Nathan (USA)
Diagnosed with AHP

Alnylam R&D Day

December 13, 2023

R&D Day Agenda

Topic	Time	Presenter
RNAi Therapeutics: The Next Chapter	8:30 – 8:45am	Akshay Vaishnaw, M.D., Ph.D.
Extending Alnylam's Leadership in RNAi Platform Innovation	8:45 – 9:00am	Vasant Jadhav, Ph.D. Karyn Schmidt, Ph.D.
Next Wave of RNAi Therapeutics to Fuel Robust Clinical Pipeline	9:00 – 9:25am	Paul Nioi, Ph.D. Anna Borodovsky, Ph.D.
Establishing New Frontiers in the CNS with RNAi	9:25 – 10:00am	Kirk Brown, Ph.D. David Werring, M.D., University College London
Q&A Session #1	10:00 – 10:30am	Kevin FitzGerald, Ph.D. (Moderator)
Intermission	10:30 – 10:45am	
Zilebesiran: Reimaging the Treatment of Hypertension	10:45 – 11:30am	Simon Fox, Ph.D. Rhian Touyz, M.D., McGill University
Building ATTR Amyloidosis Market Leadership	11:30am – 12:10pm	John Vest, M.D. Ali Murad, M.D. Tolga Tanguler
Q&A Session #2	12:10 – 12:40pm	Pushkal Garg, M.D. (Moderator)
Closing Remarks	12:40 – 12:45pm	Yvonne Greenstreet, MBChB

Reminders

- Event scheduled to end at ~12:45 p.m. ET.
- Two moderated Q&A sessions during the meeting.
- To submit a question, type your question in the “Ask a Question” field.
- Replay will be available on Investors Page of our website later today.

Alnylam Forward Looking Statements

This presentation contains 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, expectations regarding Alnylam's aspiration to become a top-tier biotech company and the planned achievement of its "*Alnylam P^{5}x25*" strategy, the potential for Alnylam to identify new potential drug development candidates and advance its research and development programs, Alnylam's ability to obtain approval for new commercial products or additional indications for its existing products, and Alnylam's projected commercial and financial performance, 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: Alnylam's ability to successfully execute on its "*Alnylam P^{5}x25*" strategy; 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, including topline results from the Company's HELIOS-B Phase 3 study of vutrisiran; 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 in the future; 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 without the need for future equity financing; the direct or indirect impact of the COVID-19 global pandemic or any future pandemic on Alnylam's business, results of operations and financial condition and the effectiveness or timeliness of Alnylam's efforts to mitigate the impact of the pandemic; 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 periodic report (Quarterly Report on Form 10-Q or 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.

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Acknowledgements and Disclosures

All speakers are employees of Alnylam Pharmaceuticals except for Dr. David Werring and Dr. Rhian Touyz, who are paid consultants to Alnylam. Alnylam Pharmaceuticals and the speakers at this event wish to thank patients, families, caregivers and dedicated researchers at their affiliated, as well as other entities, for their contributions to the findings presented.

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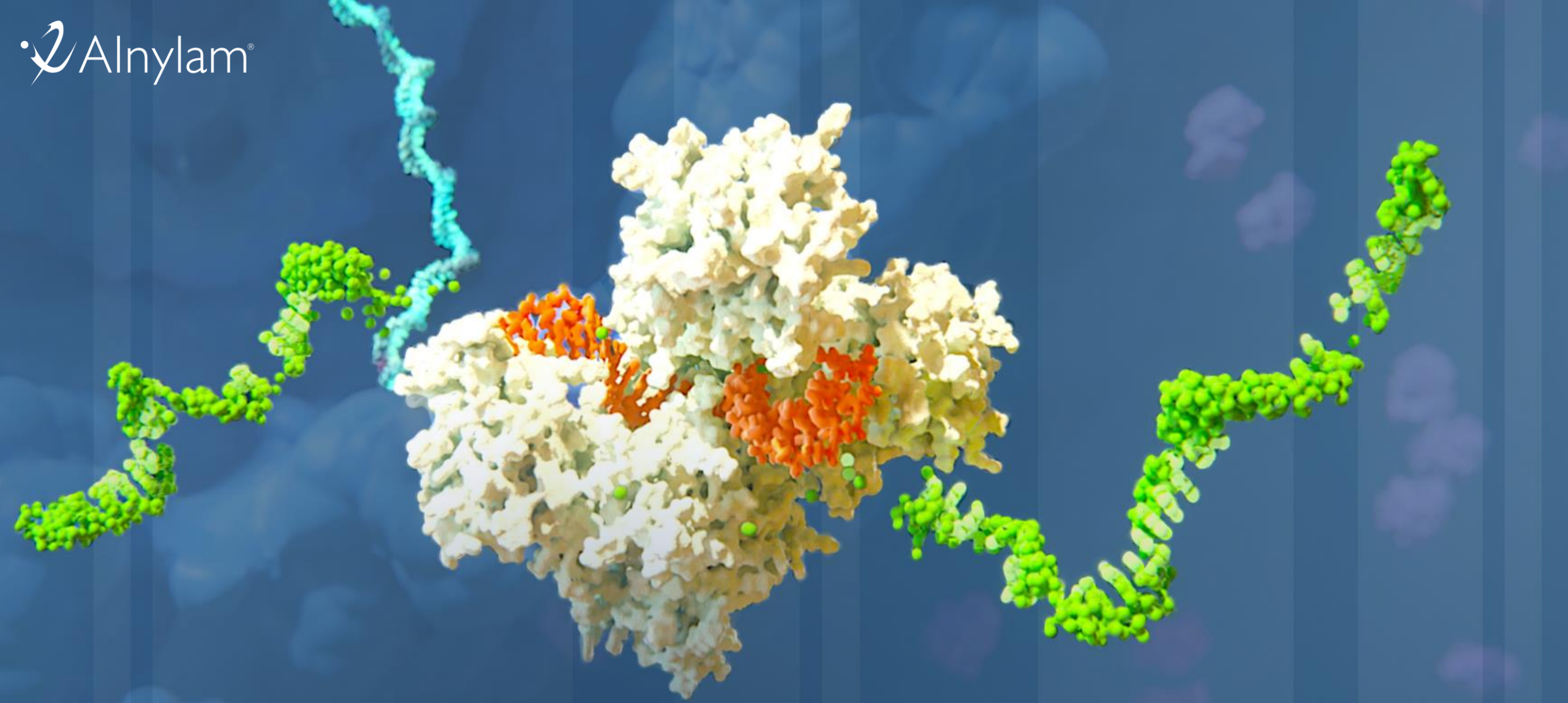

RNAi Therapeutics: The Next Chapter

Akshay Vaishnaw, M.D., Ph.D.
Chief Innovation Officer

First Draft of the Human Genome

June 26, 2000

- "It's one small piece of man… one giant leap for mankind" headlined the *Mirror* newspaper (June 27, 2000)
- A potential roadmap to the ***GENETIC*** basis of human disease

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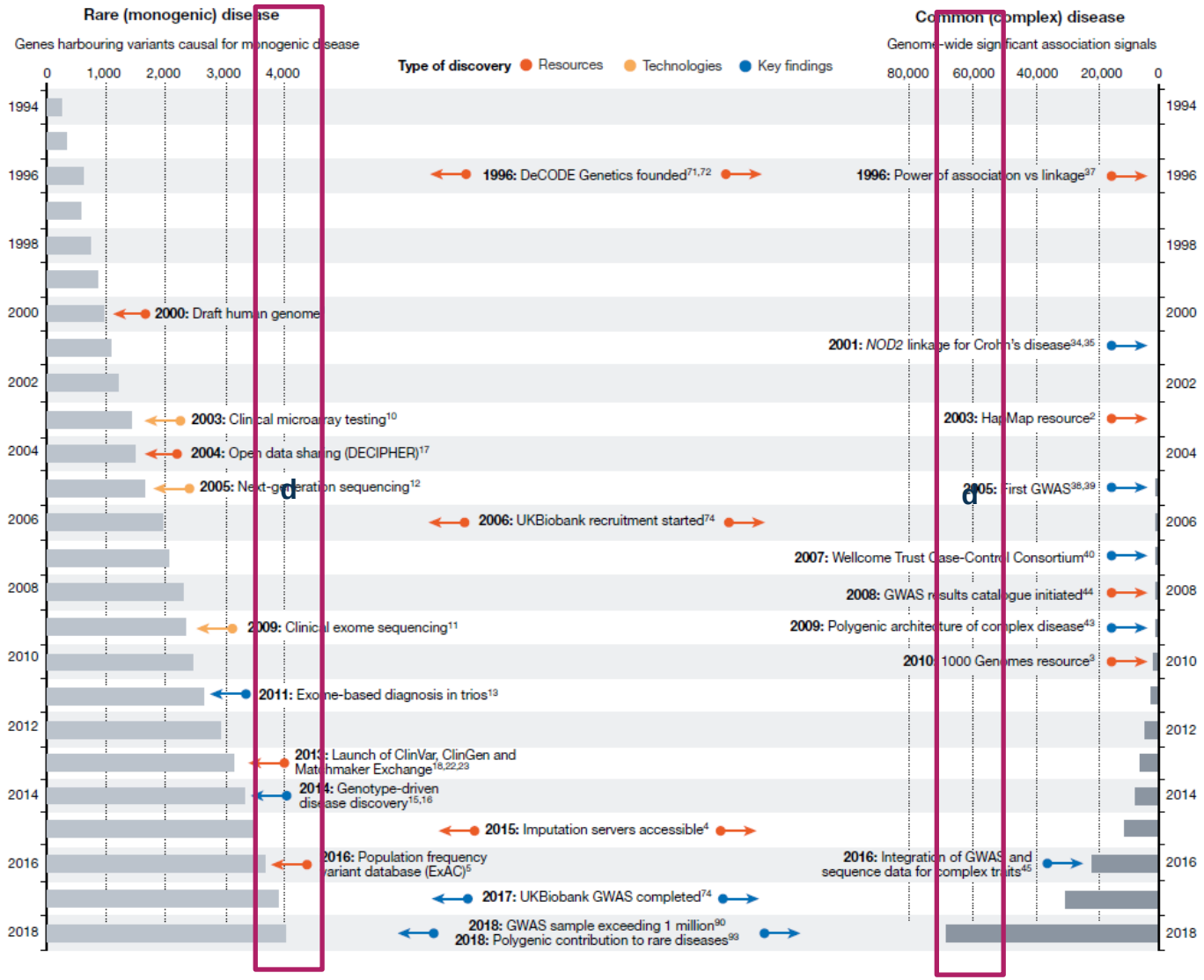
Growth in Discovery of Disease-Associated Genetic Variation

1994-2018



- Deeper understanding of molecular basis of human disease
- Dramatic increase in number of genetically validated targets
- Highlights needs for new approaches to treatment of vast array of disorders

Claussnitzer et al., Nature, 2020; 577:179-189

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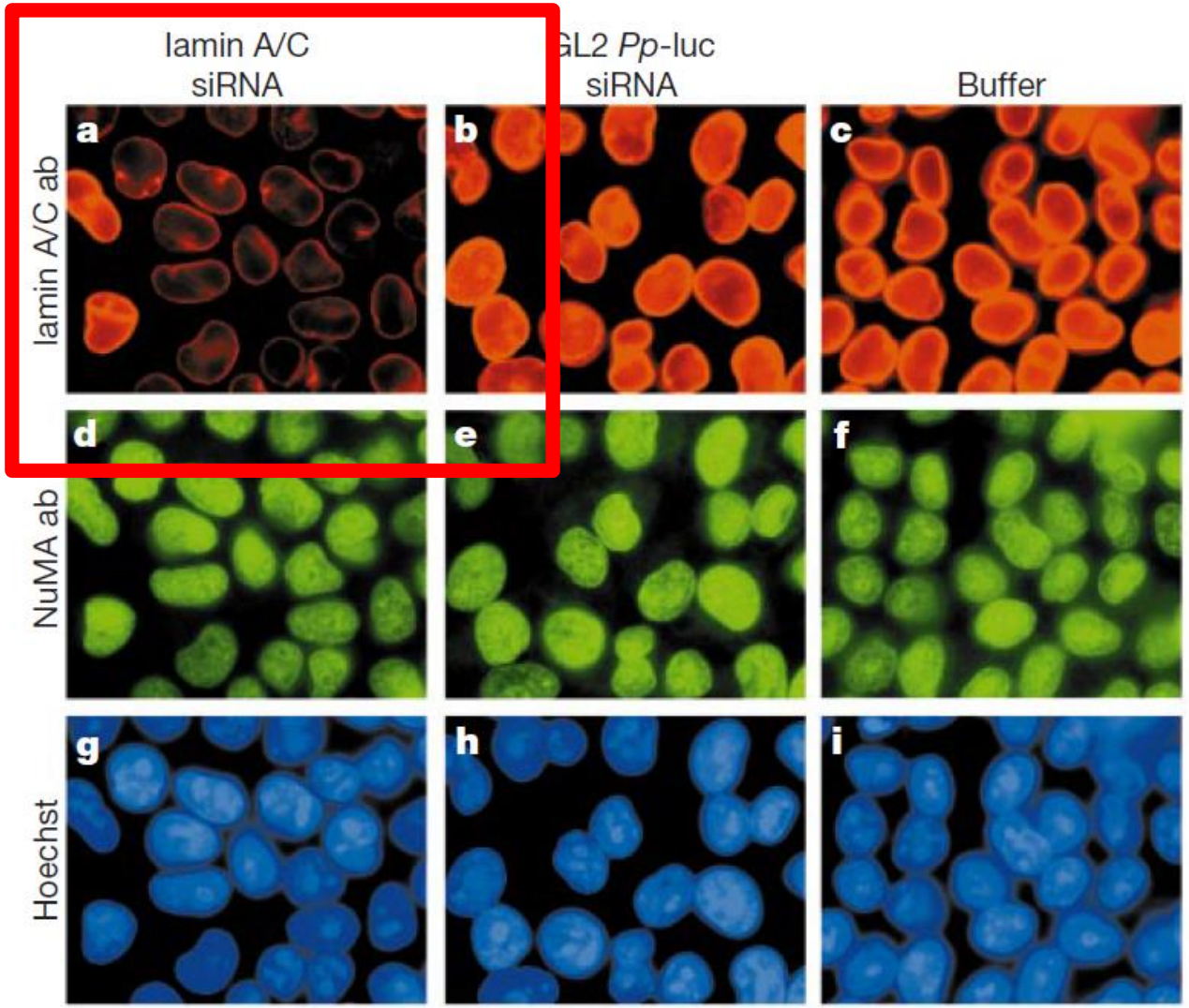
First Report of RNA Interference (RNAi) in Human Cells

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



- **Ability to harness an endogenous pathway**
- **Catalytic mechanism**
- **Ability to silence *any* gene in genome**
- **Ability to act upstream of today's medicines**
- **Potential for new way to address *GENETIC* targets using *GENETIC* medicines**

↳ ***RNAi THERAPEUTICS***

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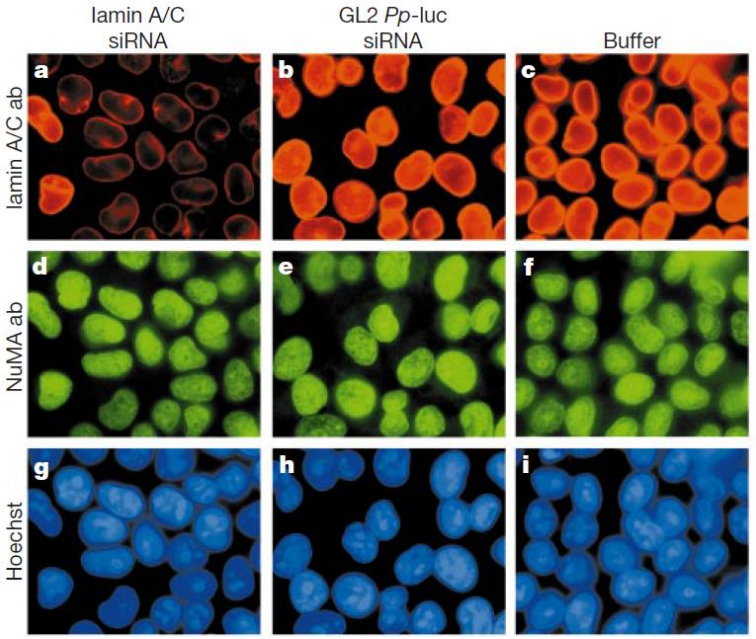
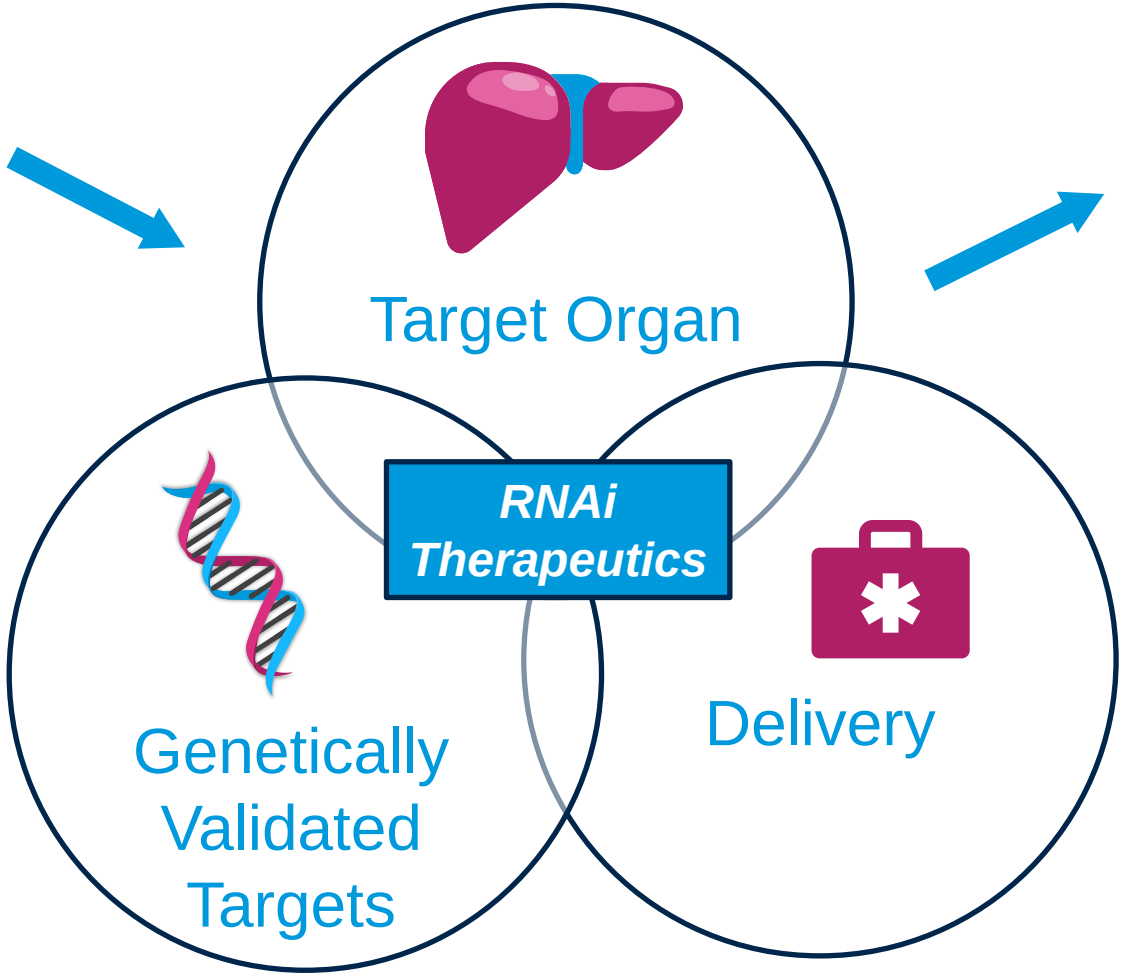
Focused R&D Strategy

Turning an *In Vitro* Observation into a New Class of Transformative Medicines



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



Multiple RNAi Therapeutics

- onpattro® (patisiran) lipid complex injection 10 mg/5 mL
- amvuttra® (vutrisiran) injection 25 mg/0.5 mL
- GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL
- OXLUMO® (lumasiran) for injection 94.5 mg/0.5 mL
- LEQVIO® (inclisiran) injection 284 mg/1.5 mL

Novartis has obtained global rights to develop, manufacture and commercialize Leqvio (inclisiran)

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RNAi Therapeutics

A New Class of Medicines

New Class of Drugs Fulfills Promise of RNA-based Medicine

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https://www.fda.gov/drugs/news-events-human-drugs/new-class-drugs-fulfills-promise-rna-based-medicine (2018)

JAMA Insights | GENOMICS AND PRECISION HEALTH

siRNAs—A New Class of Medicines

Anastasia Khvorova, PhD

Khvorova, JAMA Insights (2023)

What is the roadmap to realizing the full potential of RNAi?

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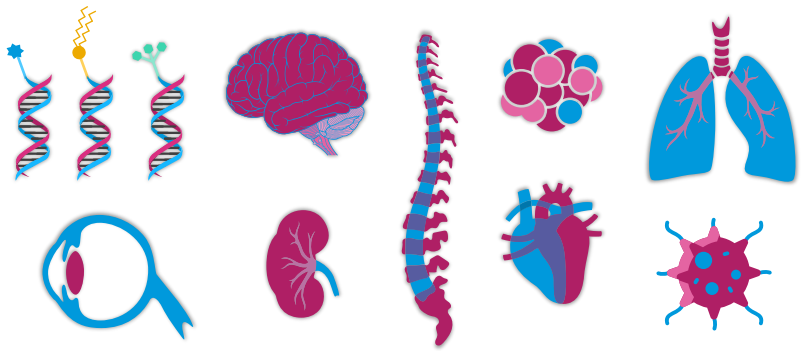
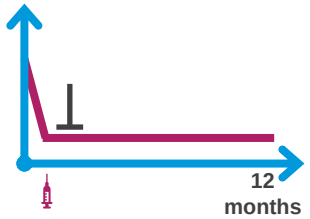
Multiple Sources of Sustainable Innovation Drive Robust Pipeline

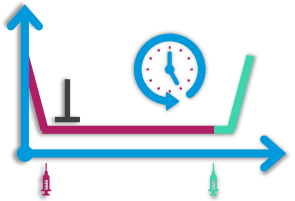
Extrahepatic Delivery



Platform Designs



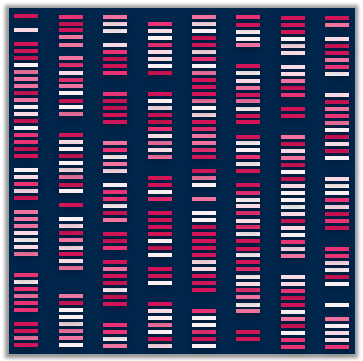
IKARIA™



Reversir™

GEMINI™

Human Genetics

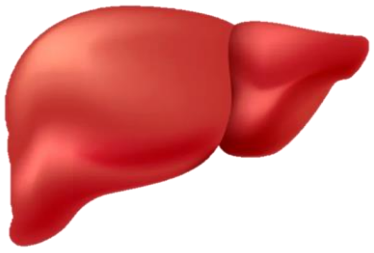


+ Our Future Health

discoverme

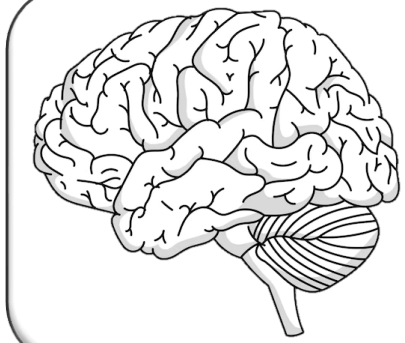
biobank uk

By end of 2025



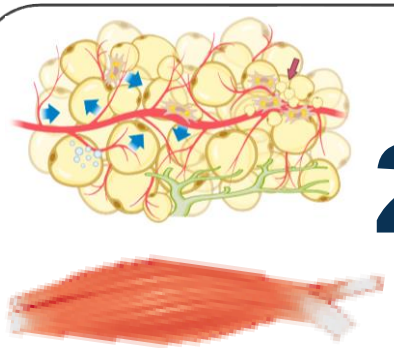
5 new **liver** INDs

10+ including partnered programs



2 new **CNS** INDs

3+ including partnered programs



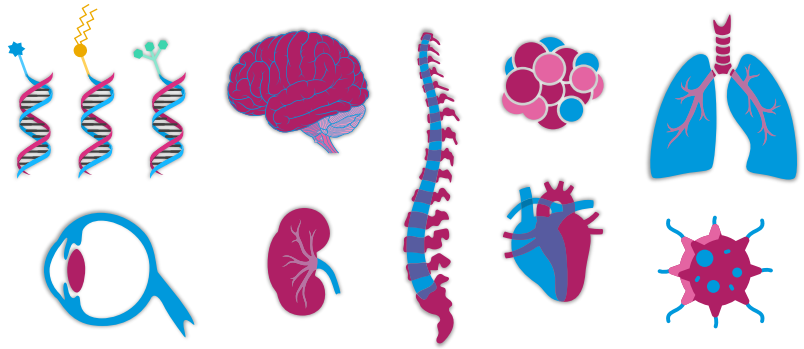
2 **new tissues** with INDs

Realizing Full Potential of RNAi Therapeutics

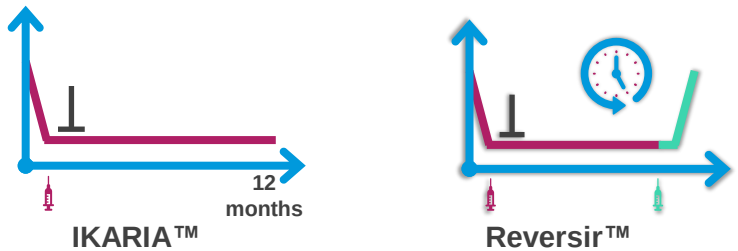
Maintaining RNAi Leadership by Advancing Alnylam Platform to New Frontiers

Platform Technologies

Extrahepatic Delivery Expansion



siRNA Designs



Vasant Jadhav, Ph.D.; Karyn Schmidt, Ph.D.

