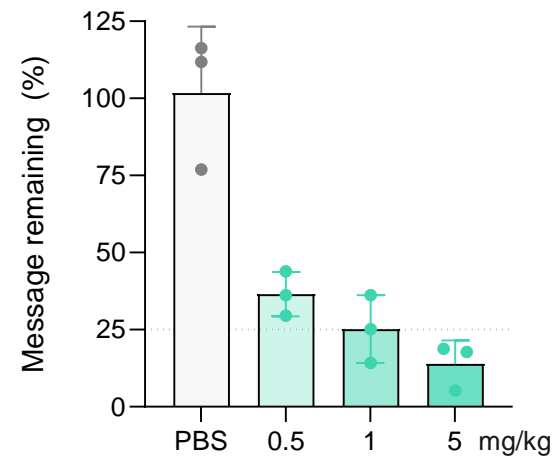
Anatomical and cellular complexity of kidney presents challenges for delivery of RNAi



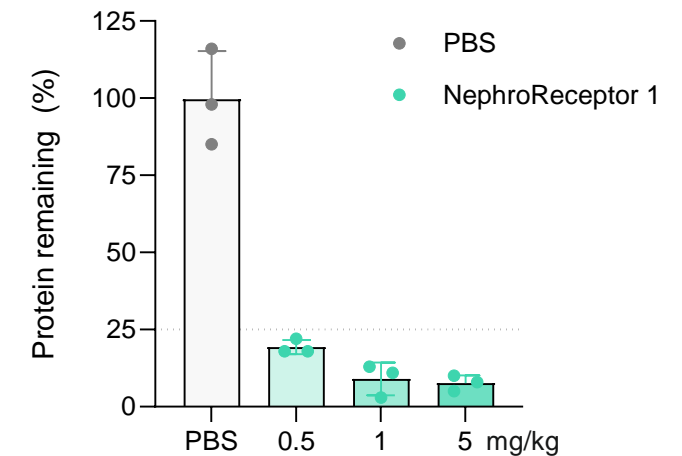
- Filtration of ~200 liters of fluid a day from renal blood flow
- Multifunction organ system:
  - Removal of metabolic waste products
  - Reabsorption of nutrients
  - Production of erythropoietin and renin
- ~30 unique cell types

## Mouse

**mRNA**  
Single dose · SC · D7



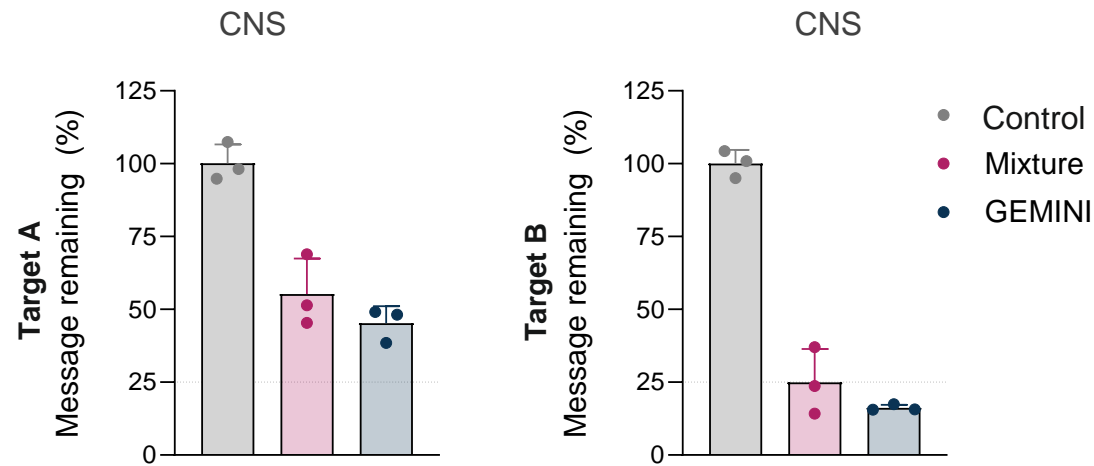
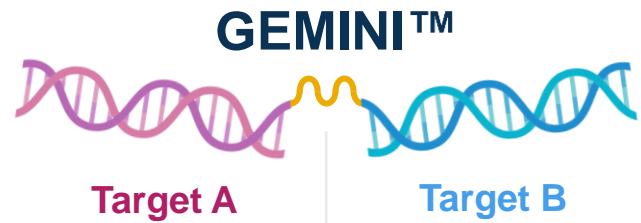
**Protein**  
Single dose · SC · D7