- Discuss large range of tissue delivery systems being studied
  - Innovative delivery solutions
- Update on recent progress with respect to CNS, muscle and adipose tissue delivery
- Highlight leadership with siRNA design with continuing work to build safer, more potent RNAi therapeutics

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Realizing Full Potential of RNAi Therapeutics

Building Pipeline for 2025 and Beyond

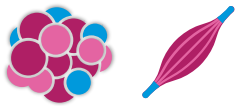
Pipeline

Preclinical → ***2025*** → **Clinical**

Genetically validated pipeline

5 new liver INDs
(10+ including partnered programs)

2 new CNS INDs
(3+ including partnered programs)



2 new tissues with INDs

Paul Nioi, Ph.D.; Anna Borodovsky, Ph.D.

- Vision for expansion of pipeline in rare, specialty and prevalent disease areas
- Discuss significant upcoming growth in liver pipeline
- Outline how tissue delivery advances are being translated to INDs in two new tissues, adipose and muscle

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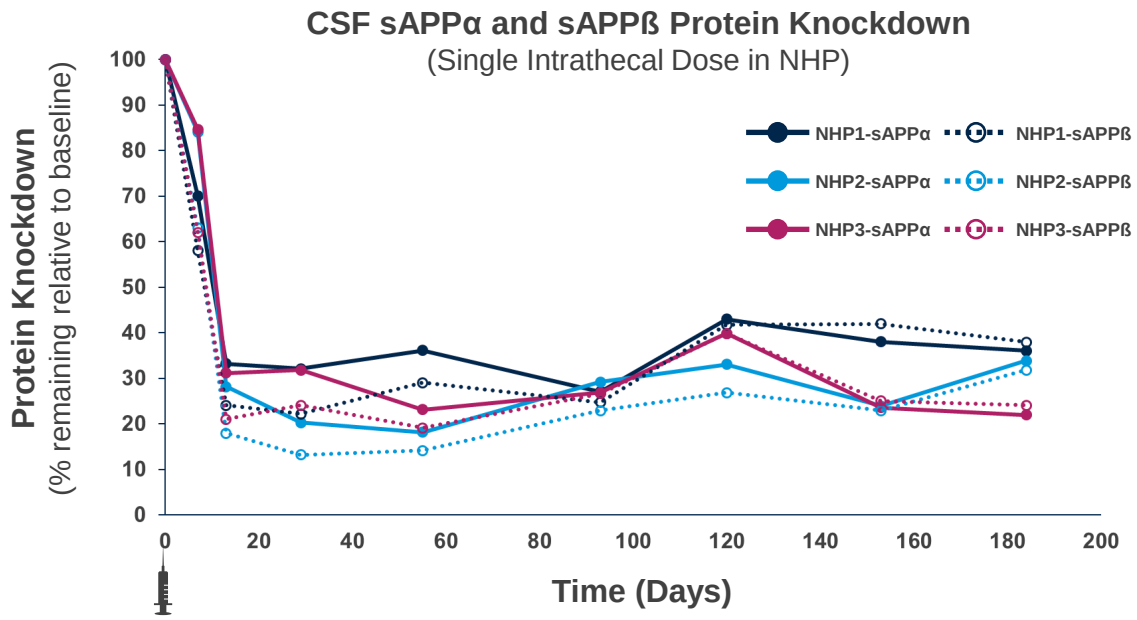
Building a Reproducible and Modular, Industry-Leading CNS Pipeline

Translating Powerful Preclinical Observations into Clinic

Single Intrathecal Dose of ALN-APP Supports Bi-Annual or Less Frequent Regimen



Kirk Brown, Ph.D.

- Industry-leading translation of RNAi from bench to bedside
  - ALN-APP proof-of-concept
- Next steps with ALN-APP
  - Phase 2
  - Deep dive into cerebral amyloid angiopathy (*Prof. David Werring, MB, Ph.D., FRCP*)
- Progress with four new CNS targets, and upcoming clinical-stage CNS pipeline

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Zilebesiran Program: Reimagining the Treatment of Hypertension

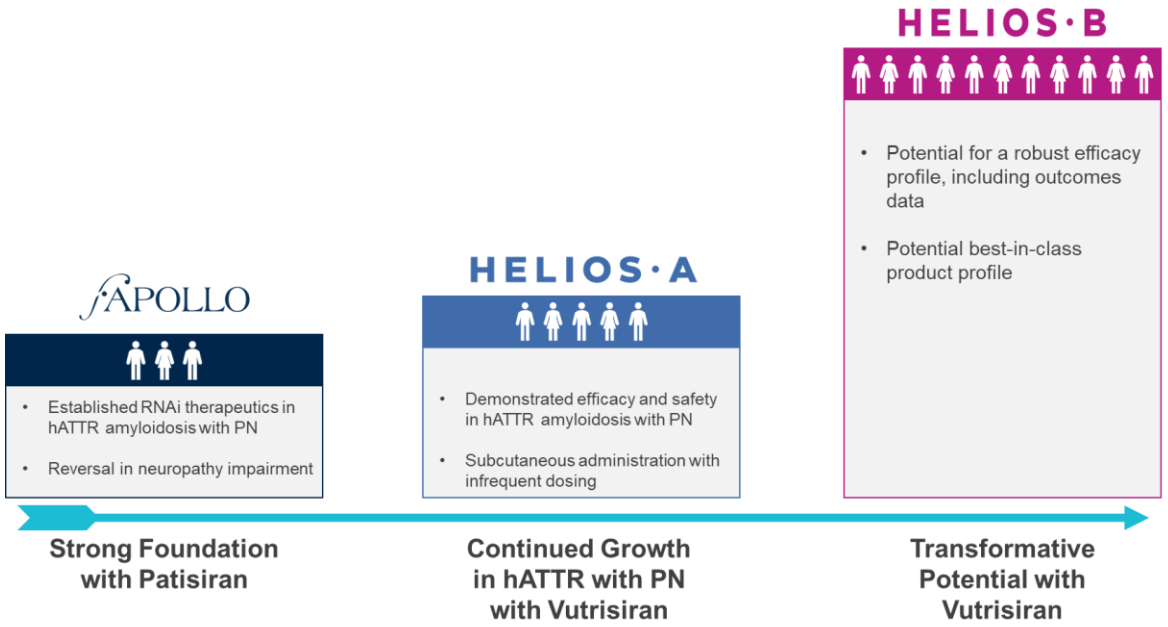
Simon Fox, Ph.D.

- Unmet need in hypertension (*Dr. Rhian Touyz, MBBCh, MSc, Ph.D., FRCP, FRSE)*
- Report complete data on Phase 1 study
- Discuss latest findings from Phase 2 KARDIA-1 study confirming potential for new way to treat elevated blood pressure
  - Q6 monthly SC injection giving addressing both qualitative and quantitative unmet need
- Address clinical development plans and timelines for Phase 2 and beyond

Desai et al., NEJM, 2023;389:228-38

RNAi Therapeutics Opportunity for ATTR Amyloidosis

Progress in Further Building Alnylam's Lead Franchise



John Vest M.D., Ph.D., Ali Murad M.D.

- Discuss continuing positive data from APOLLO-B study
- Highlight new insights leading to continued confidence in HELIOS-B study design and outcomes
- Report exciting ALN-TTRsc04 Phase 1 data
  - Potential for biannual or annual SC dosing with up to 97% mean TTR knockdown
- Update on key CDP and timelines for TTR franchise programs

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Advancing a Robust and High-Yielding Pipeline of RNAi Therapeutics

Focused in 4 Strategic Therapeutic Areas (STArs):

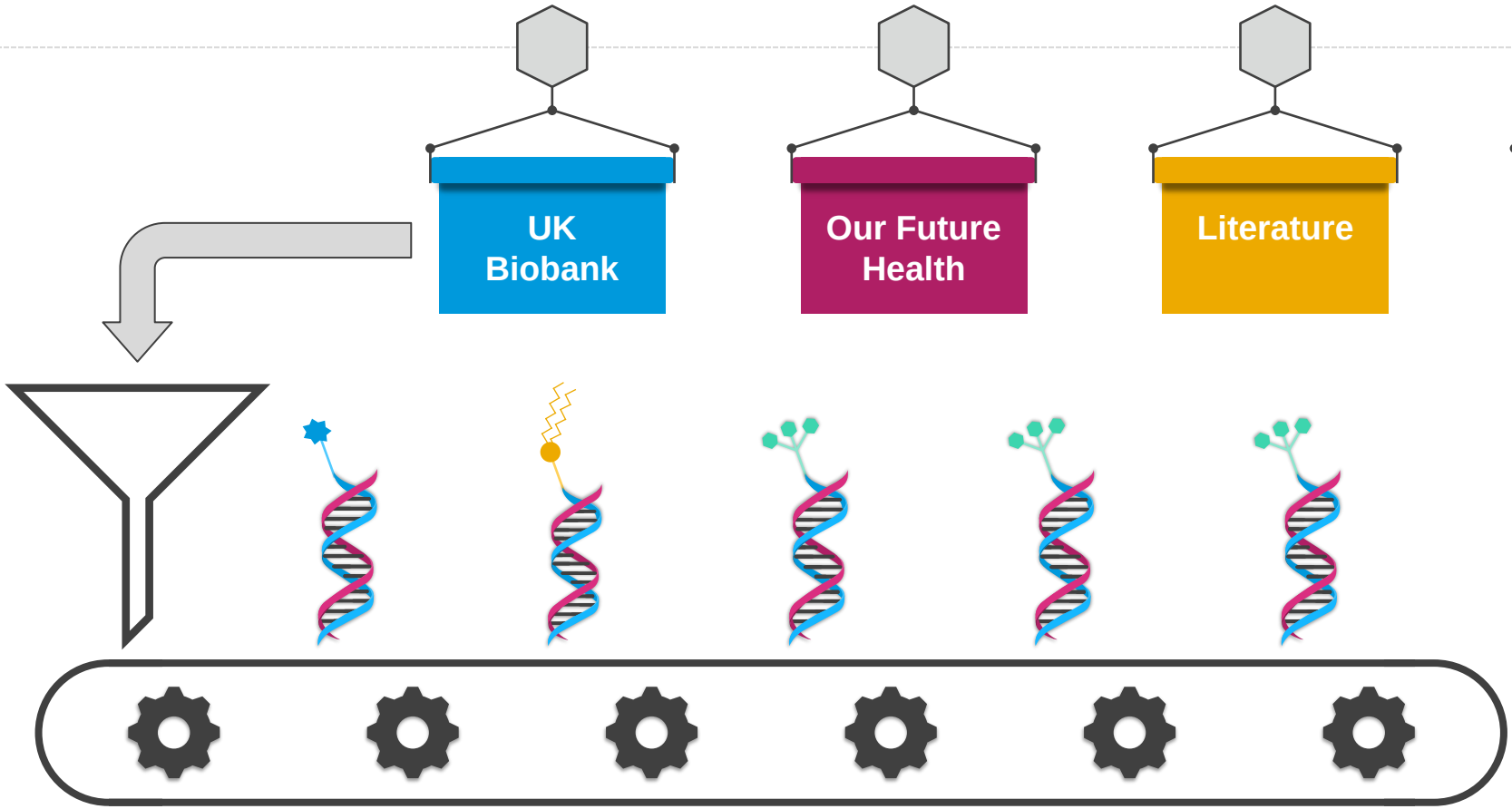
- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

		EARLY/MID-STAGE *(IND/CTA Filed-Phase 2)*	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION/ COMMERCIAL[1]	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis with PN*			●	Global
amvuttra (vutrisiran)	*hATTR Amyloidosis with PN*			●	Global
GIVLAARI (givosiran)	*Acute Hepatic Porphyria*			●	Global
OXLUMO (lumasiran)	*Primary Hyperoxaluria Type 1*			●	Global
LEQVIO (inclisiran)	*Hypercholesterolemia*			●	Milestones & up to 20% Royalties[2]
Vutrisiran	*ATTR Amyloidosis with CM*		●		Global
Fitusiran*	*Hemophilia*		●		15-30% Royalties
Cemdisiran (+/- Pozelimab)[3]*	*Complement-Mediated Diseases*		●		Global; Milestone/Royalty
ALN-TTRsc04*	*ATTR Amyloidosis*	●			Global
Belcesiran[4]*	*Alpha-1 Liver Disease*	●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)[5]*	*Hepatitis B Virus Infection*	●			50-50 option post-Phase 2
Zilebesiran*	*Hypertension*	●			U.S. 50-50; Ex-U.S. Royalties
ALN-HSD[6]*	*NASH*	●			Royalty
ALN-APP*	*Alzheimer's Disease; Cerebral Amyloid Angiopathy*	●			50-50
ALN-PNP*	*NASH*	●			50-50
ALN-KHK*	*Type 2 Diabetes*	●			Global

[1] Includes marketing application submissions; [2] Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam; [3] Alnylam and Regeneron are evaluating potential combinations of the investigational therapeutics cemdisiran and pozelimab; [4] Novo Nordisk is leading and funding development of belcesiran; [5] Vir is leading and funding development of ALN-HBV02; [6] Regeneron is leading and funding development of ALN-HSD; * Not approved for any indication and conclusions regarding the safety or efficacy of the drug have not been established. **As of December 2023**

Alnylam®

Delivering Sustainable Innovation with RNAi Therapeutics



TRANSFORMATIVE MEDICINES

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

amvuttra® (vutrisiran) injection 25 mg/0.5 mL

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

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

LEQVIO® (inclisiran) injection 284 mg/1.5 mL

Alnylam®

Novartis has obtained global rights to develop, manufacture and commercialize Leqvio (inclisiran)

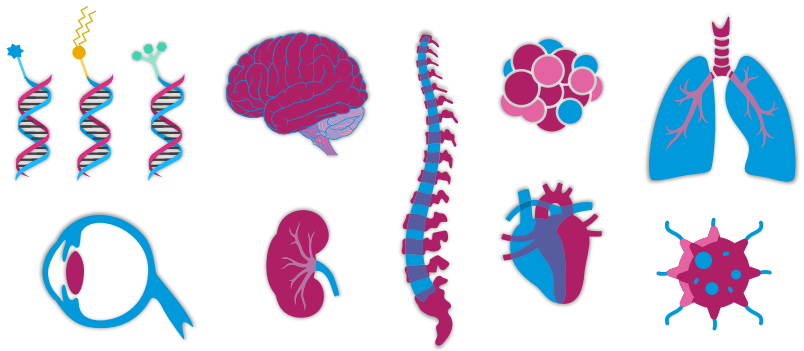
Extending Alnylam Leadership in RNAi Platform Innovation

Vasant Jadhav, Ph.D.
Chief Technology Officer

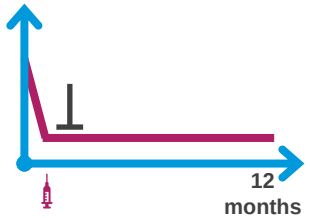
Karyn Schmidt, Ph.D.
Principal Scientist

Multiple Sources of Sustainable Innovation Drive Robust Pipeline

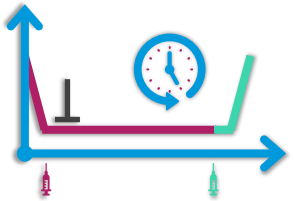
Extrahepatic Delivery



Platform Designs



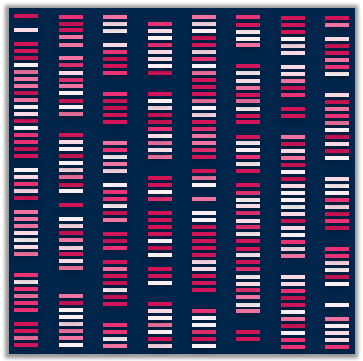
IKARIA™



Reversir™

GEMINI™

Human Genetics

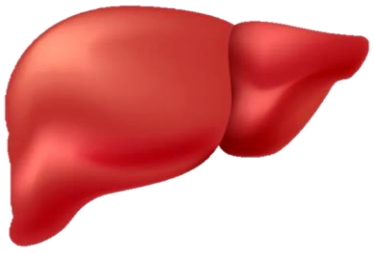


+ Our Future Health

discoverme

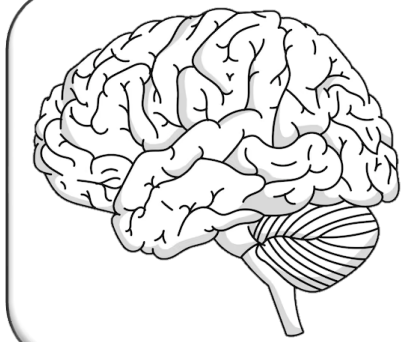
biobank uk

By end of 2025



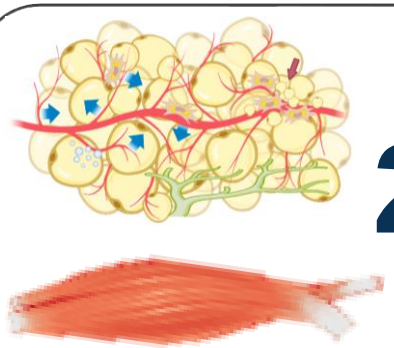
5 new **liver** INDs

10+ including partnered programs



2 new **CNS** INDs

3+ including partnered programs

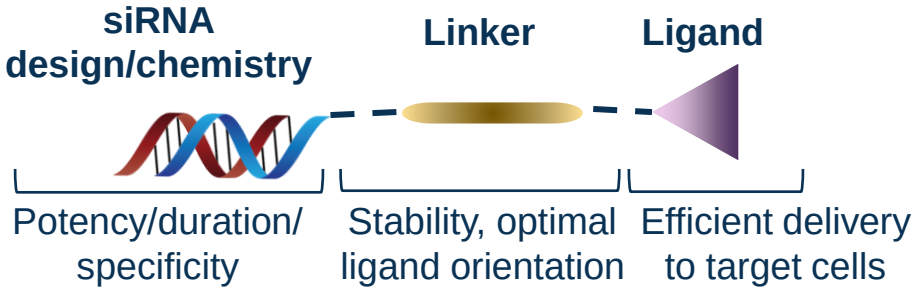


2 **new tissues** with INDs

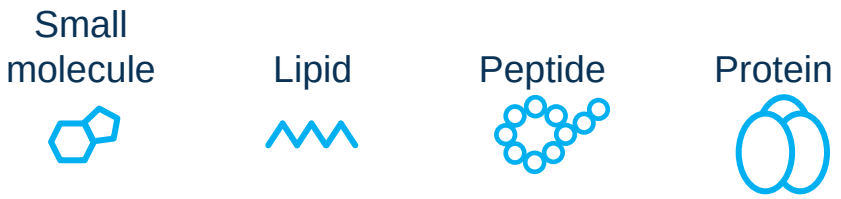
Achieving Best-in-Class Extrahepatic Delivery

Excellence in Delivery for Liver and Now CNS, and Expanding to Additional Tissues

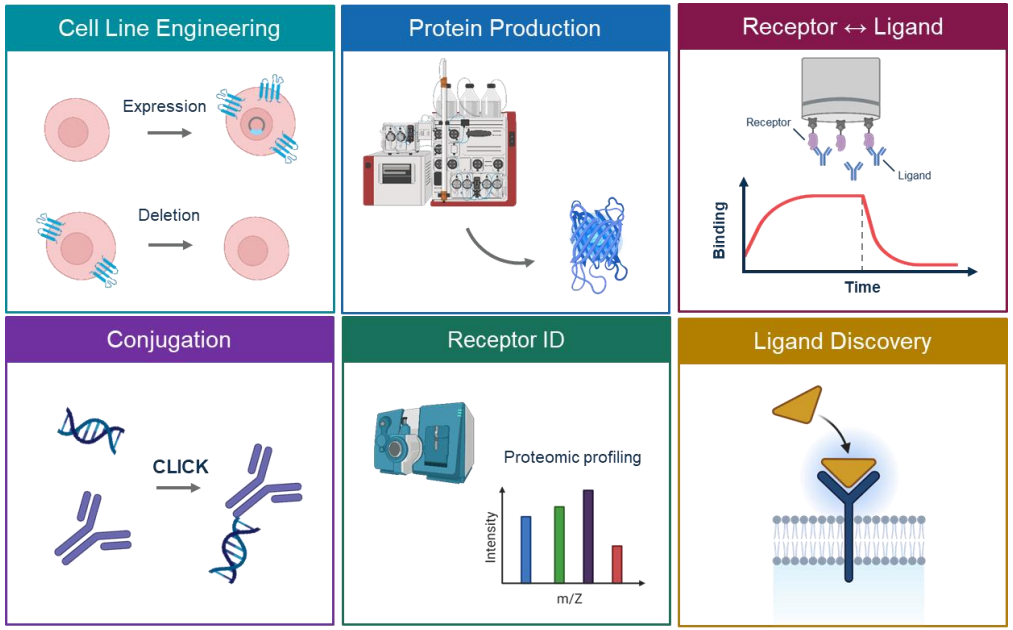
Extensive knowhow from earlier delivery efforts



Range of ligands for tissue-specific delivery



Fueled by core capabilities



Differentiated profile

- Extensive preclinical characterization provides high confidence in human translation
  - ✓ Safety
  - ✓ Efficacy
  - ✓ CMC
- Minimize liver sink to improve exposure in tissue of interest
- Potential for targeting multiple tissues (e.g., liver + adipose/muscle)
- Desired features for best-in-class differentiating profile

SC dosing → ≤ 3 mg/kg ED_{90} → Efficient Manufacturing

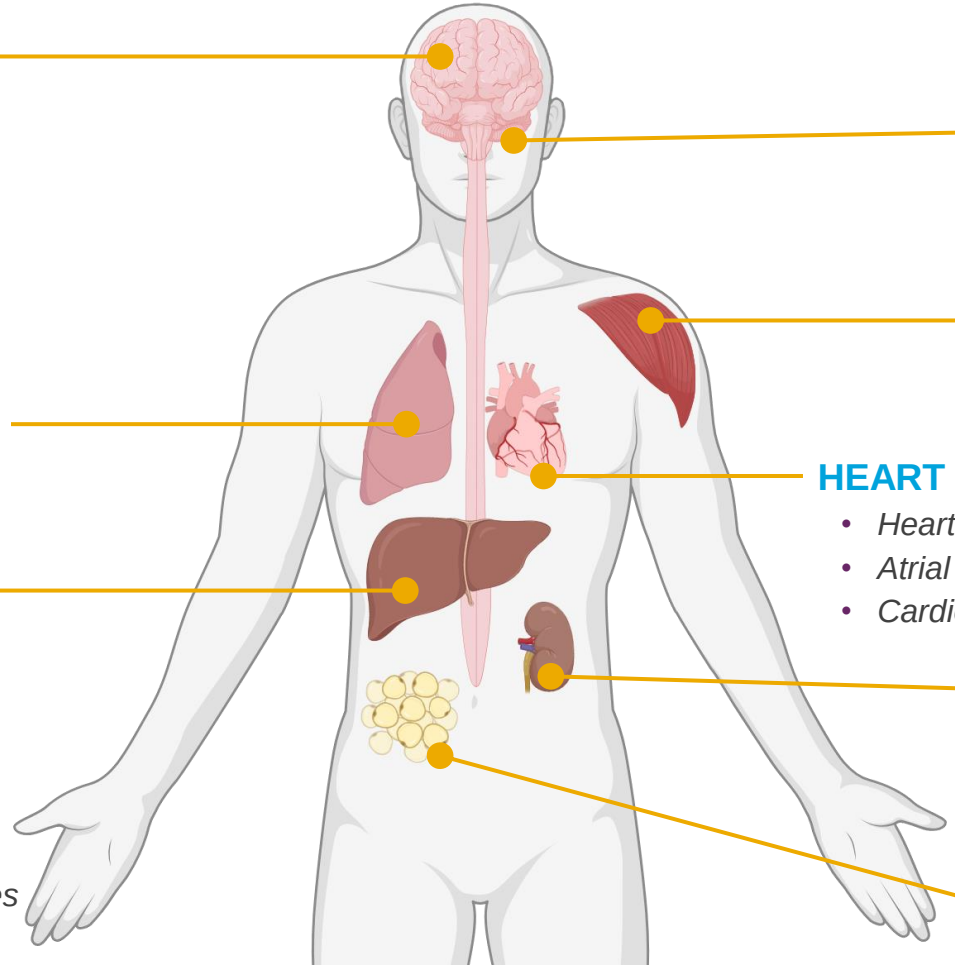
Utilizing RNAi Pathway Across Tissues for RNAi Therapeutics

Initial Tissues with Compelling Therapeutic Opportunities for RNAi

CNS
- *Alzheimer's Disease*
- *CAA*
- *Amyotrophic Lateral Sclerosis*
- *Frontotemporal Dementia*
- *Huntington's Disease*
- *Parkinson's Disease*
- *Spinocerebellar Ataxia*

LUNG
- *Asthma*
- *COPD*
- *IPF*

LIVER
- *ATTR Amyloidosis*
- *Acute Hepatic Porphyria*
- *Primary Hyperoxaluria*
- *Hypercholesterolemia*
- *Hemophilia and, other hematological disorders*
- *Complement mediated diseases*
- *Hepatitis B and delta Virus*
- *Hypertension*
- *NASH*
- *Diabetes mellitus*



EYE
- *Stargardt Disease*
- *Glaucoma*
- *Age-related Macular Degeneration*

MUSCLE
- *Metabolic Disease*
- *Duchenne Muscular Dystrophy*
- *Facioscapulohumeral Muscular Dystrophy*

HEART
- *Heart Failure*
- *Atrial Fibrillation*
- *Cardiomyopathy*

KIDNEY
- *Diabetes mellitus*
- *Glomerulonephritis*
- *Gout*

ADIPOSE
- *Obesity*
- *Metabolic Syndrome*
- *Lipodystrophy*

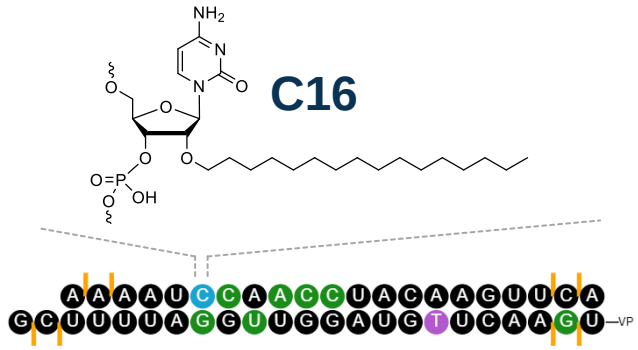
Alnylam®

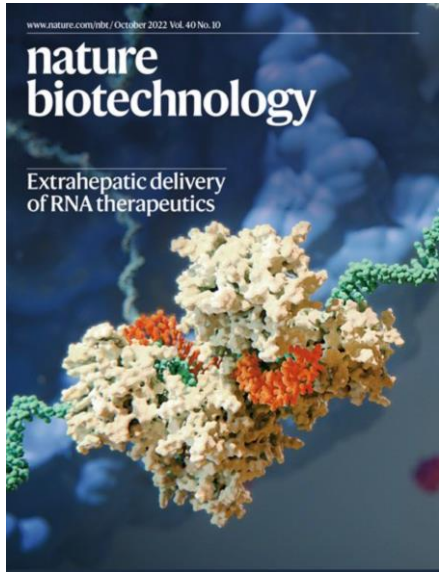
CNS Delivery

Alnylam®

Human Translation of CNS RNAi Therapeutics

Best-in-class C16-siRNA Platform





2023: First Human PoC of RNAi Therapeutics in CNS

Alnylam and Regeneron Report Positive Interim Phase 1 Clinical Data on ALN-APP, an Investigational RNAi Therapeutic for Alzheimer's Disease and Cerebral Amyloid Angiopathy

Apr 26, 2023

– Single Doses of ALN-APP Demonstrated Dose-Dependent, Rapid and Sustained Reduction of sAPPα and sAPPβ in Cerebrospinal Fluid, with Up to 90% at Highest Dose to Date –

– Encouraging Clinical Safety and Tolerability Profile Observed with Single Dosing to Date –

– Results Provide First Demonstration of Gene Silencing by RNAi Therapeutics in the Human Brain Using Alnylam's Proprietary C16 Platform –

Brown, K.M., Nair, J.K., Janas, M.M. *et al. Nat Biotechnol* **40**, 1500–1508 (2022)

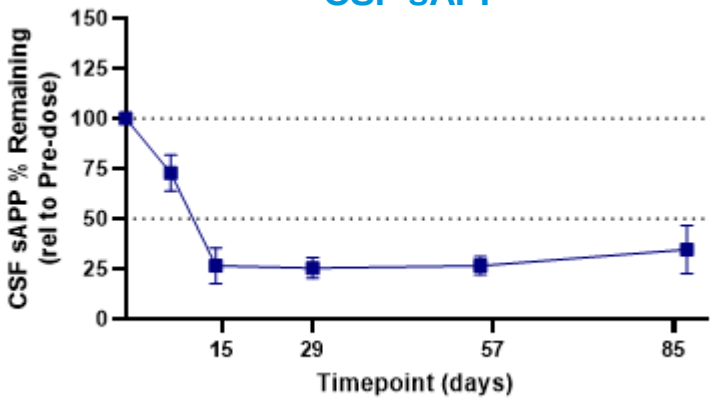
Alnylam®

Enabling CNS Pipeline in High Unmet Need Medical Disorders

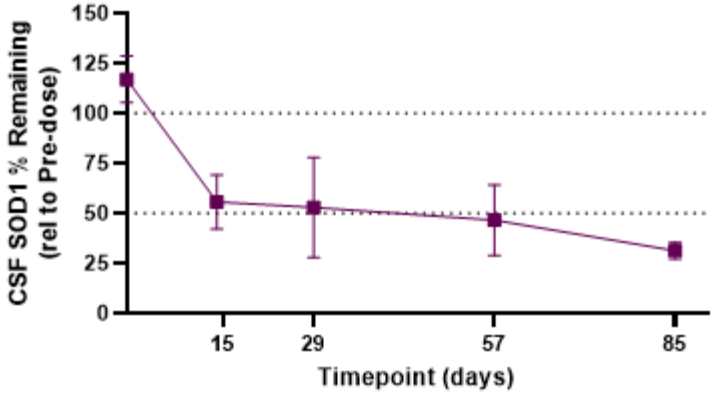
Modular and Reproducible Platform for Silencing in NHP CNS

Targets in Clinical or IND-Enabling Development

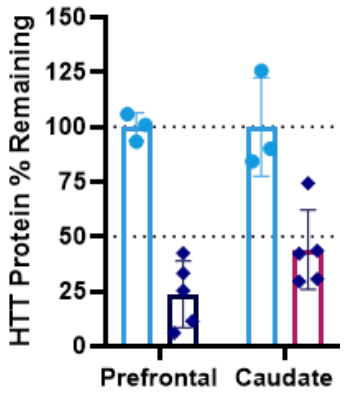
CSF sAPP



CSF SOD1

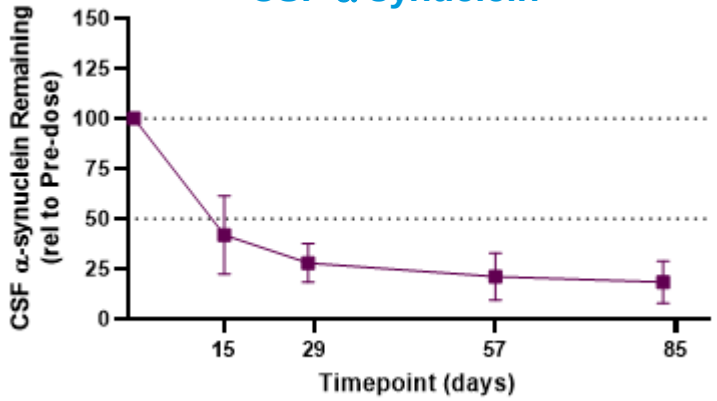


Tissue HTT protein

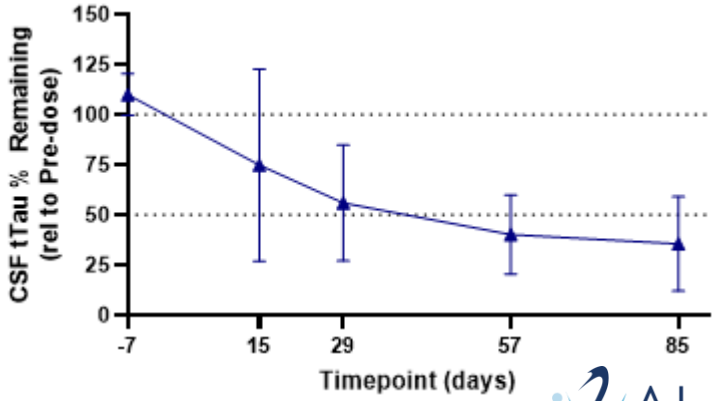


Next Wave of CNS Targets

CSF α synuclein

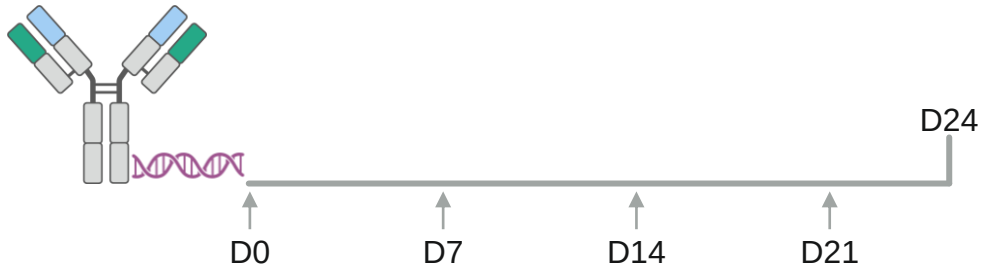


CSF Tau



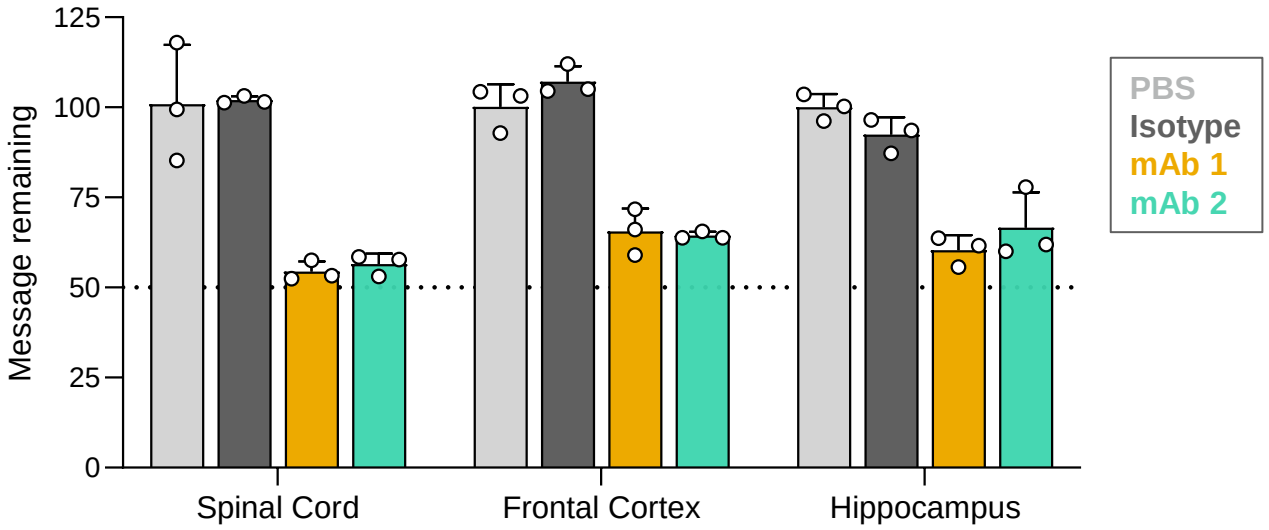
Overcoming Blood-Brain Barrier to Achieve CNS Delivery

Proof of Concept with Antibody-siRNA Conjugate in Mice

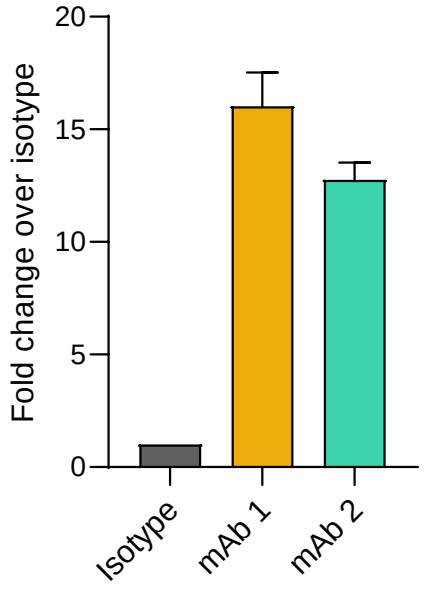


QWx4 IV @ 5 mg/kg

Activity



Whole brain exposure

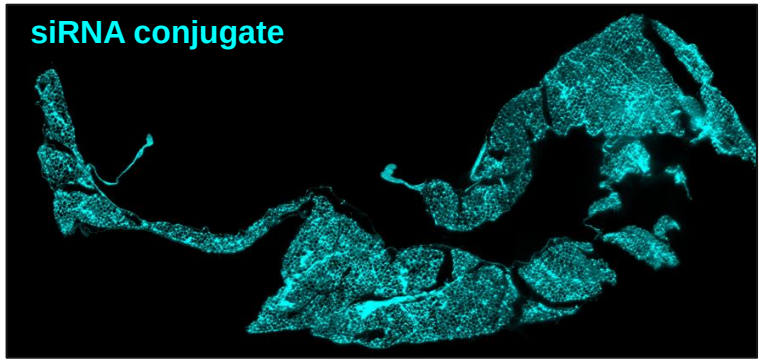


Alnylam®

Adipose Delivery

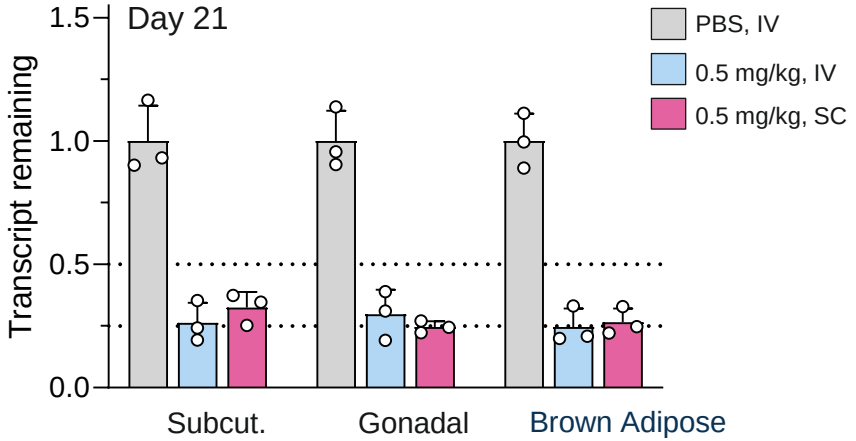
Robust RNAi Activity in Brown and White Adipose Depots of Mice

Uniform distribution in adipose

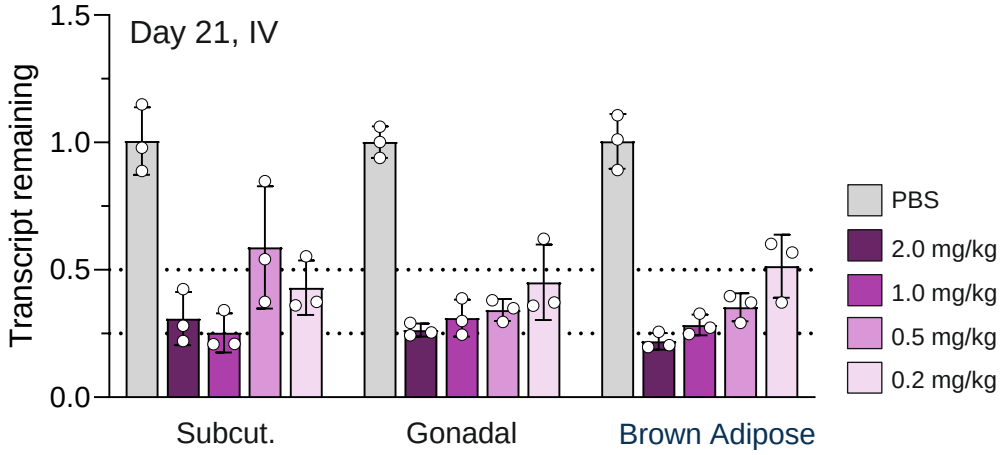


24h · 5 mg/kg · IV

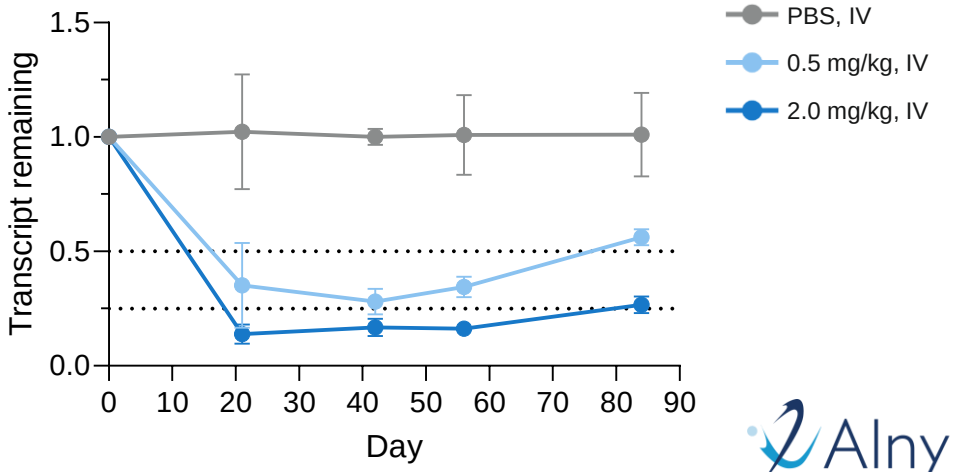
SC vs. IV dosing



Dose response

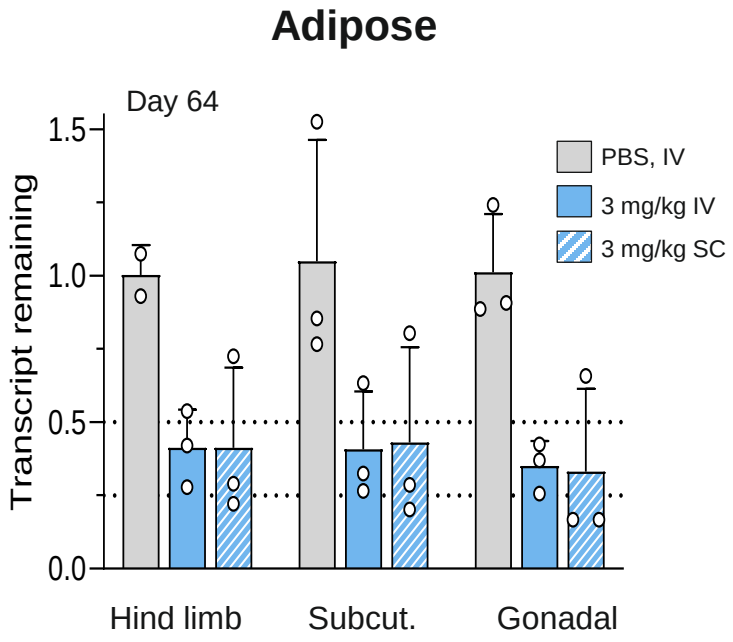


Durability of knockdown (gonadal)

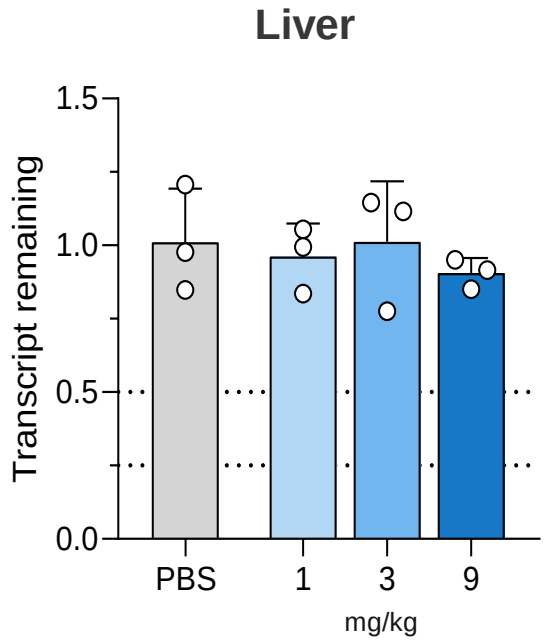


RNAi-Mediated Gene Silencing in NHP Adipose

Robust activity observed in adipose tissues



Minimal to no activity observed in other tissues (e.g., liver)