Functional delivery of siRNA conjugate

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

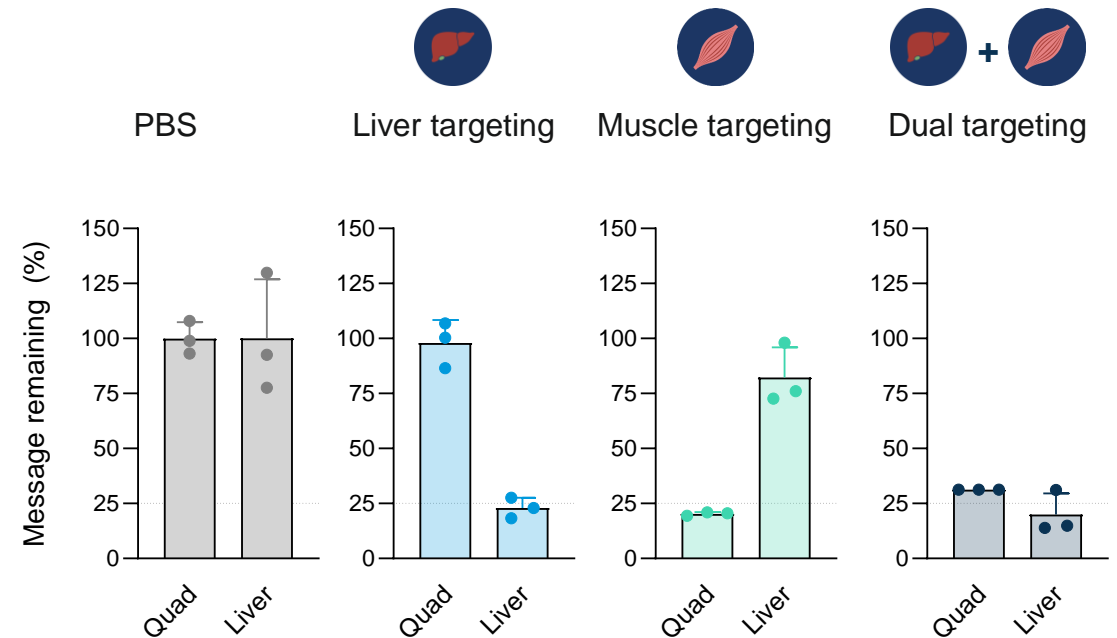
## Simultaneous Knockdown of Multiple Targets