Development Candidate expected **2024**

IND expected **2025**

Alnylam®

Muscle Delivery

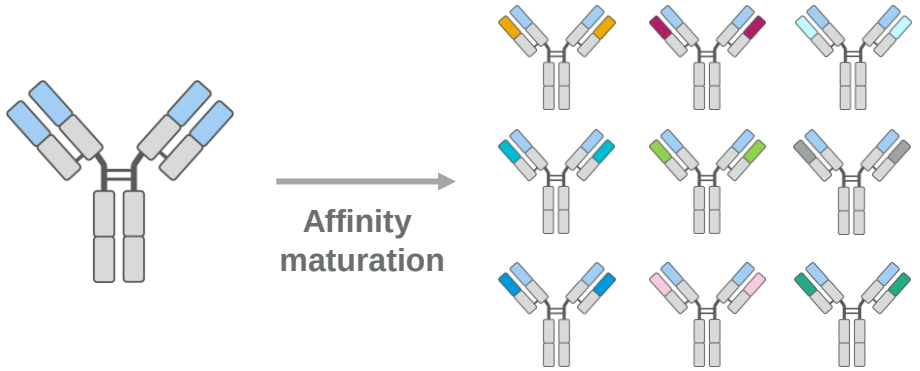
Alnylam®

Proprietary Muscle-Targeting Antibody Conjugate

Robust and Durable Knockdown in Skeletal Muscle in Mice

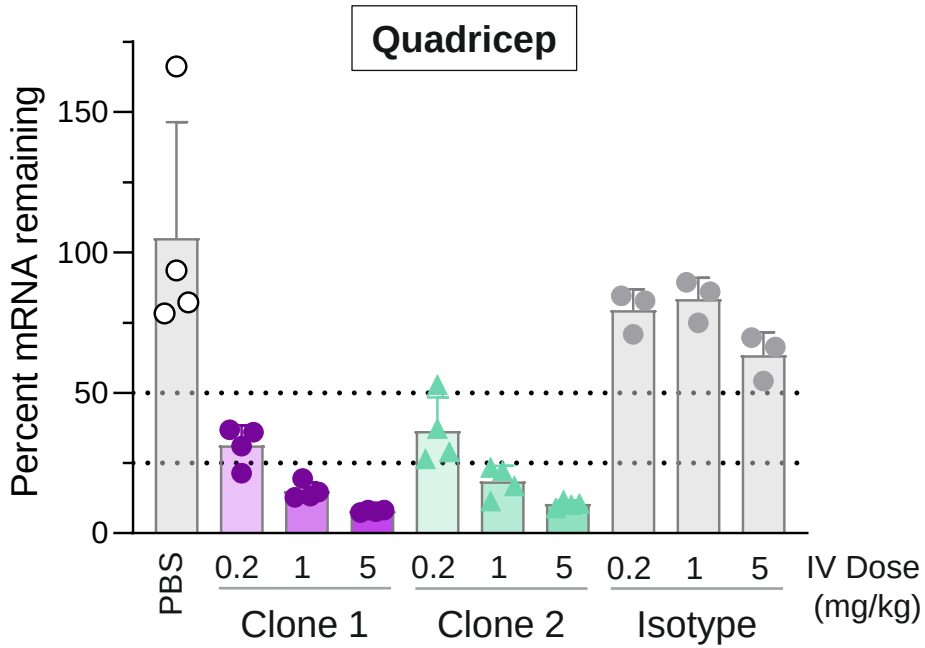
Protein | Peptide | Small molecule

Systematic approach to antibody optimization



Optimize for:
- affinity
- specificity
- cross-reactivity

Robust and dose responsive knockdown in muscle



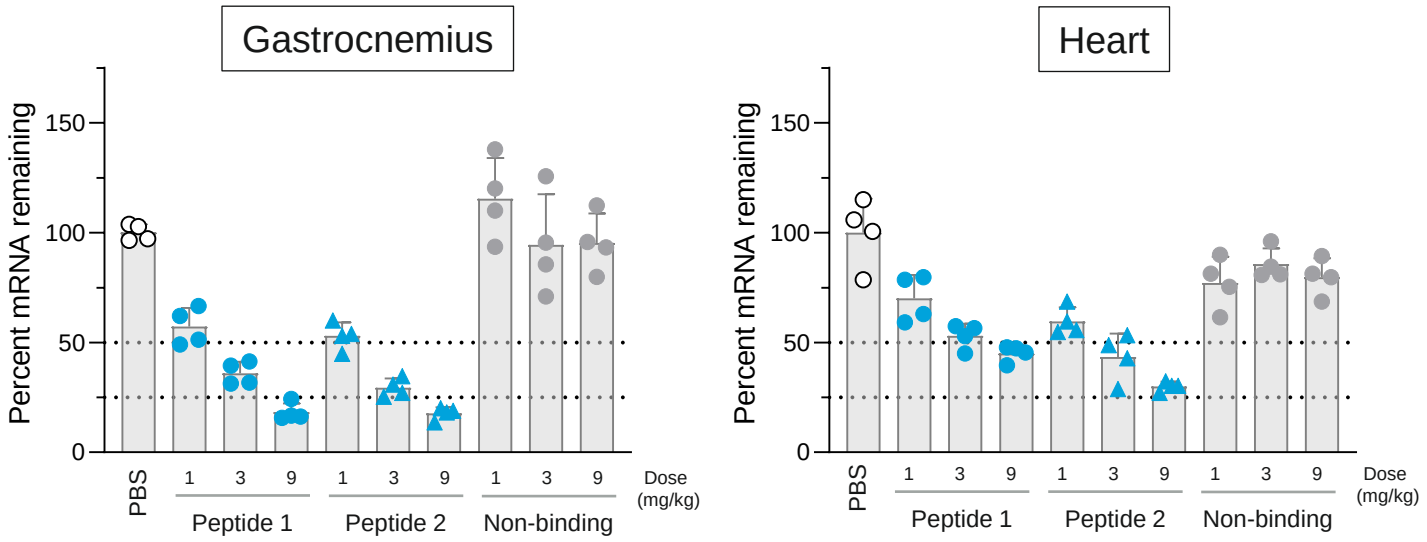
Alnylam®

Proprietary Muscle-Targeting Peptide Conjugates

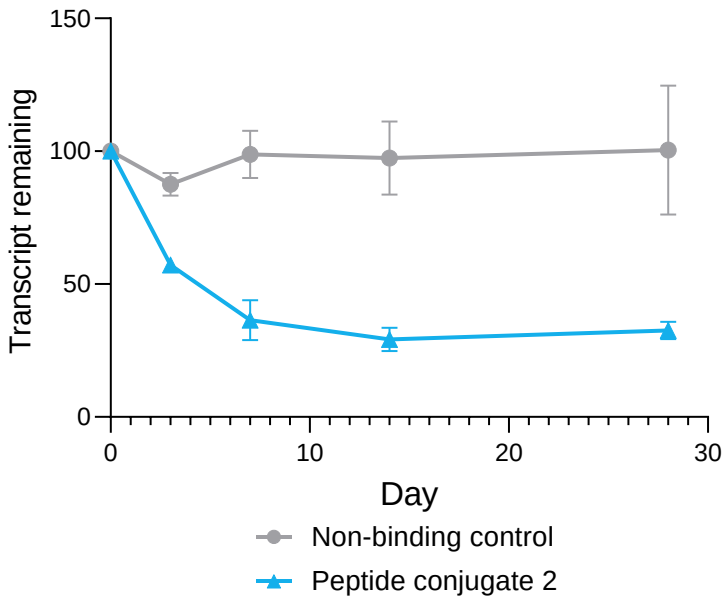
Robust and Durable Knockdown in Skeletal and Cardiac Muscle in Mice

Protein | **Peptide** | Small molecule

Robust and dose-dependent knockdown across multiple muscle types



Durable knockdown



IV dose; Day 7 time point for dose response study; 1 mg/kg dose for duration study

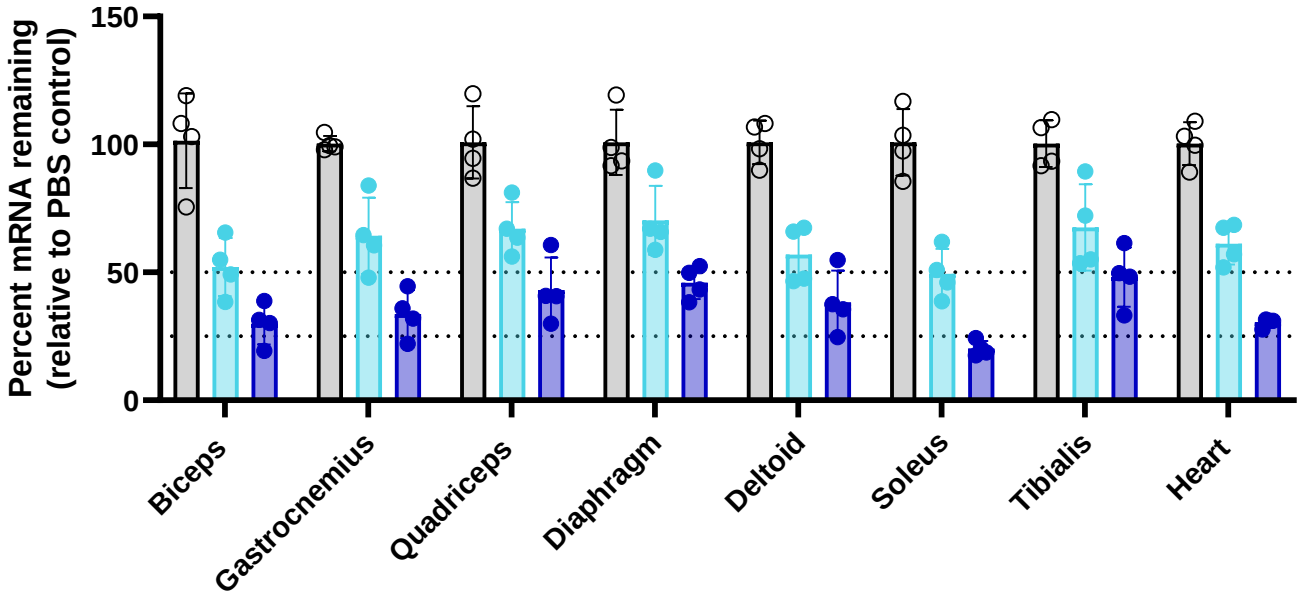
Alnylam®

Proprietary Muscle-Targeting Peptide Conjugates

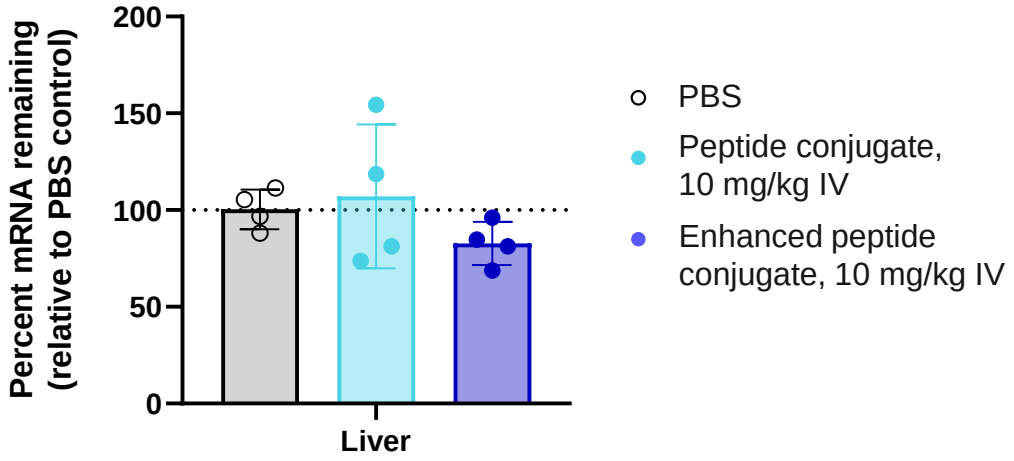
Robust Knockdown Across Skeletal and Cardiac Muscle in NHP

Protein | **Peptide** | Small molecule

Robust knockdown in skeletal and cardiac muscle



No knockdown in other tissues (e.g., liver)



- 50-80% mRNA knockdown observed across skeletal and cardiac muscle tissues with lead ‘enhanced’ peptide conjugate, developed through systematic optimization
- Highly specific; spares liver “sink”

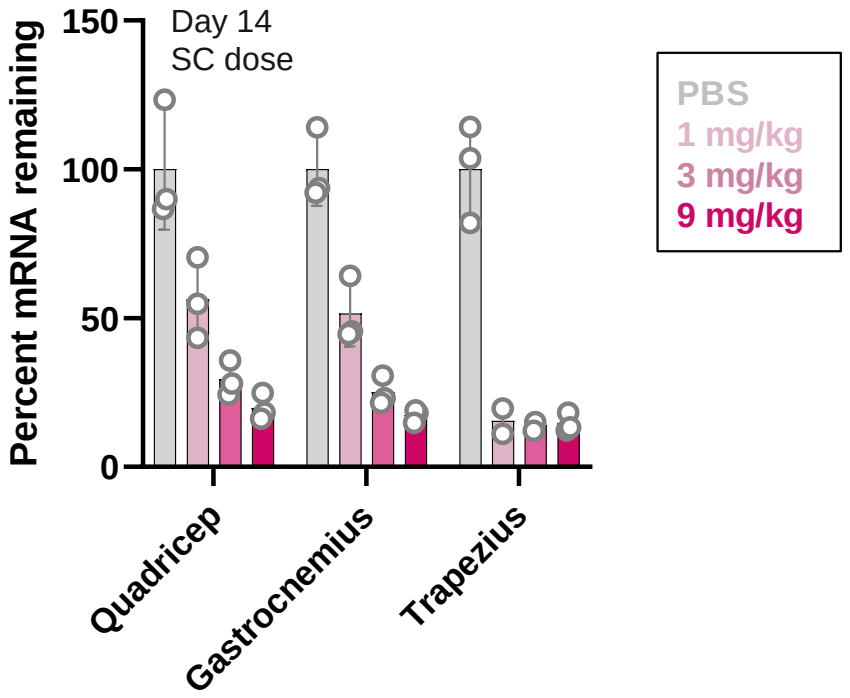
Alnylam®

Novel Muscle-Targeting Small Molecule Conjugate

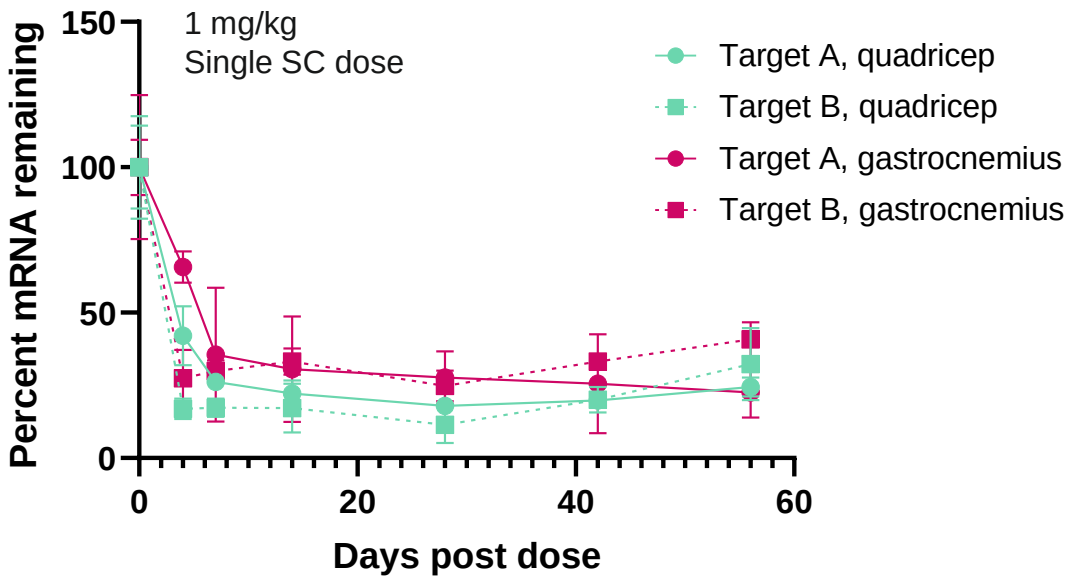
Robust and Sustained Knockdown in Mouse Muscle with SC Dosing

Protein | Peptide | **Small molecule**

Dose-dependent knockdown across multiple tissues



Rapid and durable knockdown across multiple targets



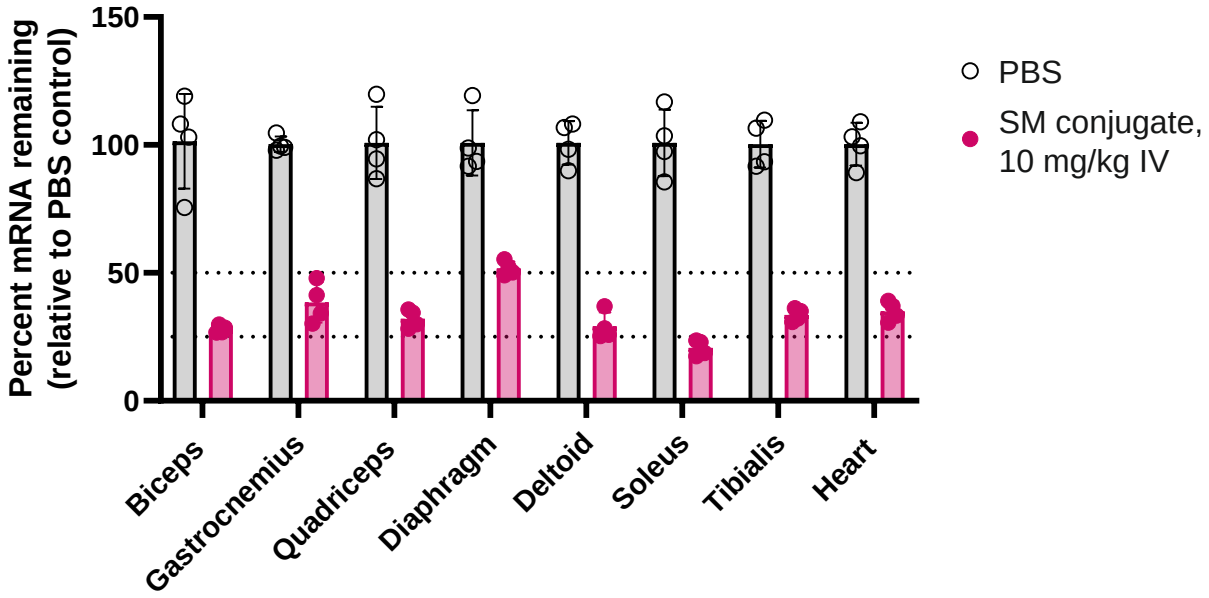
Alnylam®

Novel Muscle-Targeting Small Molecule Conjugate

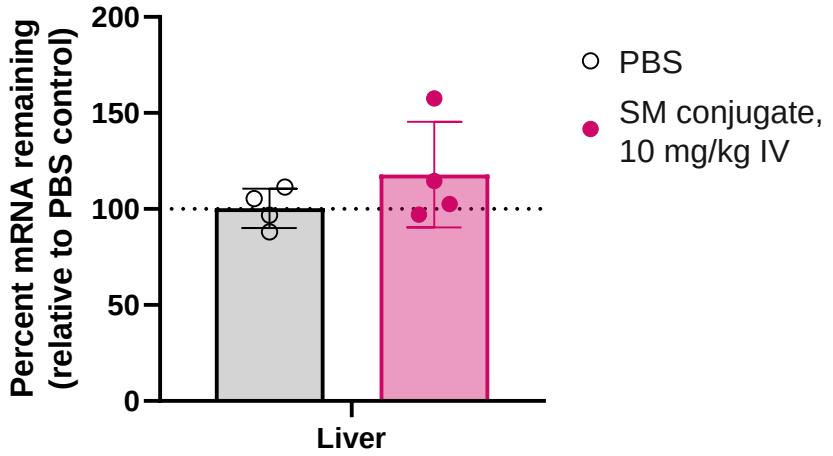
Robust Knockdown Across Skeletal and Cardiac Muscle in NHP

Protein | Peptide | **Small molecule**

Robust knockdown in skeletal and cardiac muscle



No knockdown in other tissues (e.g., liver)



- **Demonstrated NHP translation of two novel conjugates targeting two distinct receptors**

Development Candidate expected **2024**

IND expected **2025**

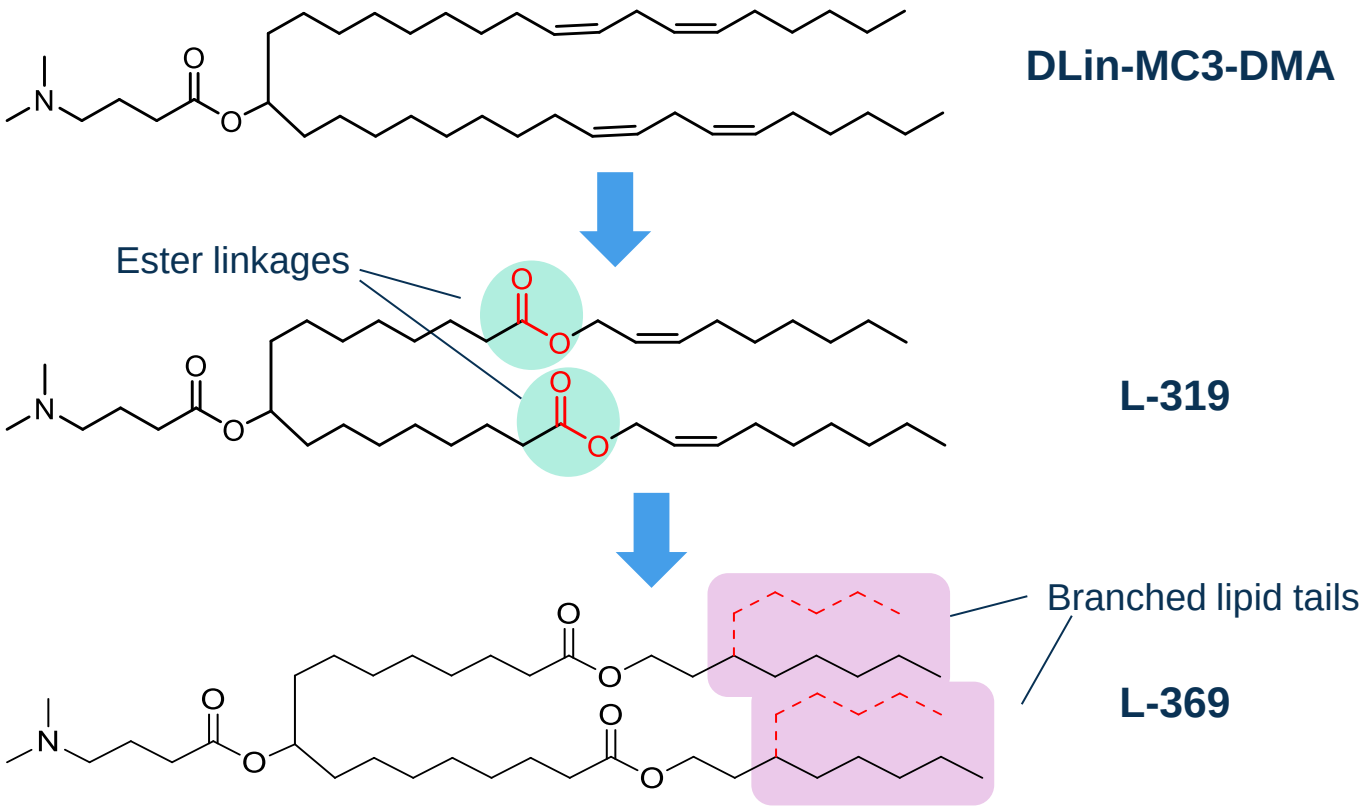
Alnylam®

Advances in reLNP

reLNP: Continuous Innovation in LNP Delivery

Rationale for rapidly eliminating LNP (reLNP) platform with biodegradable lipids:

Stable ionizable lipids found to be persistent *in vivo*, i.e., exhibit long elimination half-lives in plasma and tissues



reLNPs

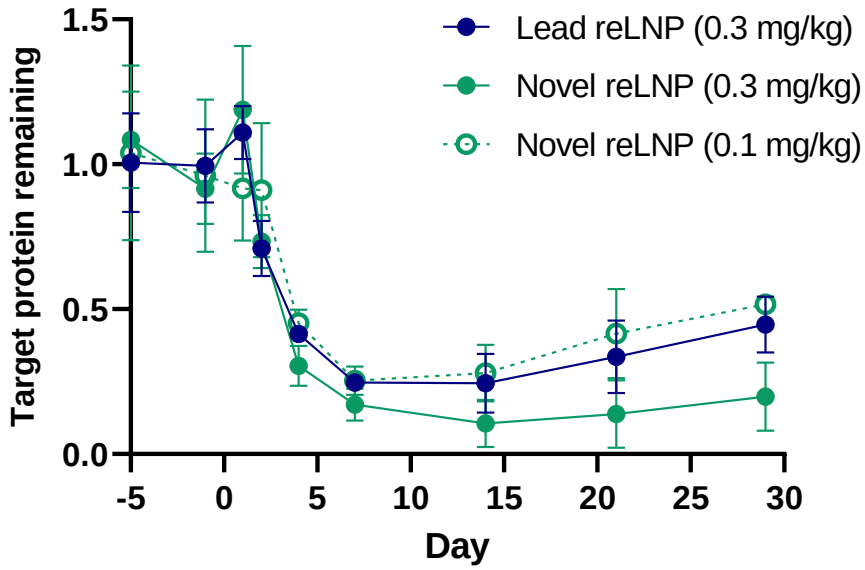
- New class of ionizable lipids with improved *in vivo* elimination profile
- Excellent translation across species, including NHP
- Wide safety margin
- Potential for efficient delivery of larger payload
- Generated expanded re-lipid family with ~25 individual compounds; additional structure-activity relationship characterization ongoing

Maier, M. et al. (2013) Molecular Therapy 21, 1570-78.

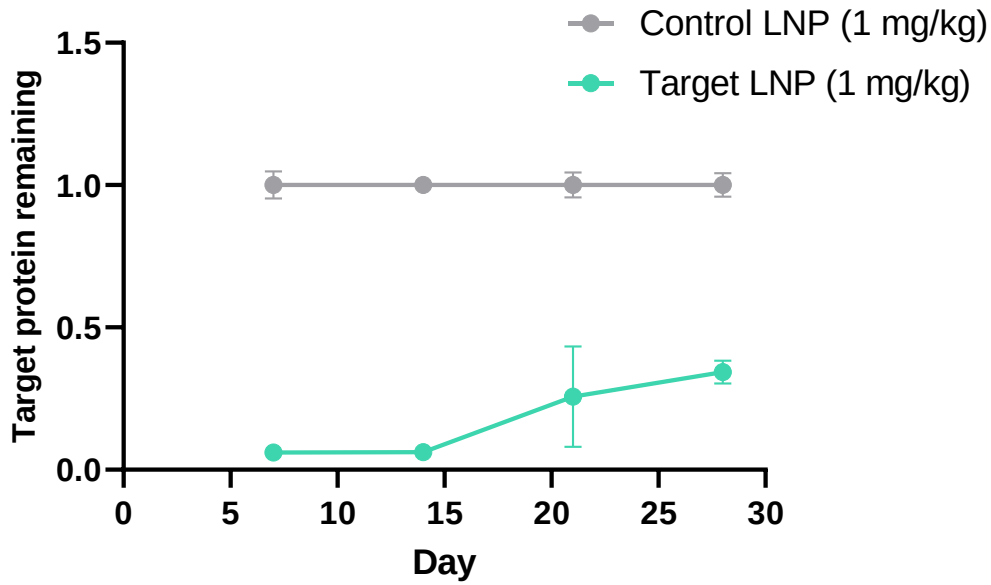
Alnylam®

Continued Advances in LNP Design and Formulation

~ 3-fold improved potency in NHP liver with new reLNP



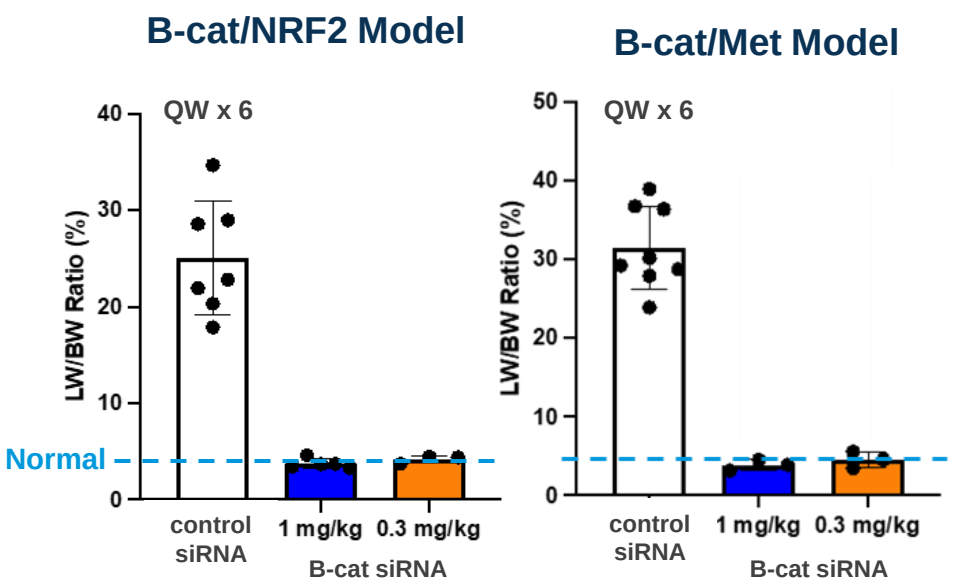
Potent and durable knockdown in mouse macrophages with new LNP formulation



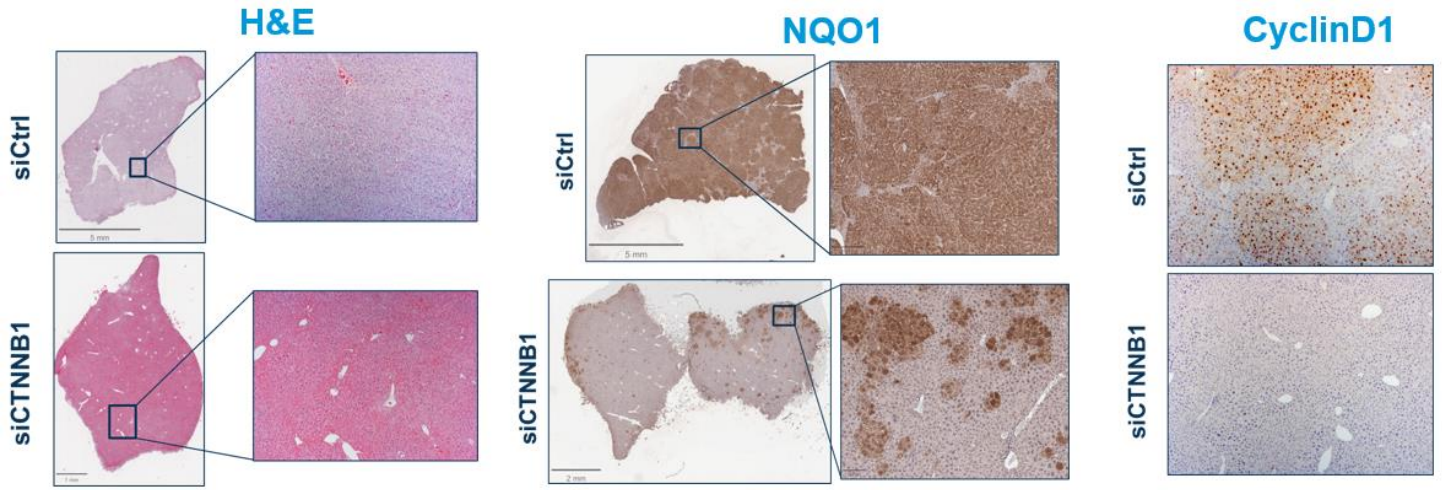
Harnessing the Power of RNAi for Oncology

ALN-BCAT: Targeting the WNT Pathway for Hepatocellular Carcinoma (HCC)

Liver-weight-to-body-weight ratio



Histology analysis



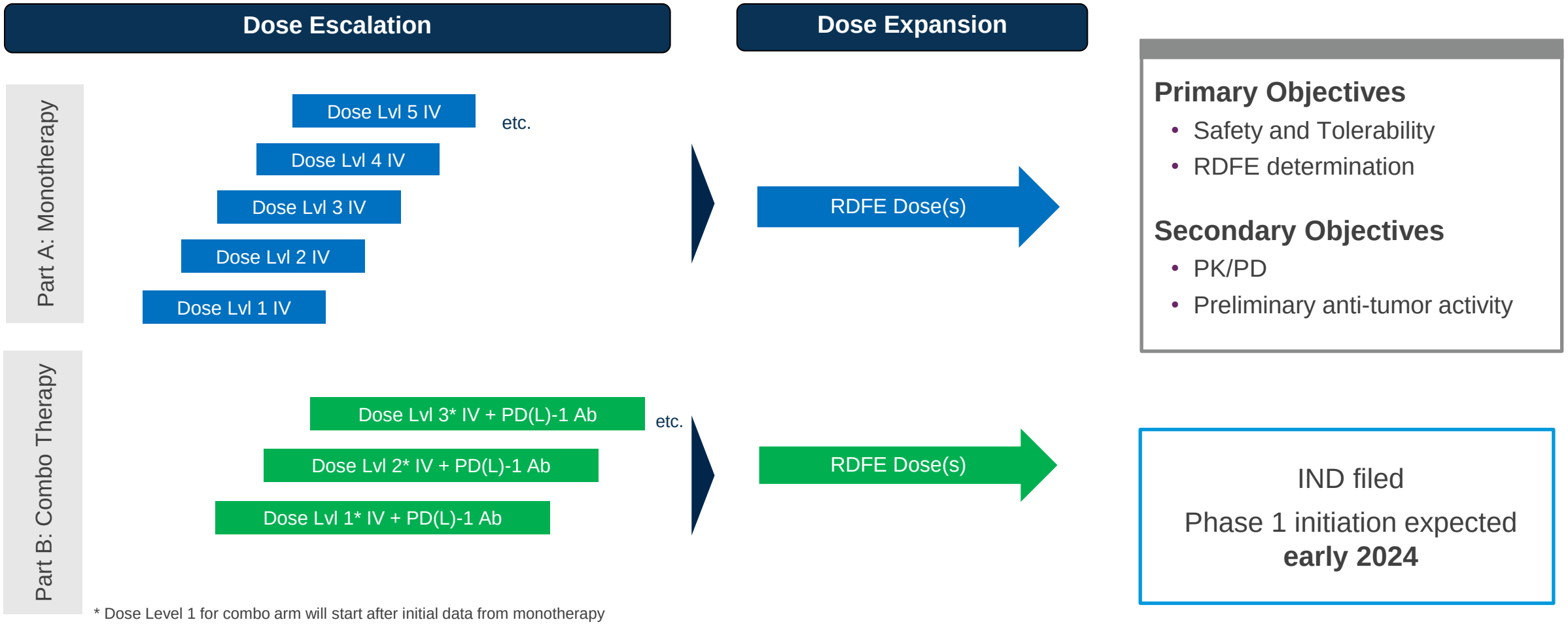
- ALN-BCAT shown to be efficacious across multiple genetic models of HCC
- Histological analysis demonstrates reduction of tumor burden

Studies conducted with ALN-BCAT surrogate siRNA sequence in collaboration with Paul Monga at University of Pittsburgh

Alnylam®

Advancing ALN-BCAT to Phase 1

Open-Label Dose Escalation Study as Monotherapy and Combo with Immunotherapy in Advanced HCC Patients



Primary Objectives

- Safety and Tolerability
- RDFE determination

Secondary Objectives

- PK/PD
- Preliminary anti-tumor activity

IND filed

Phase 1 initiation expected **early 2024**

* Dose Level 1 for combo arm will start after initial data from monotherapy

RDFE = Recommended Dose For Expansion

Alnylam®

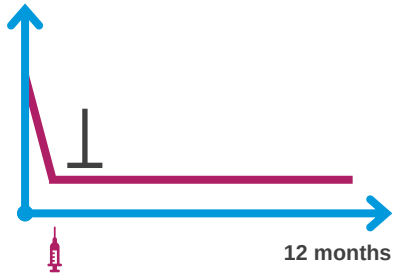
Advances in siRNA Designs

Alnylam®

State-of-the-Art Designs for RNAi Therapeutics

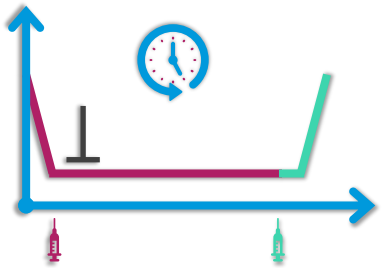
Over Two-Decade Track Record of RNAi Leadership

IKARIA™



- Annual dosing potential
- Promising profile with ALN-TTRsc04 in humans

Reversir™

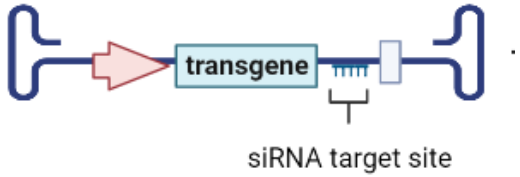


- Advanced to DC status

GEMINI™

- Simultaneous knockdown of two targets

Rheostat



- Reported RNAi-based switch for titratable AAV gene therapy[1]

[1]Subramanian *et al. Nature Communications* **14**, 1970 (2023)

Alnylam®

Driving a Large Multi-Organ Pipeline to Clinic by 2025

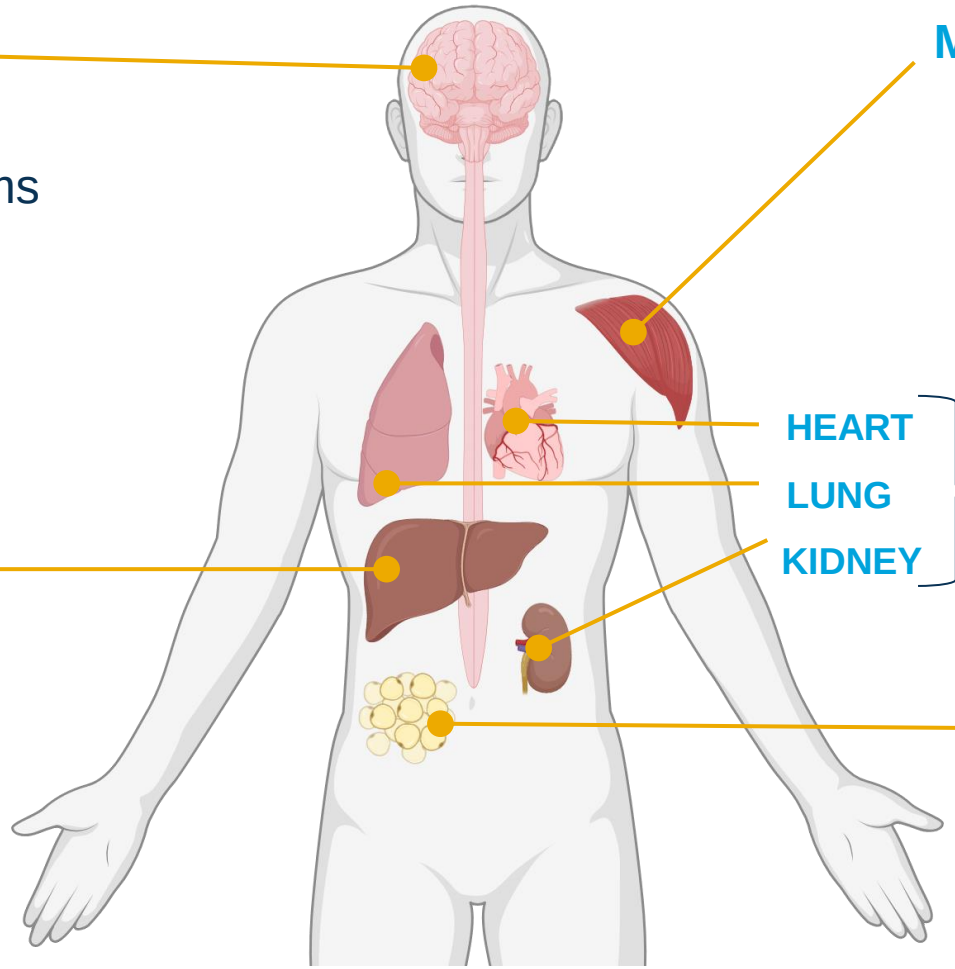
From Liver Delivery to CNS Human PoC; Now Advancing to Adipose, Muscle, and More

CNS

2 new ALNY-led CNS INDs
3+ including partnered programs

LIVER

5 new ALNY-led liver INDs
10+ including partnered programs



MUSCLE

First ALNY
IND by 2025

HEART
LUNG
KIDNEY

Preclinical PoC;
IND timelines TBD

ADIPOSE

First ALNY
IND by 2025

Going forward, we will also be targeting multiple tissues simultaneously

Alnylam®

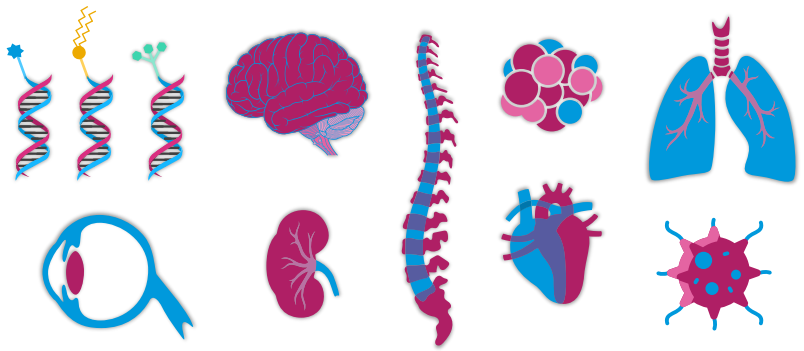
Next Wave of RNAi Therapeutics to Fuel Robust Clinical Pipeline

Paul Nioi, Ph.D.
SVP, Research

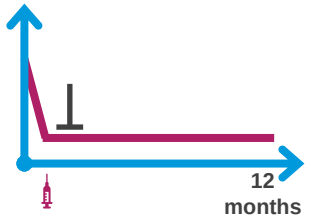
Anna Borodovsky, Ph.D.
VP, Research

Multiple Sources of Sustainable Innovation Drive Robust Pipeline

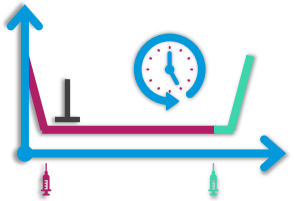
Extrahepatic Delivery



Platform Designs



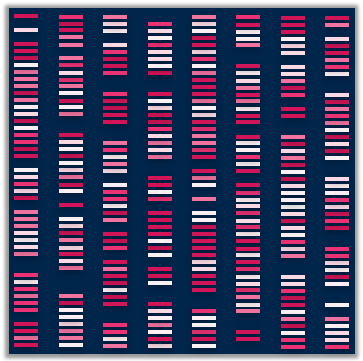
IKARIA™



Reversir™

GEMINI™

Human Genetics

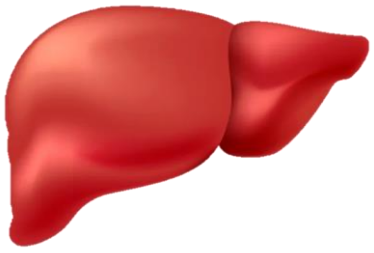


+ Our Future Health

discoverme

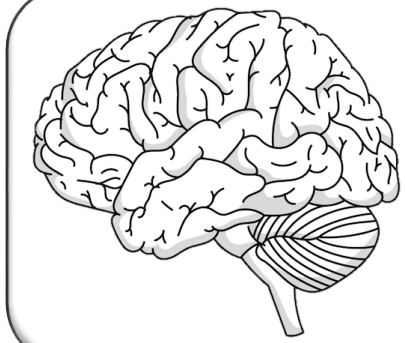
biobank uk

By end of 2025



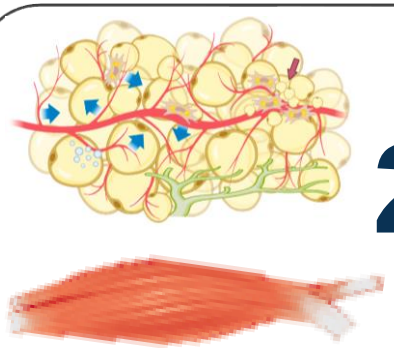
5 new **liver** INDs

10+ including partnered programs



2 new **CNS** INDs

3+ including partnered programs

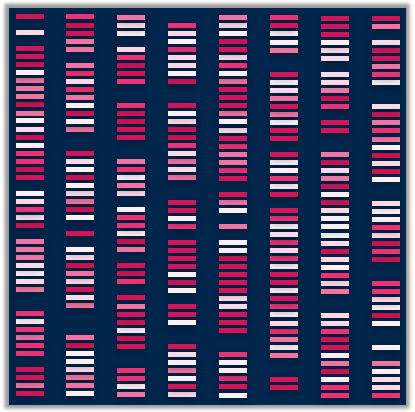


2 **new tissues** with INDs

Differentiated Pipeline of Genetically Validated Targets

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

Human Genetics



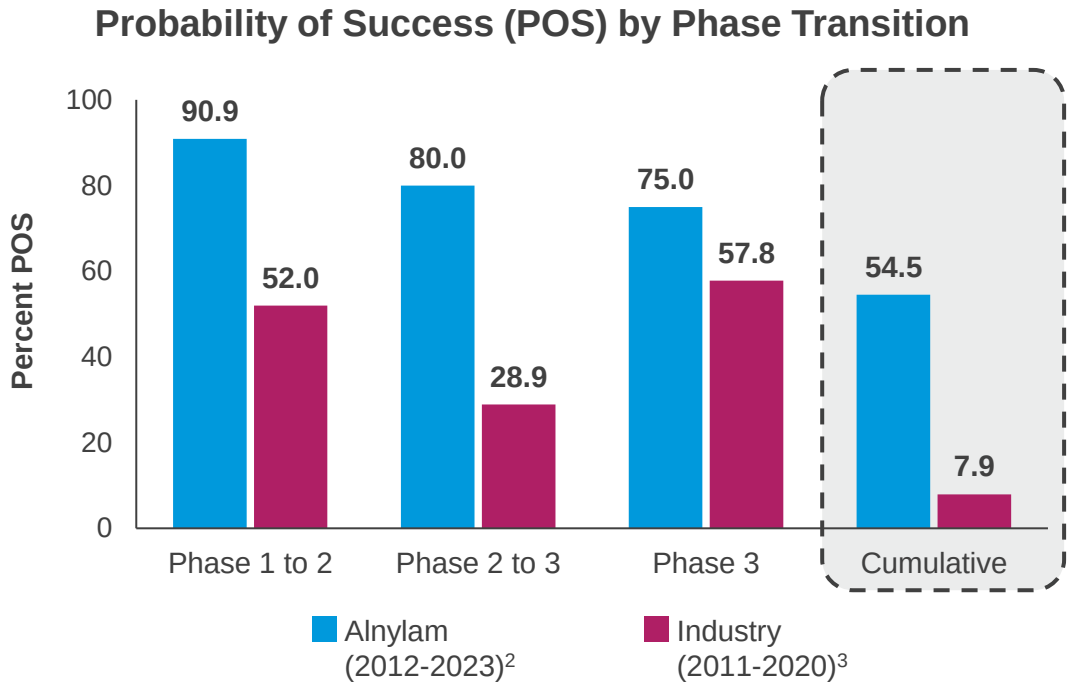
+ Our Future Health

discoverme

biobank uk

- Sourcing novel, genetically validated targets
- Secured access to large PheWAS databases
- Proven ability to uncover novel gene targets (e.g., *INHBE*, Gene Y for T2D, Gene D for AMD, and more)

Targets with High PoS[1]



[1] Past rates of Alnylam and industry respectively may not be predictive of the future

[2] Figures include Alnylam-originated molecules now being developed by partners

[3] https://www.bio.org/clinical-development-success-rates-and-contributing-factors-2011-2020

Alnylam®

Genetically Validated Pipeline Across Rare, Specialty and Prevalent Indications

Rare

Target/Drug	Indication	Stage
Gene B	Cholestatic liver disease	DC 2024
Gene F	Glutaric Acidemia	DC 2024
ALN-REGN1	TBA	IND-enabling
ALN-REGN2	TBA	IND-enabling
Patisiran	hATTR-PN	Approved
Vutrisiran	hATTR-PN	Approved
Givosiran	AHP	Approved
Lumasiran	PH1	Approved

Specialty

Target/Drug	Indication	Stage
Gene A	Bleeding disorders	IND-enabling
Gene G	Inflammatory disorders	DC 2023
Gene H	Pruritus	DC 2024
ALN-REGN3	TBA	IND-enabling
ALN-HBV	HBV Infection	Ph 2
Fitusiran	Hemophilia	Ph 3
Vutrisiran	ATTR-CM	Ph 3

Prevalent

Target/Drug	Indication	Stage
INHBE	Obesity	DC 2024
Gene C	Obesity	DC 2024
Gene D	Obesity	DC 2024
Gene Y	T2DM	IND-enabling
ALN-KHK	T2DM	Ph 1
ALN-PNP	NASH	Ph 1
ALN-HSD	NASH	Ph 2
Zilebesiran	Hypertension	Ph 2
Leqvio	Hyperlipidemia	Approved

Genetically Validated Targets

ALNY proprietary Partnered DC = Development Candidate; TBA = To Be Announced

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Genetically Validated Targets

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Gene A: Differentiated Opportunity in Bleeding Disorders

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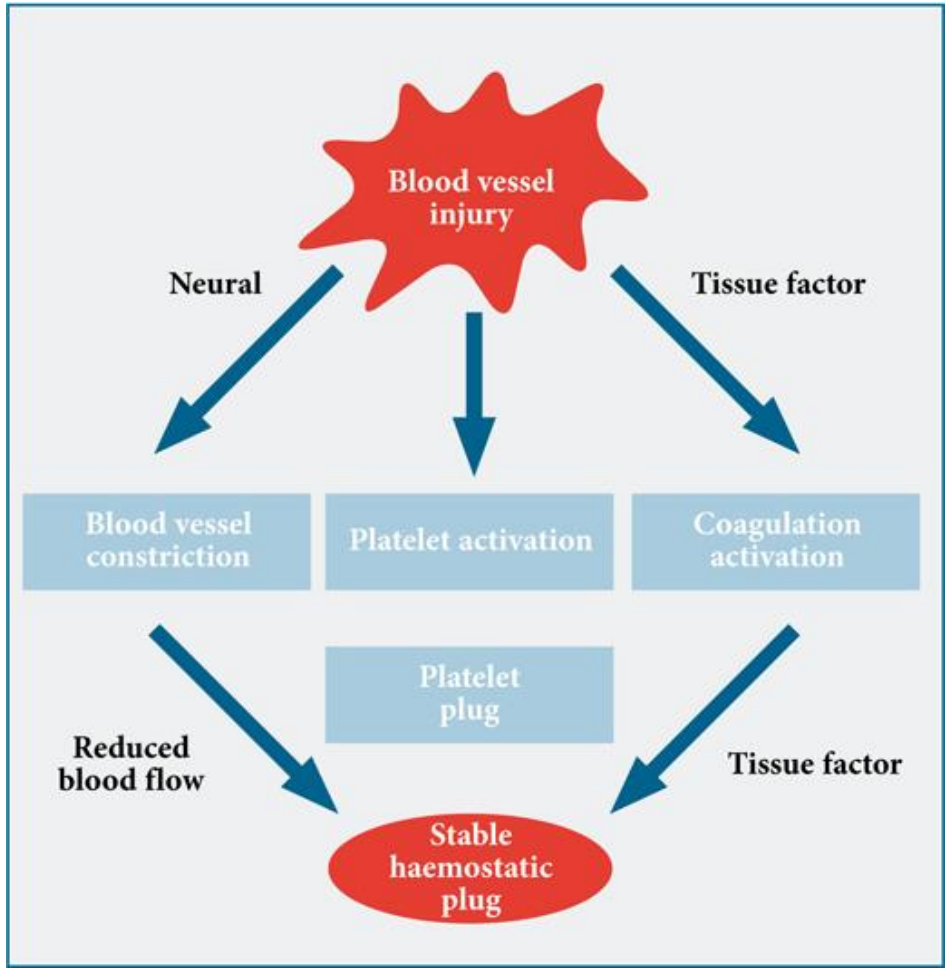
No Universal Hemostatic Agent for Bleeding Disorders