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

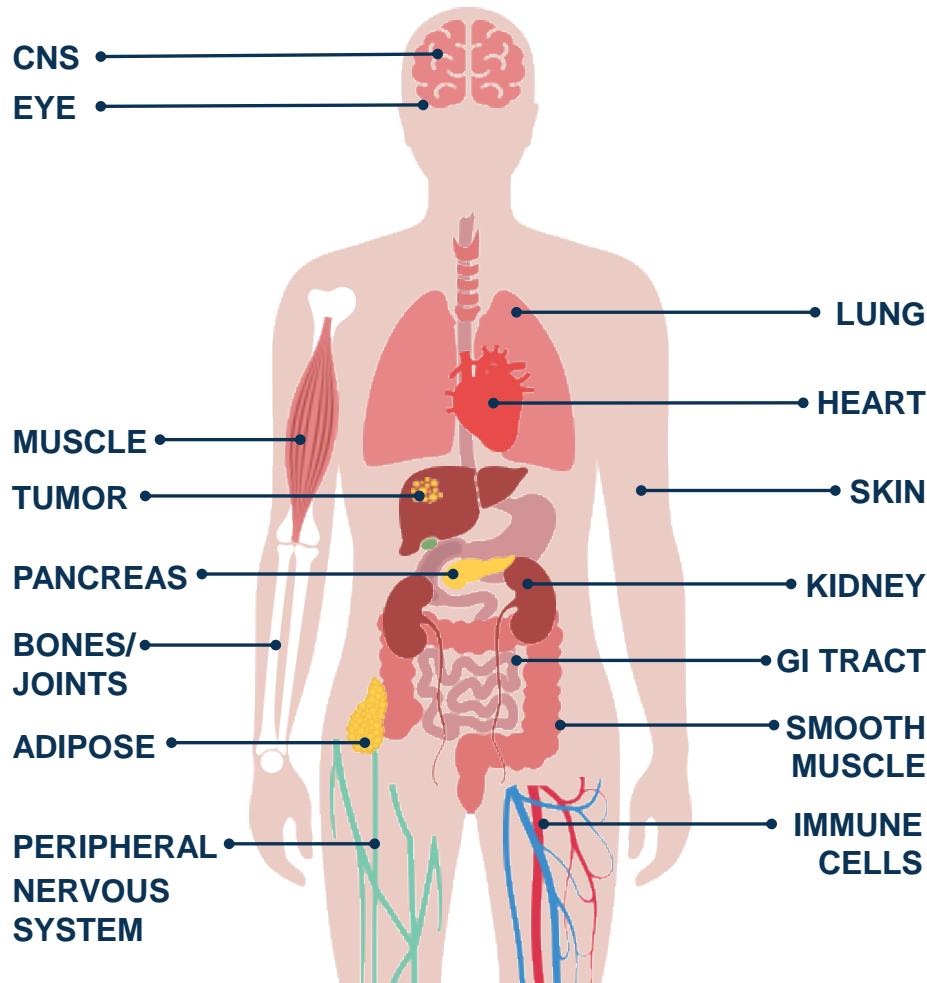


1 mg/kg; IV dosing in mice · D7

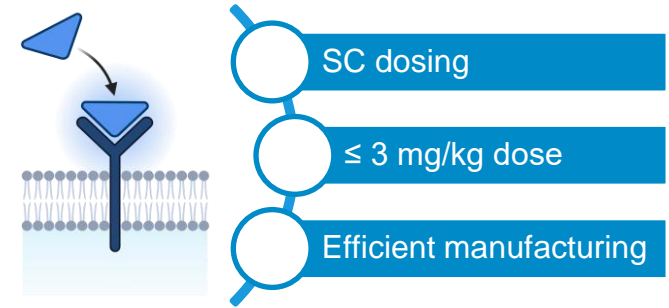
# Continue to Define the Leading Edge of RNAi Technology

## Expanding Delivery, Fine Tuning of siRNAs and Manufacturing

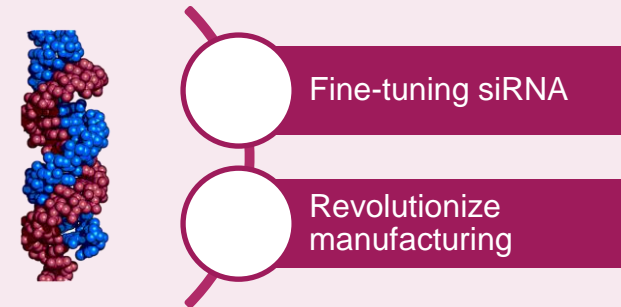
**Our Ambition:**  
**All Major Tissues with Therapeutic Target Opportunities by 2030**  
At least one CTA-enabling solution per year



### Best-in-Class Delivery Solutions

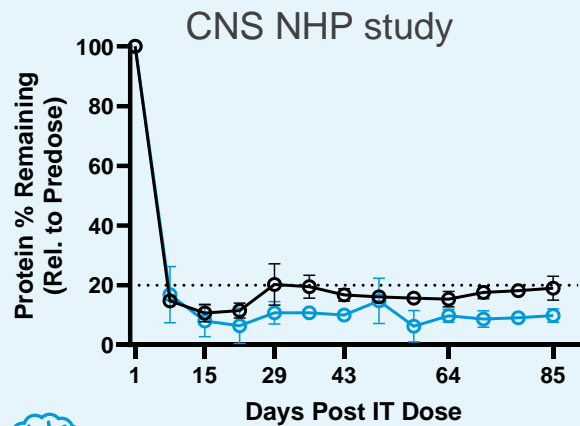
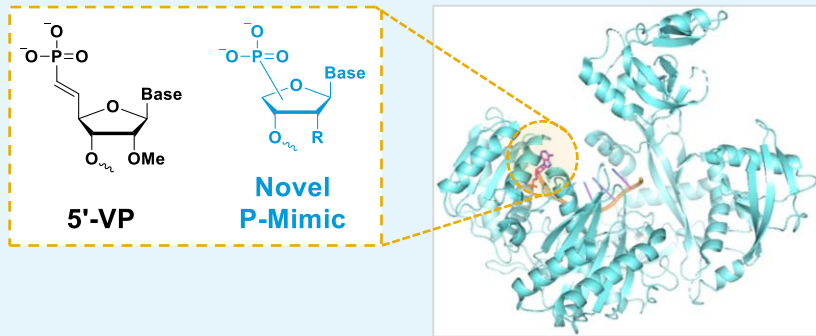


### Continued innovation siRNA design and manufacturing

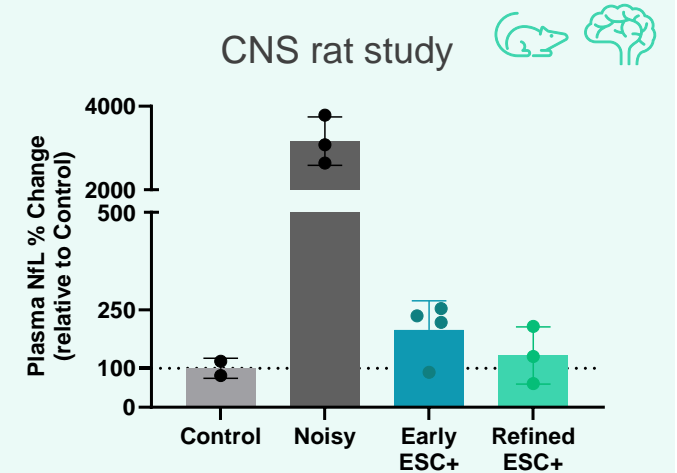
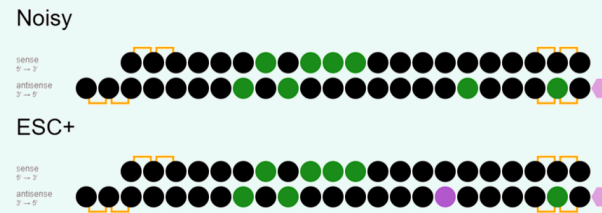