Unmet Need Remains for Hemostatic Agent that Does Not Increase Risk of Thrombosis

Vessel wall defects
- e.g. Hereditary hemorrhagic telangiectasia, angiodysplasia

Factor deficiency
- e.g. HemA, Von Willebrand disease

Platelet disorders
- e.g. Glanzmann's thrombasthenia



Lack of treatment options

Current therapies increase risk of thrombosis

High treatment burden

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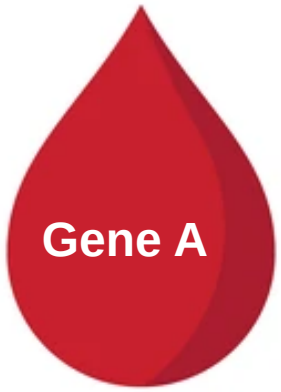
UK Biobank Analyses Support Targeting Gene A in Bleeding Disorders



↑ Circulating Gene A protein levels

- ↑ Heavy Menstrual Bleeding
- ↑ GI bleeding

Gene A loss of function

- ↓ Heavy Menstrual Bleeding
- ↓ GI 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 serum level)	p value
Protein S	1.23	2e-24
Protein C	1.11	1e-06
Gene A	**1.00**	**0.91**

In house proteomics analyses

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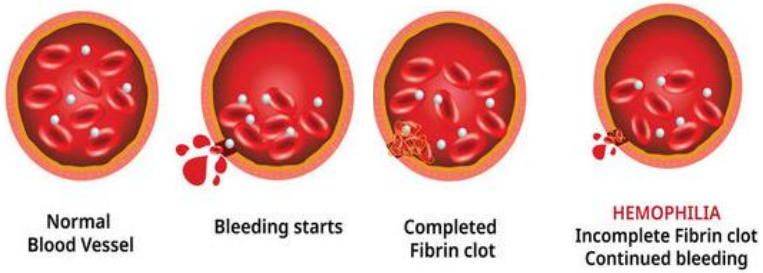
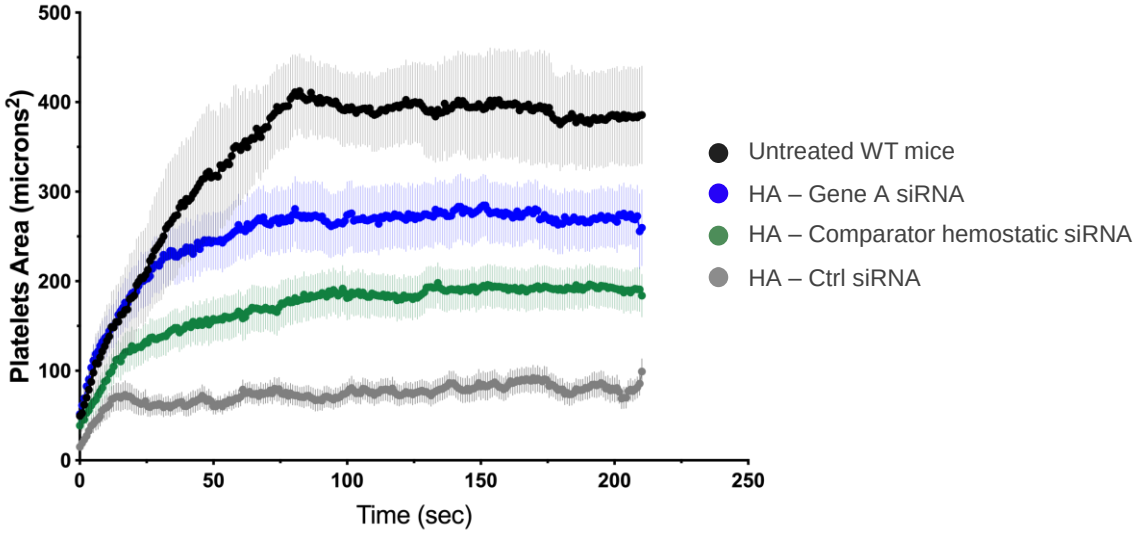
Gene A siRNA Improves Hemostasis in Hemophilia A mice

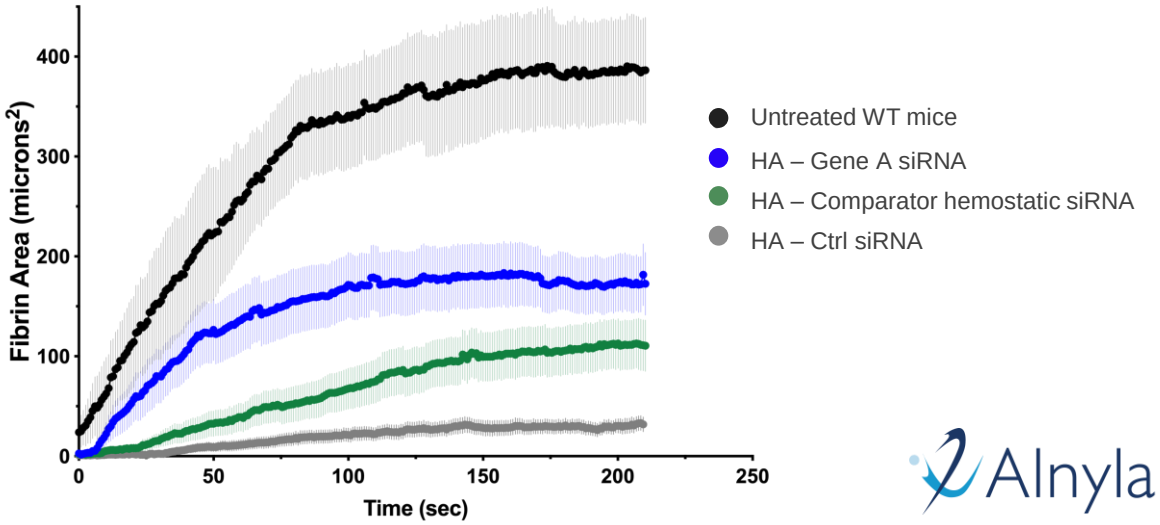
siRNA dose → 14 days → Assessment of platelet and fibrin at vessel laser injury site



Platelet accumulation



Fibrin accumulation



In collaboration with Drs. R. Camire and L. Ivanciu at Children's Hospital of Philadelphia

Alnylam®

Normal Thrombotic Response in Wild-Type Mice with Gene A Silencing

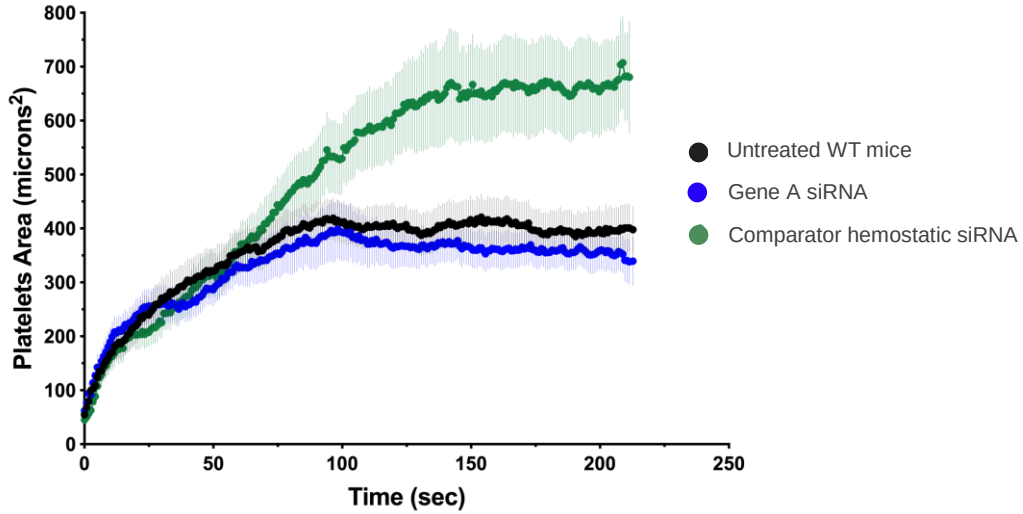
siRNA dose → 14 days → Assessment of platelet and fibrin at vessel laser injury site

Silencing of Gene A:

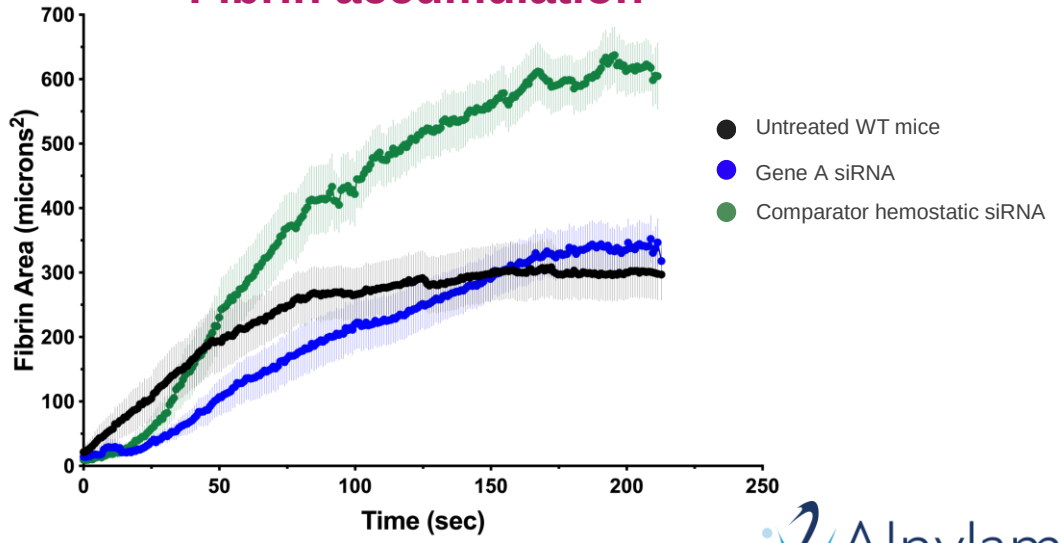
Improves hemostasis in Hemophilia A mice

Normal thrombotic response in WT mice

Platelet accumulation



Fibrin accumulation



In collaboration with Drs. R. Camire and L. Ivanciu at Children's Hospital of Philadelphia

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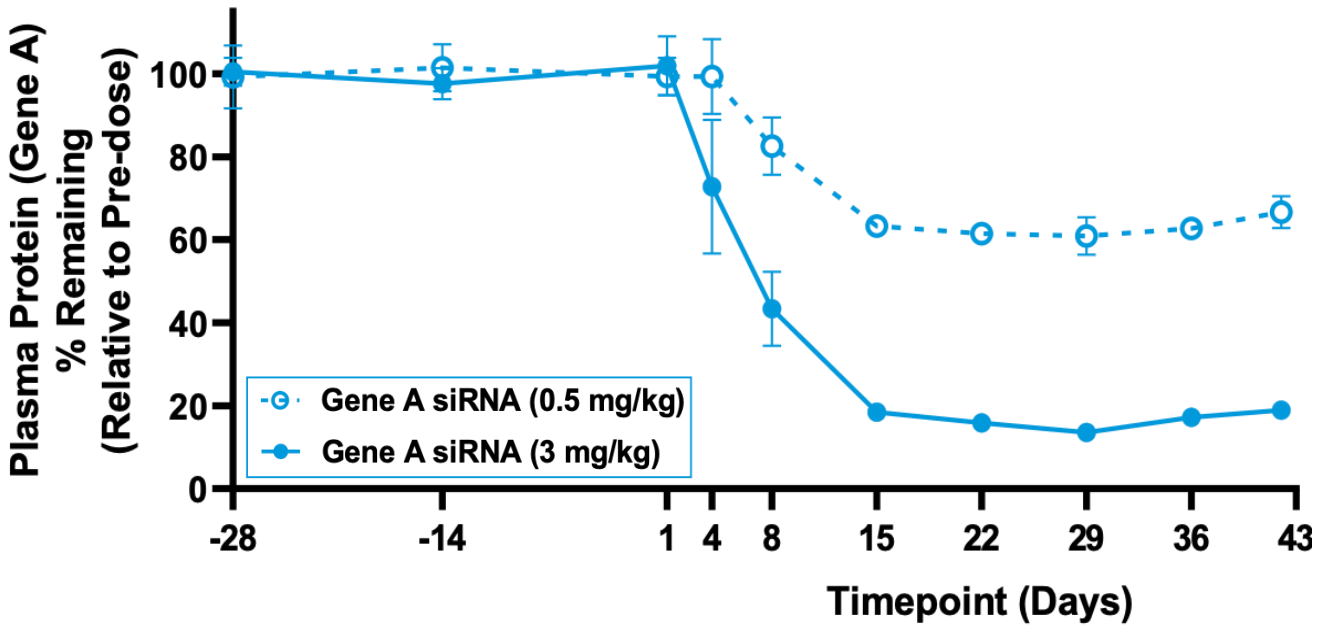
Gene A GalNAc-siRNA: A Potential Universal Hemostatic Agent

Deep and Durable Knockdown Achieved in Non-Human Primate



- Gene A silencing has potential to address hemostasis in multiple bleeding disorders
  - Vessel wall defects
  - Factor deficiency
  - Platelet disorders
- Targeting of Gene A could result in improved hemostasis without increased thrombotic risk

ALN-Gene A
IND expected in **2024**

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Gene B: Innovative Approach to Cholestatic Disease

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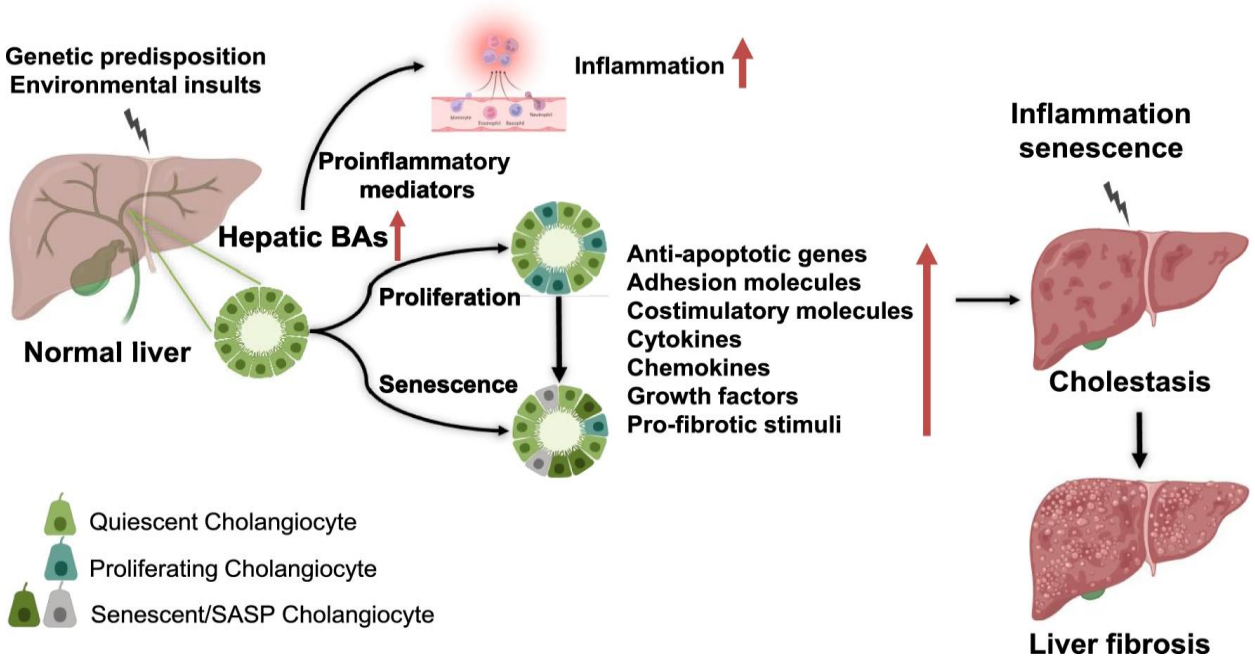
Cholestatic Liver Disease – Cholestasis, a Unifying Mechanism

Targeting Gene B to Improve Bile Flow and Cholestasis



Disease	Primary biliary cholangitis	Primary sclerosing cholangitis	Progressive familial intrahepatic cholestasis
Pathophysiology	Autoimmune	Autoinflammatory?	Genetic defect in bile transport
Cholestatic mechanism	Yes	Yes	Yes
US prevalence	~100K	~25K	~3K

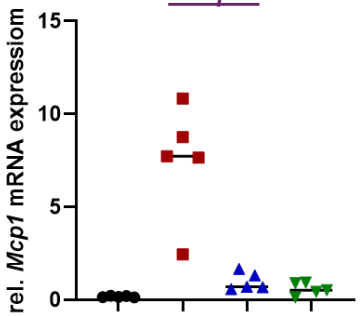
https://cellandbioscience.biomedcentral.com/articles/10.1186/s13578-023-01035-1

Gene B Knockdown Highly Protective Against DDC-Induced Bile Duct Damage

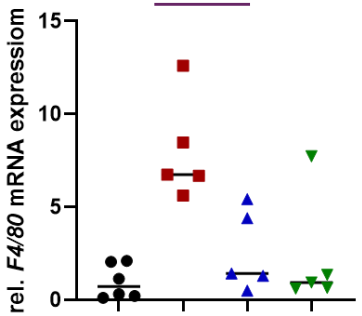
Improvements in Markers of Inflammation, Ductular Reaction, and Fibrosis

Inflammation

Mcp1

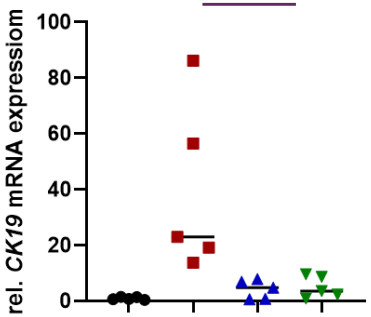


F4/80

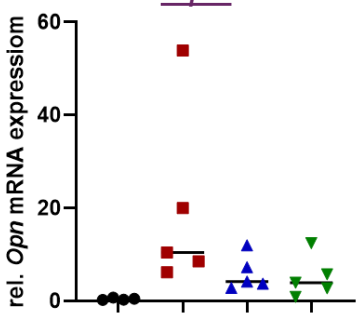


Ductular reaction

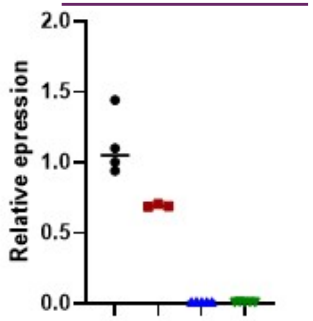
CK19



Opn

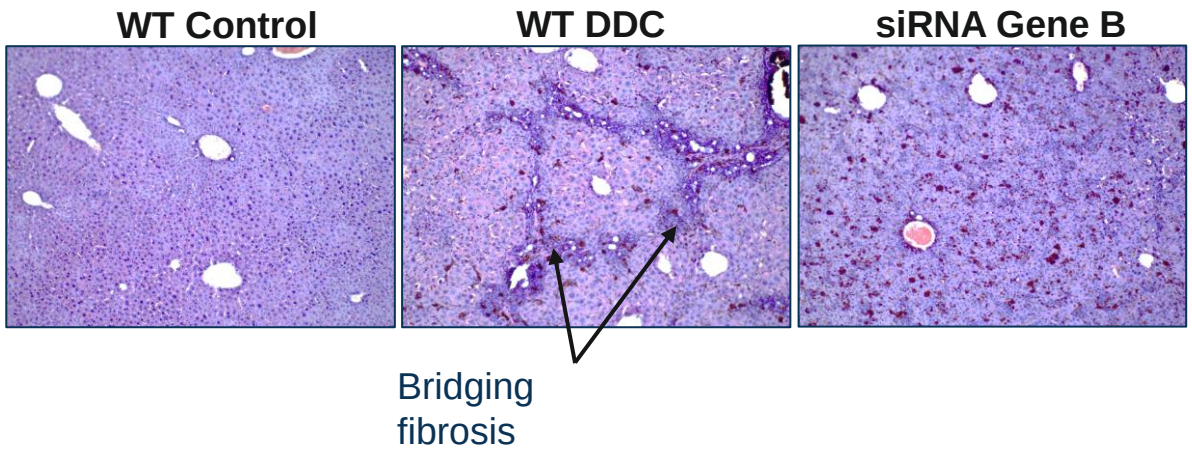


Gene B mRNA

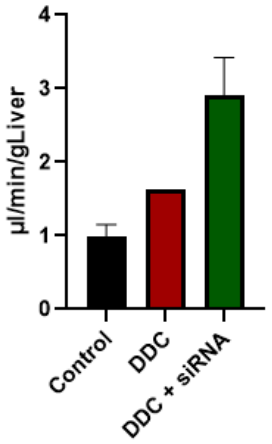


- No DDC control
- DDC, no siRNA
- DDC, Gene B siRNA #1
- DDC, Gene B siRNA #2

Fibrosis



Bile Flow



DC expected in 2024

Fuchs & Trauner DDC- 3,5-Diethoxycarbonyl-1,4-Dihydrocollidine

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Leqvio	Hyperlipidemia	Approved

Genetically Validated Targets

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New Horizons: Genetically Validated siRNA Targets for Cardiometabolic Disease

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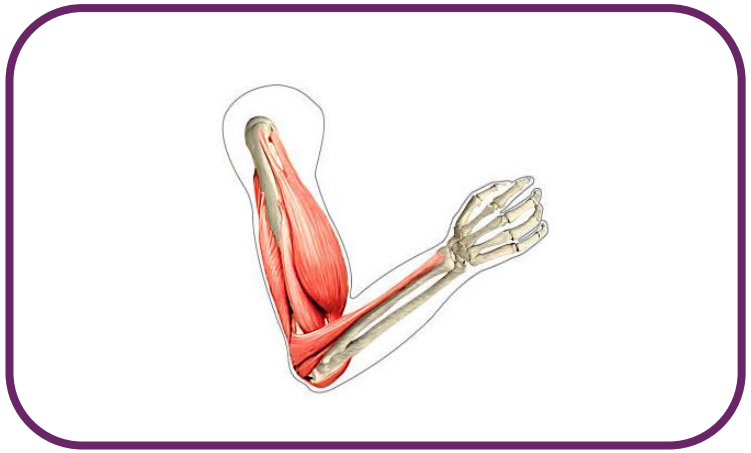
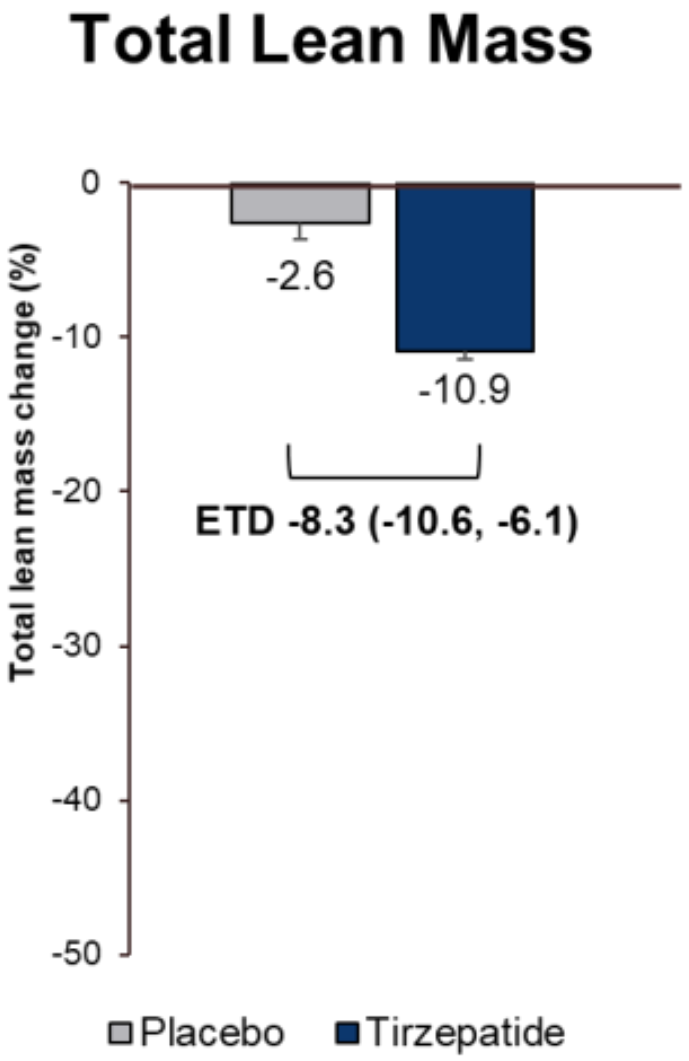
GLP-1 Receptor Agonists Redefine Unmet Need in Obesity



Loss of lean mass

30-40% of weight loss



Muller TD, et al Anti-obesity drug discovery: advances and challenges. Nature Reviews Drug Discovery 2022; 21, 201–223 ; Wilding JPH, BatterhamRL, CalannaS, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021;384(11):989-1002; Jastreboff AM, et al Tirzepatide Once Weekly for the Treatment of Obesity. NEJM 2022; 387 (3): 205-216; Diabetes Obes Metab.2022;24:1553–1564.