# Fine-Tuning Alnylam's Best In Class siRNA Designs

## Ensuring Maximal Activity with Novel 5'-Phosphate Mimics

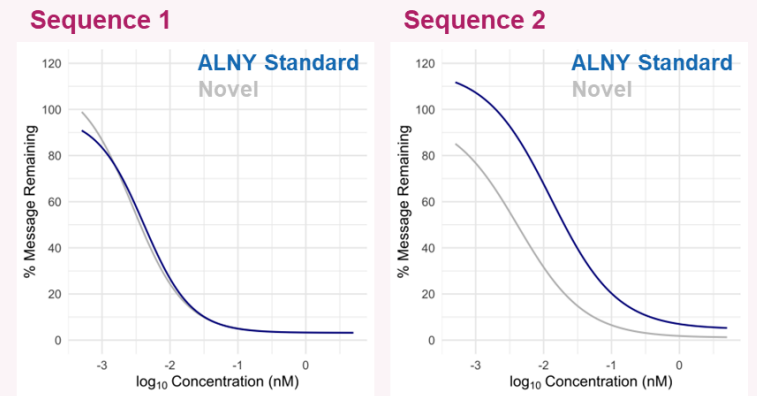


## Optimizing Safety Through Novel Modification Patterns



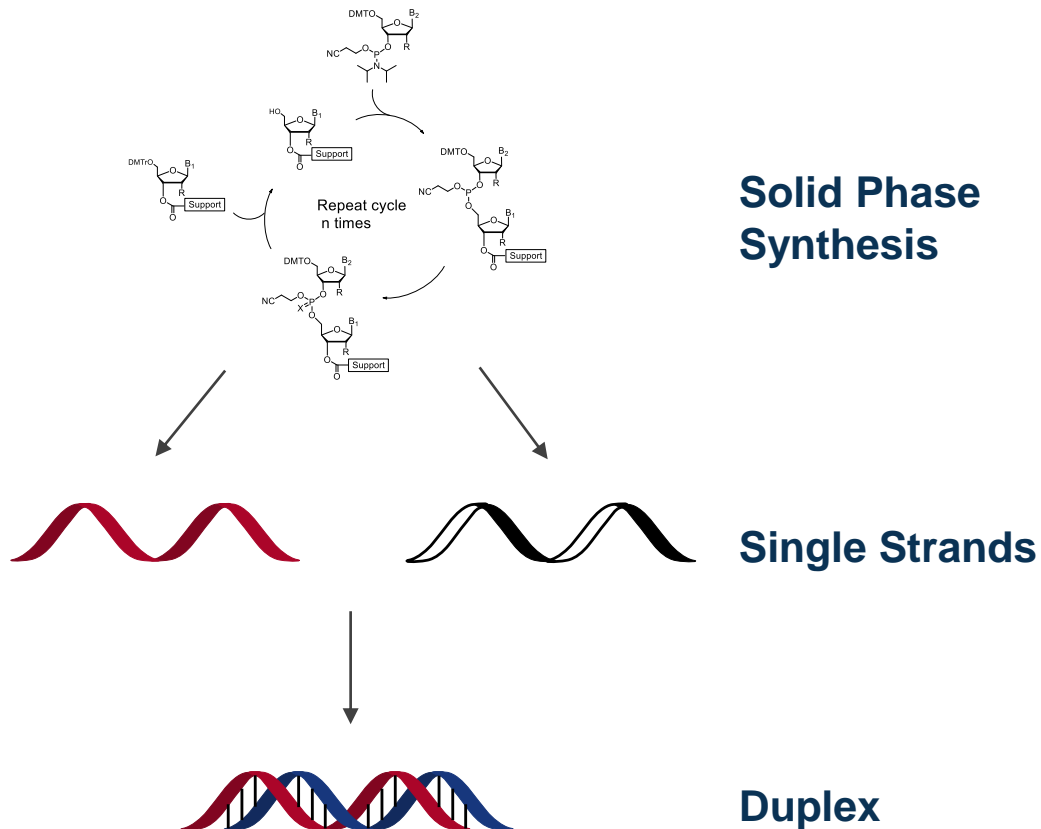
## Fine-tuning siRNA Modification Pattern to Improve Potency