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GLP-1 Receptor Agonists Redefine Unmet Need in Obesity

Tolerability

~50% persistence at 1 year

Adverse Event	Semaglutide (N=1306)			Placebo (N=655)		
	No. of participants (%)	No. of events	Events/100 person-yr	No. of participants (%)	No. of events	Events/100 person-yr
Any adverse event	1171 (89.7)	9658	566.1	566 (86.4)	3302	398.0
Serious adverse events	128 (9.8)	164	9.6	42 (6.4)	53	6.4
Adverse events leading to discontinuation of drug or placebo	92 (7.0)	123	7.2	20 (3.1)	23	2.8
Gastrointestinal disorders	59 (4.5)	78	4.6	5 (0.8)	5	0.6

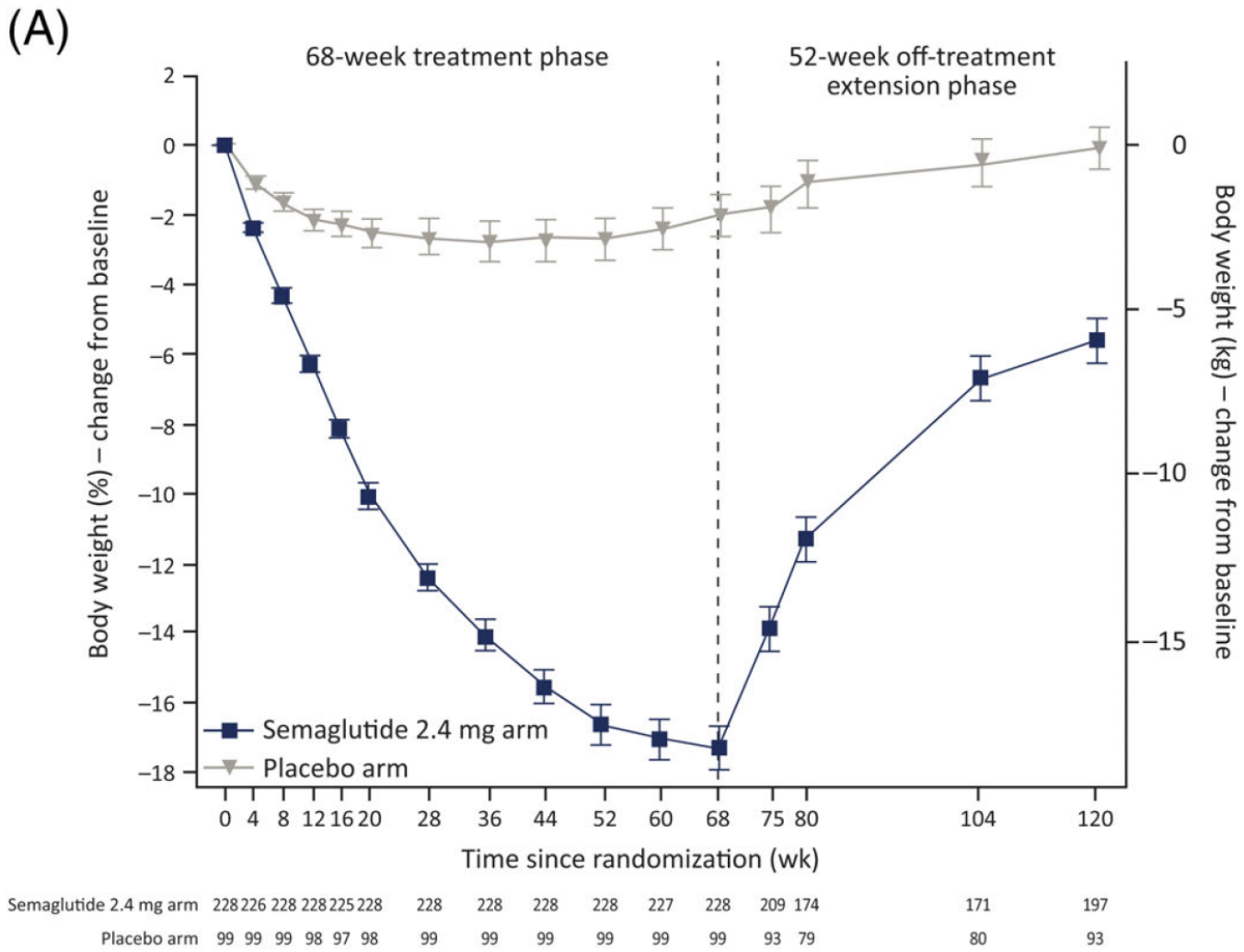
Mody et al., Clin Ther 2022;44(4):537-554; Uzoigwe at al., Diabetes Ther 2021;12(5):1475-1489

GLP-1 Receptor Agonists Redefine Unmet Need in Obesity

Weight regain

2/3 of weight lost regained

1-year post-treatment



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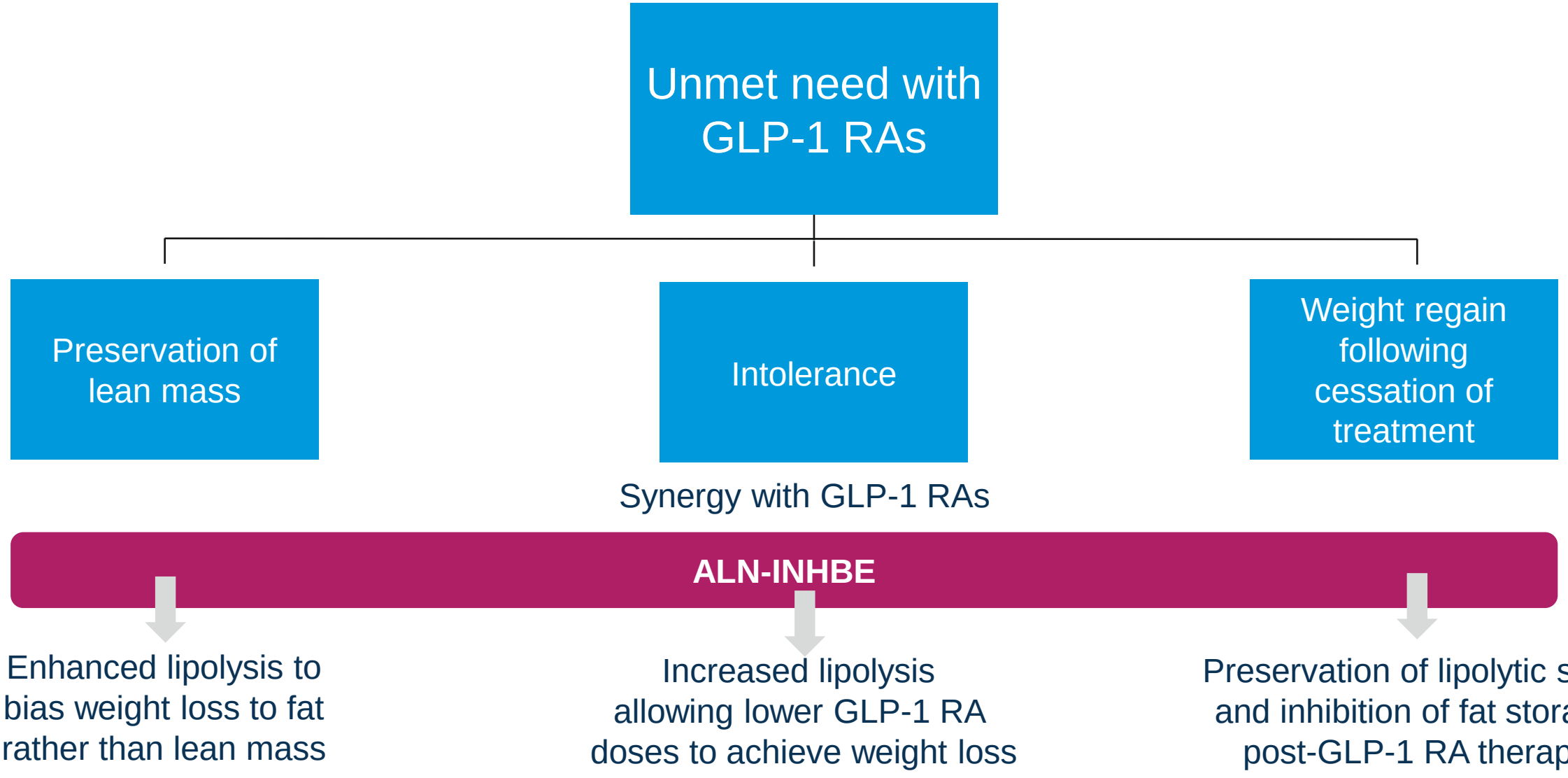
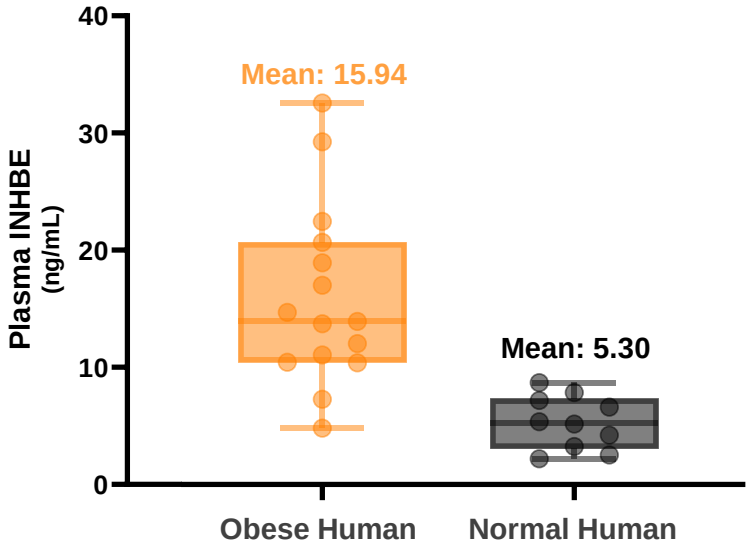
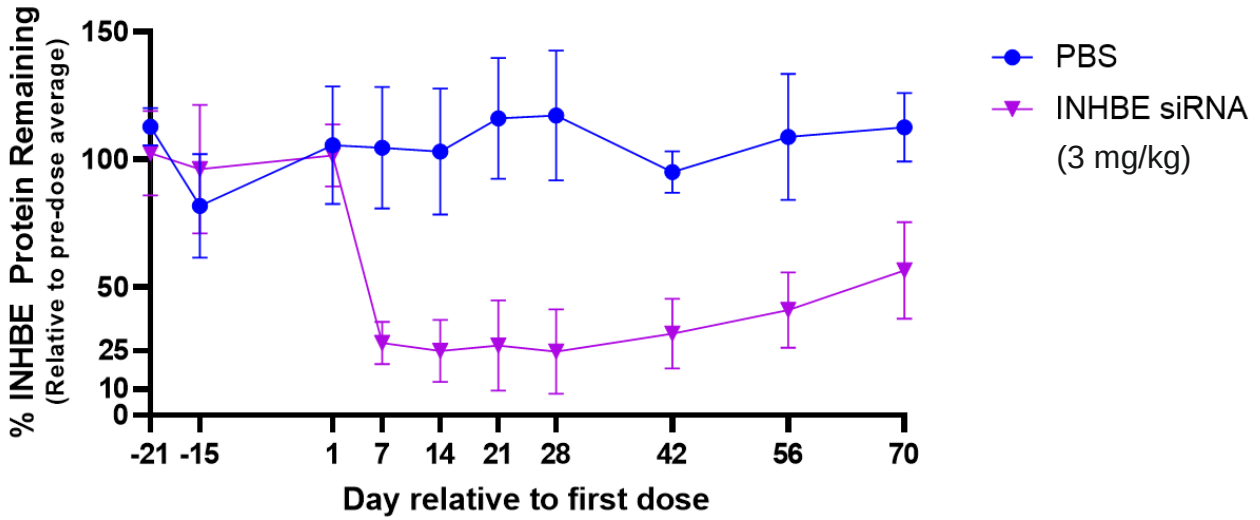


Robust INHBE Silencing in NHP with GalNAc-siRNA

INHBE Levels are Elevated in Human Obesity



NHP Silencing with INHBE GalNAc siRNA



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Lipolysis Markers Increased in INHBE Loss-of-Function Carriers

INHBE LOF Carriers Show Evidence of Lipolysis with No Impact on Muscle Markers

Trait	Variant set (UKB 470k exomes)	P-value	Effect (standard deviations)	N carriers measured	
Waist-to-hip ratio (adjusted for BMI)	*INHBE* LOF	3.13E-08	-0.17	950	
3_Hydroxybutyrate	*INHBE* LOF	1.29E-03	0.22	209	Fat loss
Acetone	*INHBE* LOF	4.24E-03	0.19	212	
Acetate	*INHBE* LOF	0.04	0.14	212	
Hand grip strength	*INHBE* LOF	0.45	-0.02	951	Muscle maintenance
Creatinine	*INHBE* LOF	0.45	-0.02	906	
Whole body fat free mass	*INHBE* LOF	0.66	0.01	922	

Increasing lipolysis without causing a catabolic state in muscle is promising for a combination with incretin and could allow weight loss maintenance and lowering of incretin dose reducing side effects

On track for ALN-INHBE DC in 2024

1. Deaton et al., Nat Comm 2022 https://doi.org/10.1038/s41467-022-31757-8
2. Akbari et al, Nat Comm 2022 https://doi.org/10.1038/s41467-022-32398-7
3. Adam et al, PNAS 2023 https://www.pnas.org/doi/full/10.1073/pnas.2309967120

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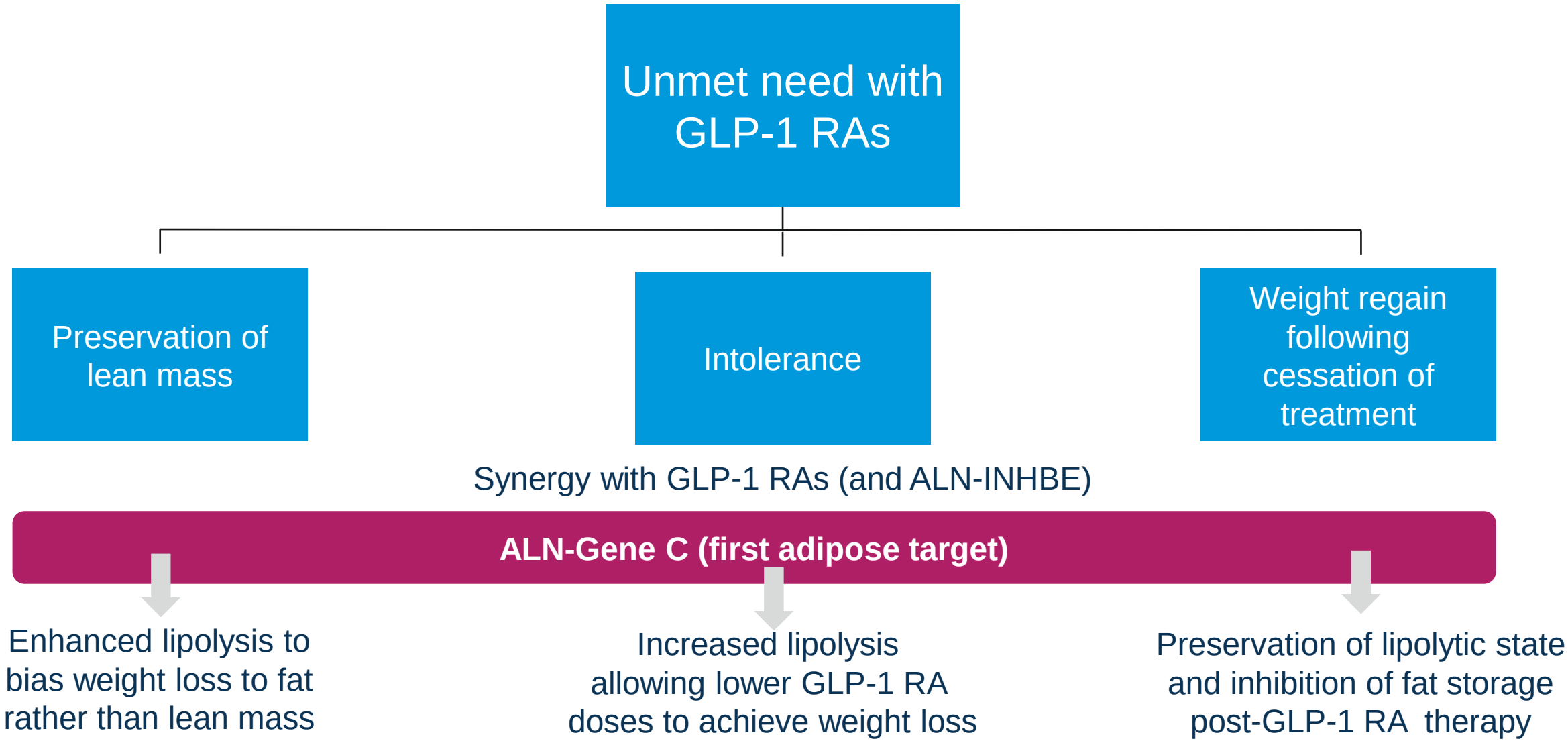
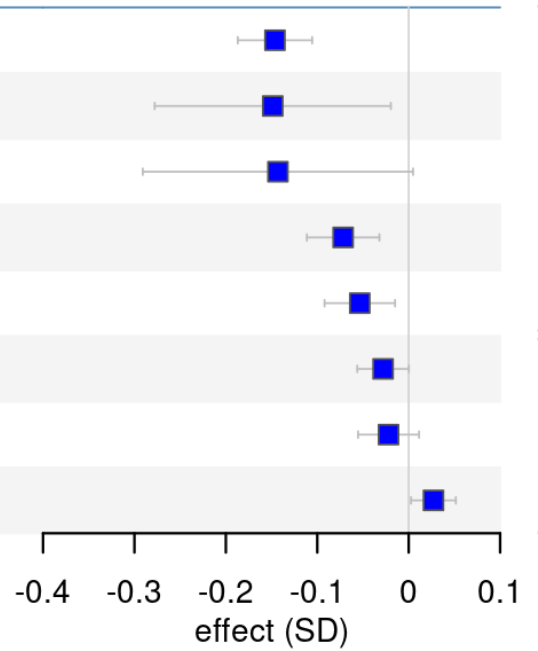
GLP-1 Receptor Agonists Redefine Unmet Need in Obesity



Gene C Rare Variants Associate with Favorable Metabolic Profile and Protection From Type 2 Diabetes

- *Gene C* LOF + damaging missense variants associate with lower waist-to-hip ratio (adjusted for BMI), lower visceral and liver fat, lower triglycerides, and lower HbA1c with no impact on lean mass

Trait	P-value	N carriers
Waist-to-hip ratio	1.8e-12	2067
Visceral adipose volume	0.02	167
Liver fat	0.06	161
Triglycerides	3.9e-04	1970
HbA1c	6.6e-03	1968
Grip strength	0.05	2066
Creatinine	0.19	1971
Whole body fat free mass	0.03	2029



Loss of visceral fat

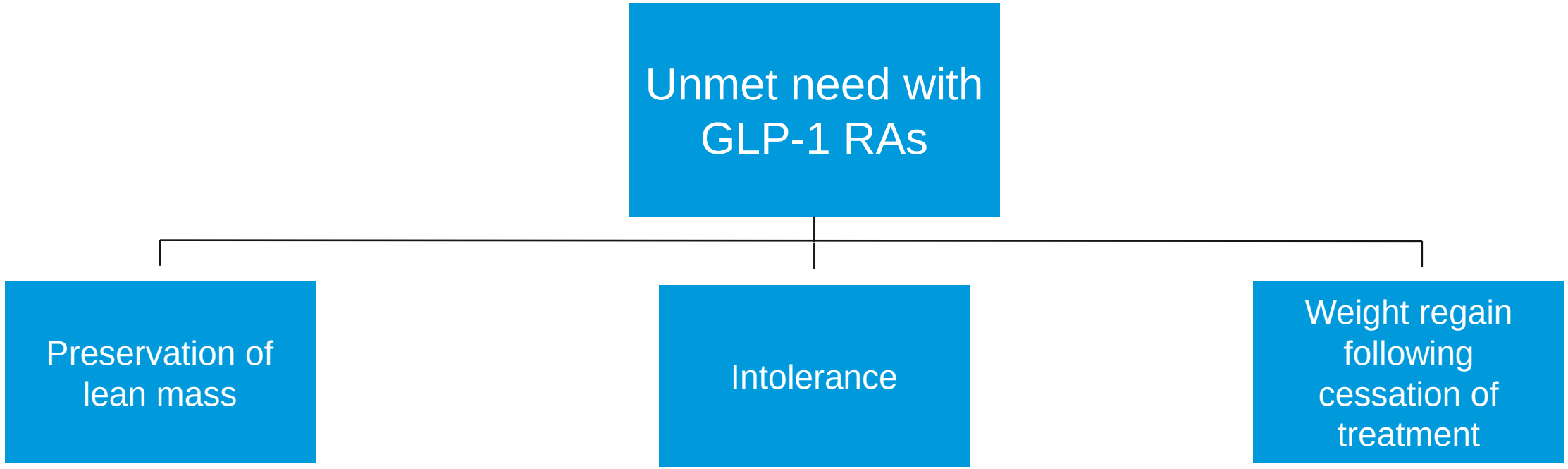
Muscle maintenance

title	Variant set	pvalue	Odds ratio
Type 2 diabetes	*Gene C* LOF+missense	0.003	0.77

On track for ALN-Gene C DC in 2024

Alnylam

Substantial Opportunity for Alnylam Medicines to Synergize with GLP-1 RAs and Improve Outcomes in Obesity



Alnylam opportunities to synergize with GLP-1 RAs

ALN-INHBE

ALN-Gene C (first adipose target)