### In vitro activity of siRNAs



# Current Status of siRNA Manufacturing

## Solid Phase Based (SPB) Process

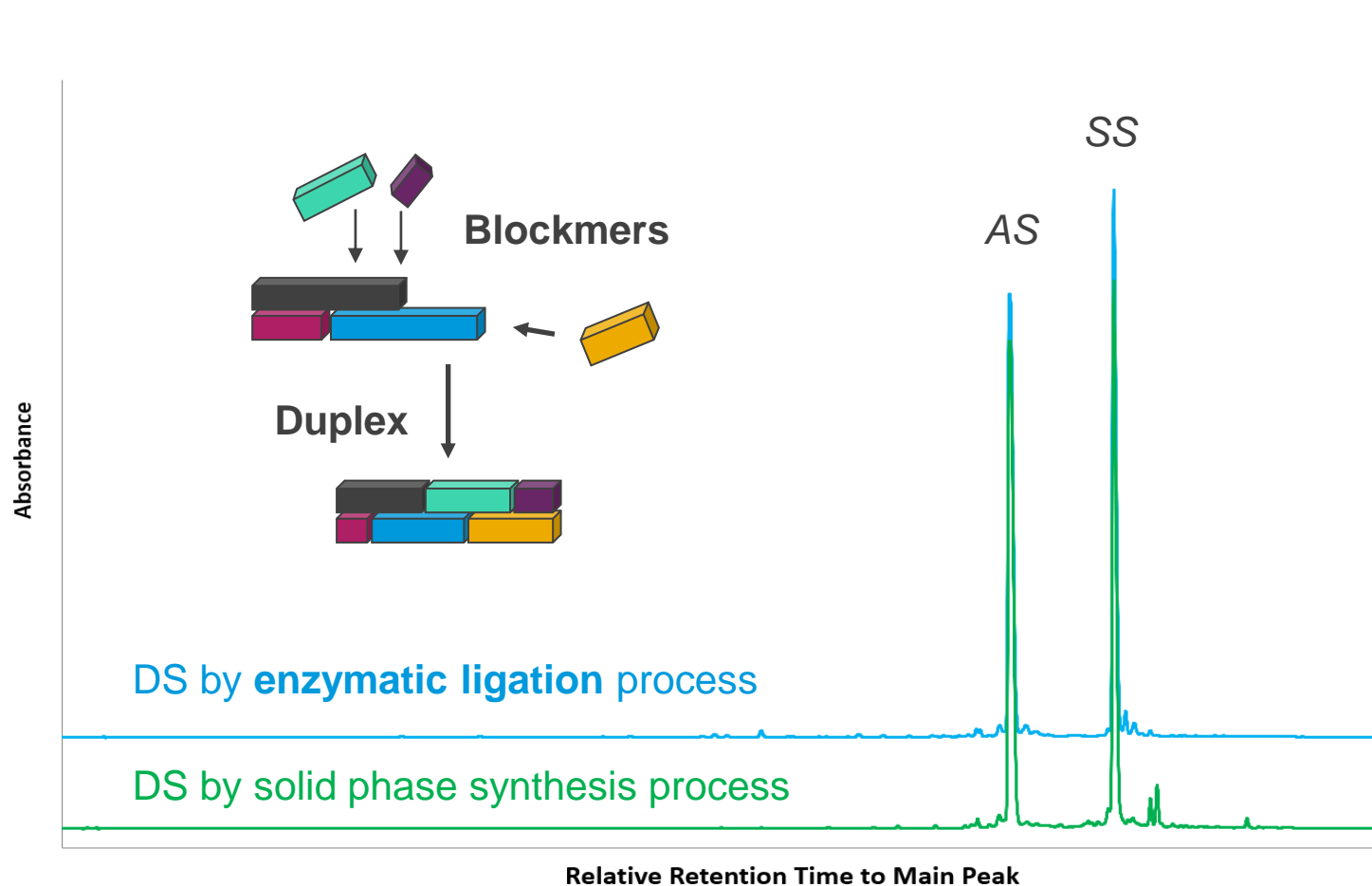


- Solid-phase synthesis is supporting our current pipeline and approved therapies
- Well-suited for low demand, shorter development time programs
- It will be challenging for solid-phase synthesis alone to meet the supply demand or COGS necessary for prevalent indications
- A new technology for manufacturing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

**Enter Enzymatic Ligation**

# Enzymatic Ligation: Meet the Demand and Lower the Cost

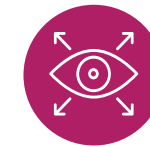
## Anylam Continues to Lead a Revolution in Biology by Revolutionizing Oligonucleotide Manufacturing



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

# || 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



AInylam<sup>®</sup>

# 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.,<br>Chief Development Officer                |
| Next Wave of RNAi Therapeutics to Fuel a Robust Clinical Pipeline | Paul Nioi, Ph.D., SVP, Research<br>Anna Borodovsky, Ph.D., VP, Research |
| Platform Innovation   | Vasant Jadhav, Ph.D., Chief Technology Officer                          |

The logo features a stylized white symbol on the left, consisting of a small circle and a curved, arrow-like shape that loops back to the right.





Alylam<sup>®</sup>



## Closing Remarks

**Pushkal Garg, M.D.**  
**Chief Medical Officer**

# A Inylam 2025 Goals

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

\* 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

# Alnylam 2025 Goals

|     |  | Combined Net Product Revenue Guidance<br>\$2,050M – \$2,250M | 2025                         |
|--|--|--|------------------------------|
| VUTRISIRAN   | ATTR Amyloidosis   | U.S. FDA Approval  | PDUFA date<br>March 23, 2025 |
| NUCRESIRAN*<br>(ALN-TTRsc04)   | <div style="background-color: #1a3d4d; color: white; padding: 20px; border-radius: 20px;"> <p><b>6 commercial products</b><br/>(4 WHOLLY OWNED)</p> <hr/> <p><b>3 Phase 3 study starts</b></p> <hr/> <p><b>Vutrisiran launch in ATTR-CM</b></p> <hr/> <p><b>≥4 new INDs</b></p> <hr/> <p><b>KARDIA<sub>3</sub></b><br/>Phase 2 results</p> <hr/> <p><b>Achieve sustainable non-GAAP profitability</b></p> </div> | Q2, Q3   |                              |
| ZILEBESIRAN*   |  | H1   |                              |
| MIVELSIRAN*  |  | H2   |                              |
| ALN-6400*  |  | H2   |                              |
| ADDITIONAL   |  | H2   |                              |
| FITUSIRAN* (Sanofi)  |  | H2   |                              |
| ELEBSIRAN* (Vir)   | Chronic HBV/HDV  | Initiate Phase 3 study in HDV                                | 2025                         |
|  |  | Phase 2 HBV Functional Cure Results                          | PDUFA date<br>March 28, 2025 |
| CEMDISIRAN* (Regeneron)  | Complement-Mediated Diseases   | Phase 3 MG Results   | H1                           |
|  |  |  | Q2                           |
|  |  |  | H2                           |



Silence disease

Amplify life™

 Alnylam®



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**Please share your feedback**