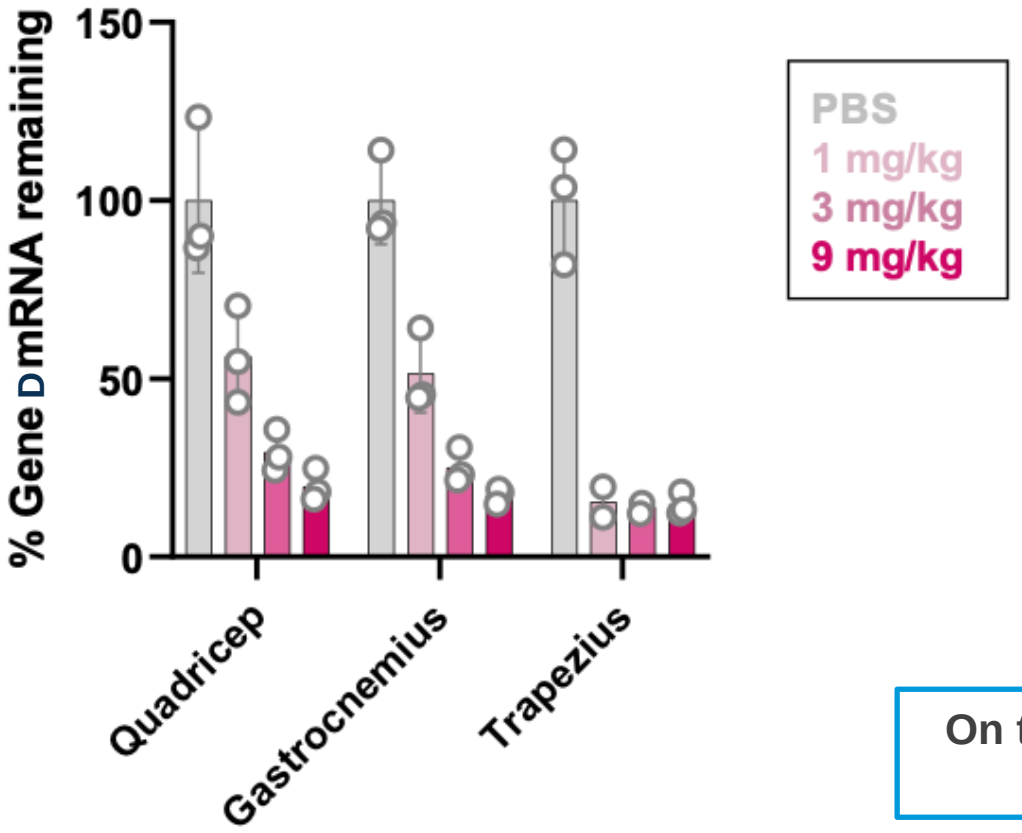
ALN-Gene D (first muscle target)

Alnylam®

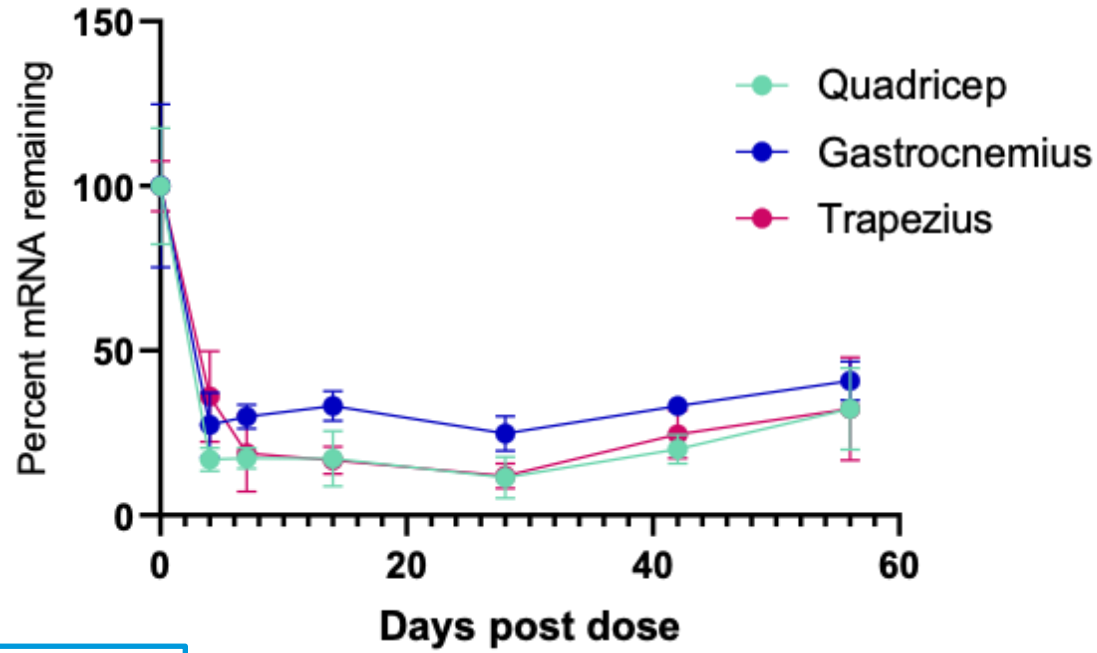
Novel Conjugate Allows Robust Silencing of Gene D in Mice

Gene D is genetically validated with loss-of-function carriers having substantially increased muscle mass

Gene D silencing across muscle groups



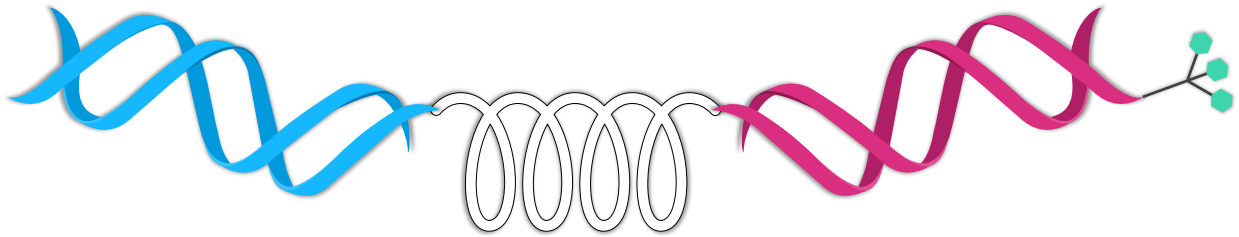
Rapid and durable knockdown of Gene D



On track for ALN-Gene D DC in 2024

Alnylam

Potential for Combinations in Obesity with GEMINI™ Platform



Combination of 2+ siRNAs to achieve desired clinical profile

ALN-INHBE + **ALN-Gene C** + **ALN-Gene D**

Single Q3M – Q6M subcutaneous injection to address obesity

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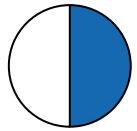
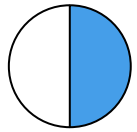
Therapeutic Unmet Need for T2D Remains Given Progressive Nature of Disease and Poor Attainment of HbA1c Goals

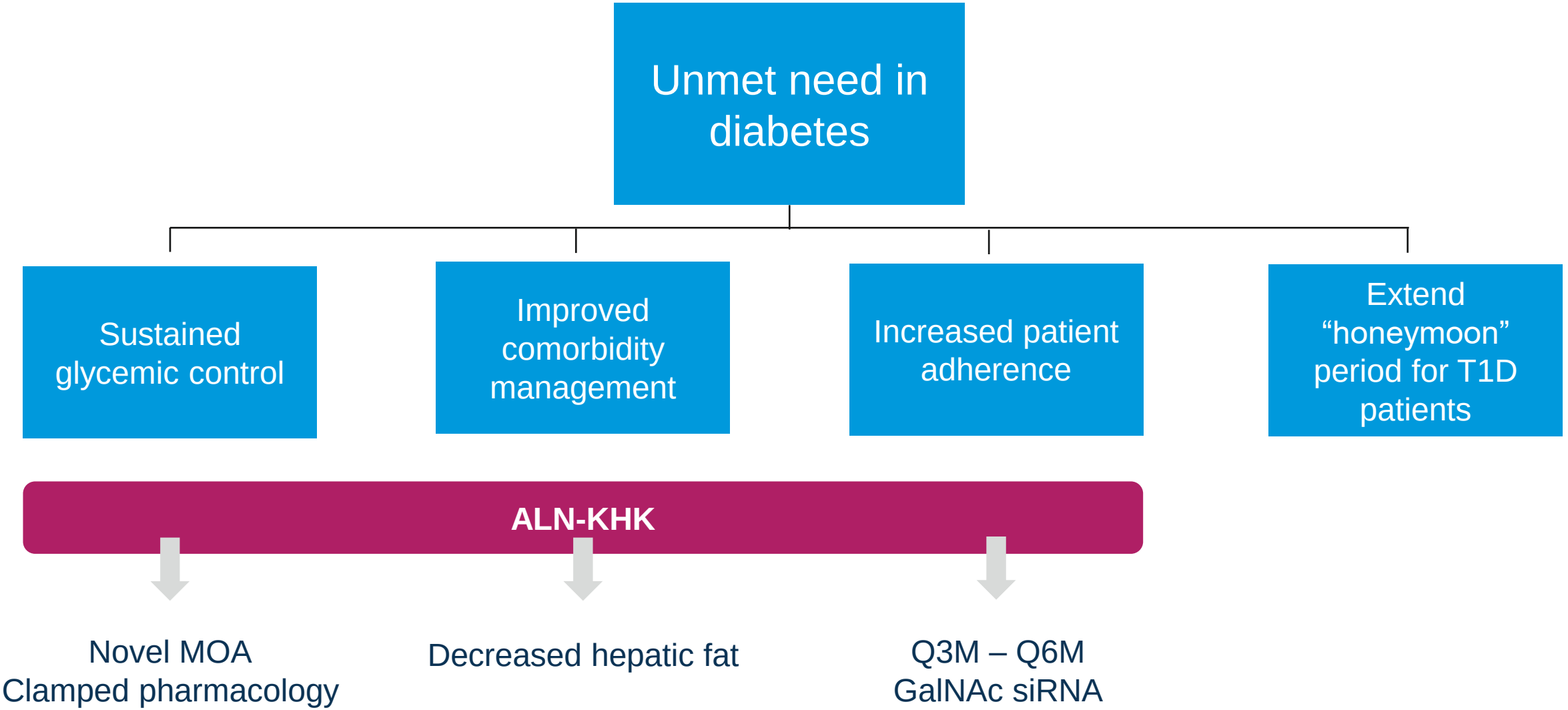
Unmet Need	Degree of Need	Description
Sustained Glycemic Control		• Majority of patients continue to progress through lines of therapy to insulin • 50% of patients above HbA1c target • Ideal therapy would improve glycemia & stop or reverse progression
Improved Comorbidity Management		• T2D mortality driven by CVD and other comorbidities such as CKD • Residual need despite recent advances in CV outcomes from SGLT2i's and GLP-1s
Increased Patient Adherence		• Recent metanalysis shows <60% adherence to oral anti-diabetic agents • 1-year persistence to injectable GLP-1's is modest, ranging from 50–70%

"We see patients have initial results of improved glycemic control and weight loss, but after a few years most rebound and need additional treatment. What we really need is something that modifies the underlying pathology."– US Endocrinologist

Proportion of Patients in HbA1c Range:	
HbA1c Range	**Percent of Individuals**
7 to 8%	22.4%
8 to 8.9%	13.2%
>9%	14.6%

Source: GlobalData, 2021 PMR, Up-to-Date; Mody et al, Clinical Therapeutics, 2022 (Sponsored by Lilly)(Howley, Diabetes Care 2022), Piragine et al 2023

Addressing Unmet Need in Diabetes with RNAi Therapeutics



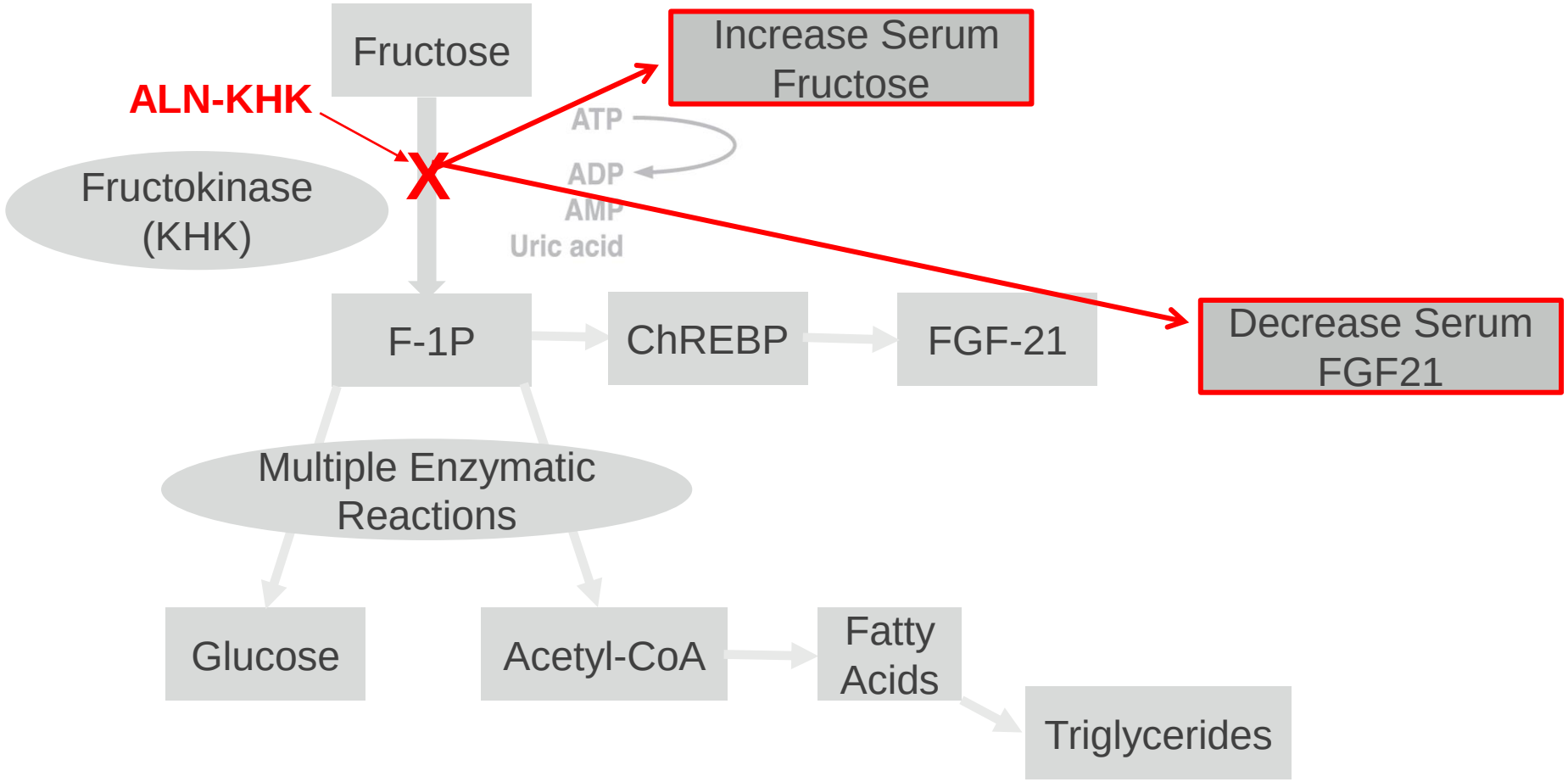
AsiPu et al.,Diabetes 2003, 52(9):2426-32; Miller et al., Am J Physiol Endocrinol Metab 2018, ;315(3):E386-E393; DiNicolantonio et al., Open Heart 2017;4(2):e000631

Alnylam®

Silencing of Ketohexokinase (KHK) to Treat T2DM

KHK Regulates Fructose Metabolism

- KHK-mediated fructose metabolism contributes to hepatic steatosis and insulin resistance
- LOF mutations in humans cause essential fructosuria, a benign and asymptomatic condition



AsiPu et al.,Diabetes 2003, 52(9):2426-32; Miller et al., Am J Physiol Endocrinol Metab 2018, ;315(3):E386-E393; Johnston et al., PLoS One 2021, 16(2):e0247683.

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ALN-KHK Phase 1 Overview

Randomized, Double-Blind Study in Two Parts

Part A: Single Ascending Dose in overweight to obese healthy volunteers

Part B (PoC): Multiple Dose in obese patients with T2DM

Primary Objective:
Safety and tolerability of ALN-KHK

Secondary Objective:
Pharmacology of ALN-KHK

Goals of PoC study:
Measure changes in HbA1c and hepatosteatosis in T2DM patients

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ALN-KHK: First-in-Human Single Ascending Dose Study (Part A)

40 Overweight to Obese Healthy Volunteers

Patient Population (N=8/dose cohort):

- Adults 18 to 65 years of age
- BMI ≥27 and ≤34.9 kg/m^2
- No history of diabetes
- HbA1c <6.5%

3:1 RANDOMIZATION (active:placebo)

- ALN-KHK Dose 1 SC x 1
- ALN-KHK Dose 2 SC x 1
- ALN-KHK Dose 3 SC x 1
- ALN-KHK Dose 4 SC x 1
- ALN-KHK Dose 5 SC x 1

OR

- Placebo SC x 1

Primary Endpoint:

- Frequency of Adverse Events

Secondary Endpoints:

- Plasma and urine PK
- Percent change from baseline in serum and urine fructose and serum FGF21 after fructose tolerance test
- HOMA-IR and AUC response to glucose tolerance test

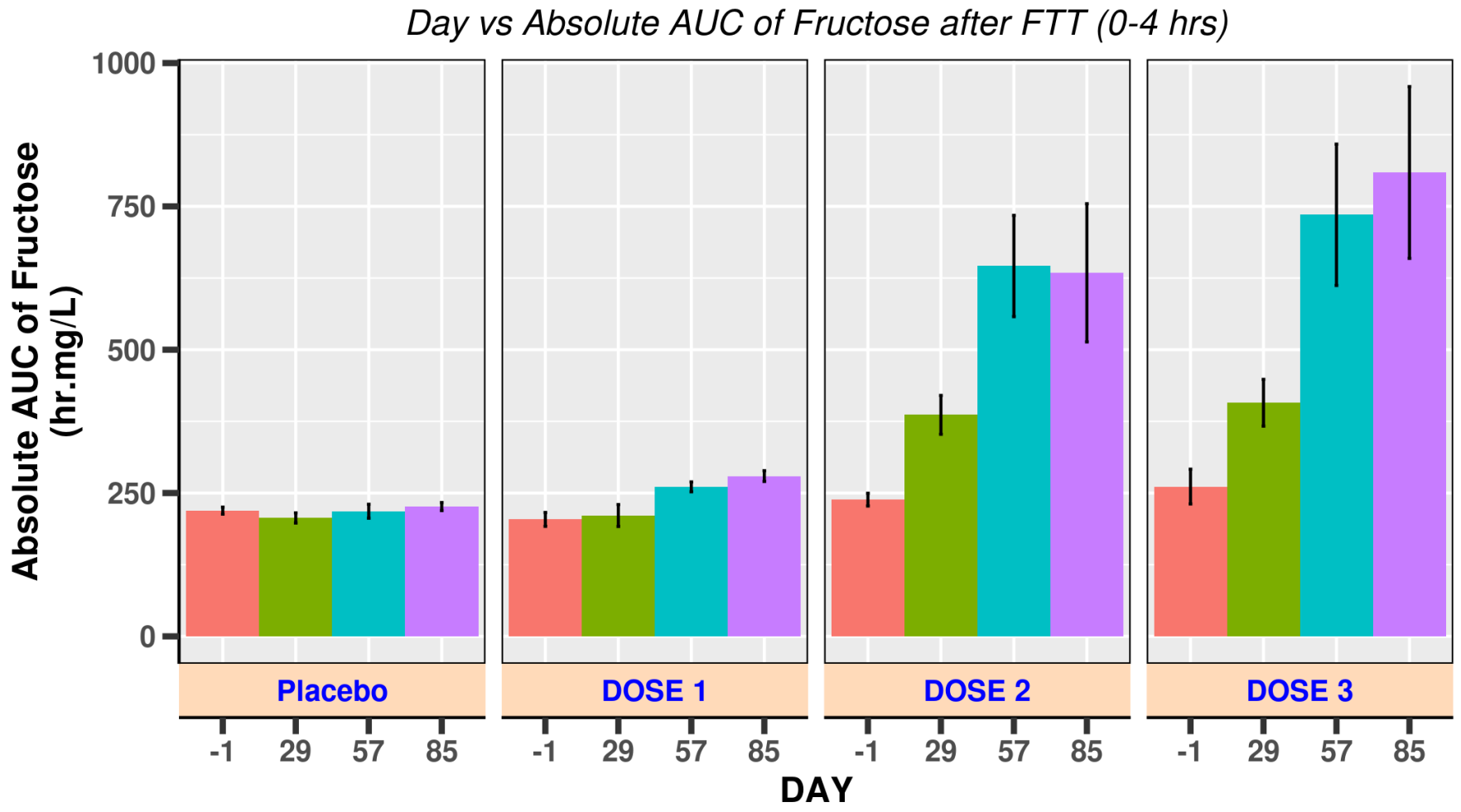
Dosing of Cohorts 1 through 5 complete

ClinicalTrials.gov Identifier: NCT05761301
Data cutoff 06Nov2023

HbA1c: Hemoglobin A1c - BMI: Body Mass Index - SC: Sub Cutaneous - PK: Pharmacokinetics - FGF21: Fibroblast Growth Factor 21 - HOMA-IR: Homeostatic Model Assessment of insulin resistance - AUC: Area Under the Curve

Clear Evidence of Target Engagement Observed for ALN-KHK

Fructose Results: Mean (SE) AUC by Treatment and Days



Decreased FGF21 also observed in a dose- and time-dependent fashion

Data cutoff 06Nov2023

AUC: Area Under the Curve; FGF21: Fibroblast Growth Factor 21; FTT: Fructose Tolerance Test

ALN-KHK Appears Safe and Well Tolerated; Target Engagement Confirmed

Safety

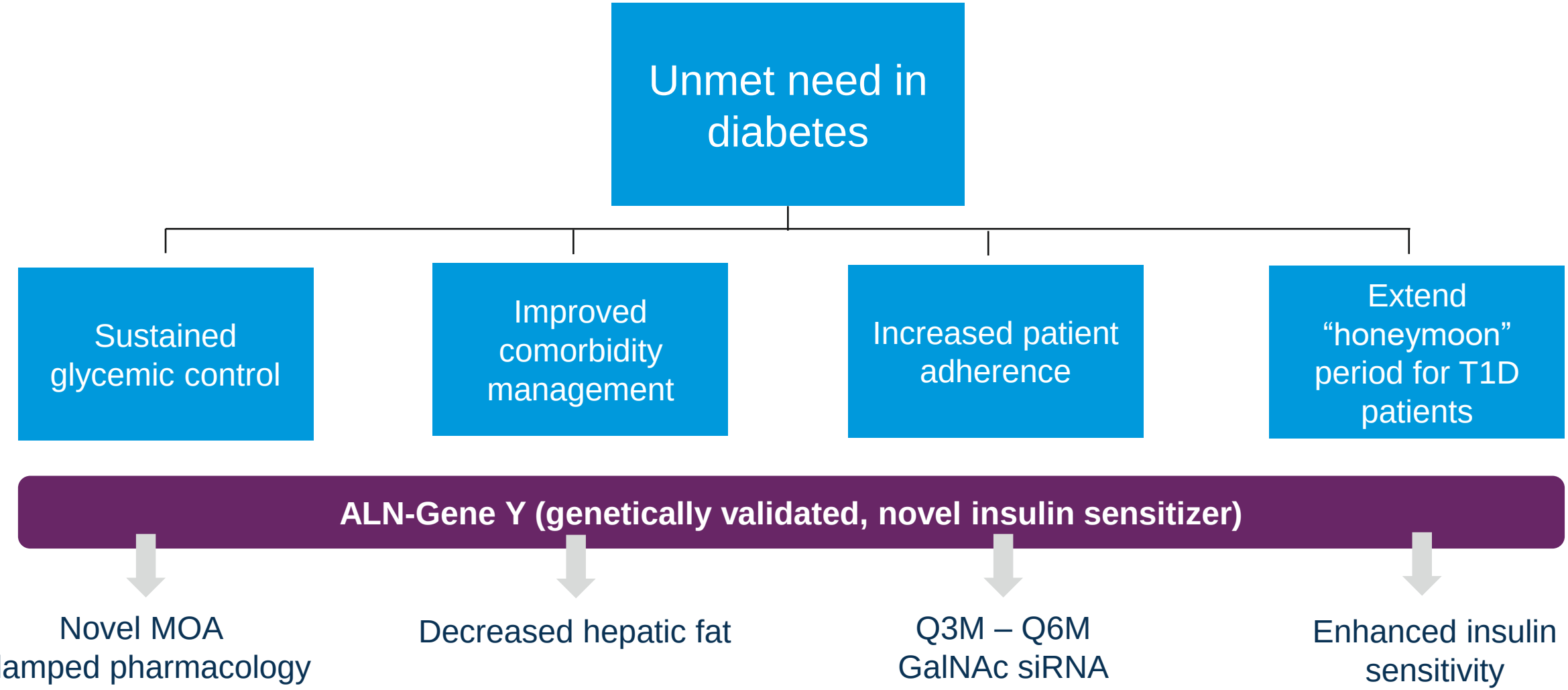
- All adverse events mild and non-serious and resolved
  - Generally balanced between ALN-KHK and placebo
  - Injection site reactions in 2 (7%) ALN-KHK participants
- No safety signals identified, including hepatic safety signals

Next Steps

- Multi-dose study in obese T2DM patients initiating in 2024
- Primary endpoint: change in HbA1c
- Additional parameters:
  - Response to glucose load
  - MRI-PDFF
- Topline results expected in 2025

- T2D: Type 2 diabetes; MRI-PDFF : Magnetic Resonance Imaging Proton Density Fat Fraction

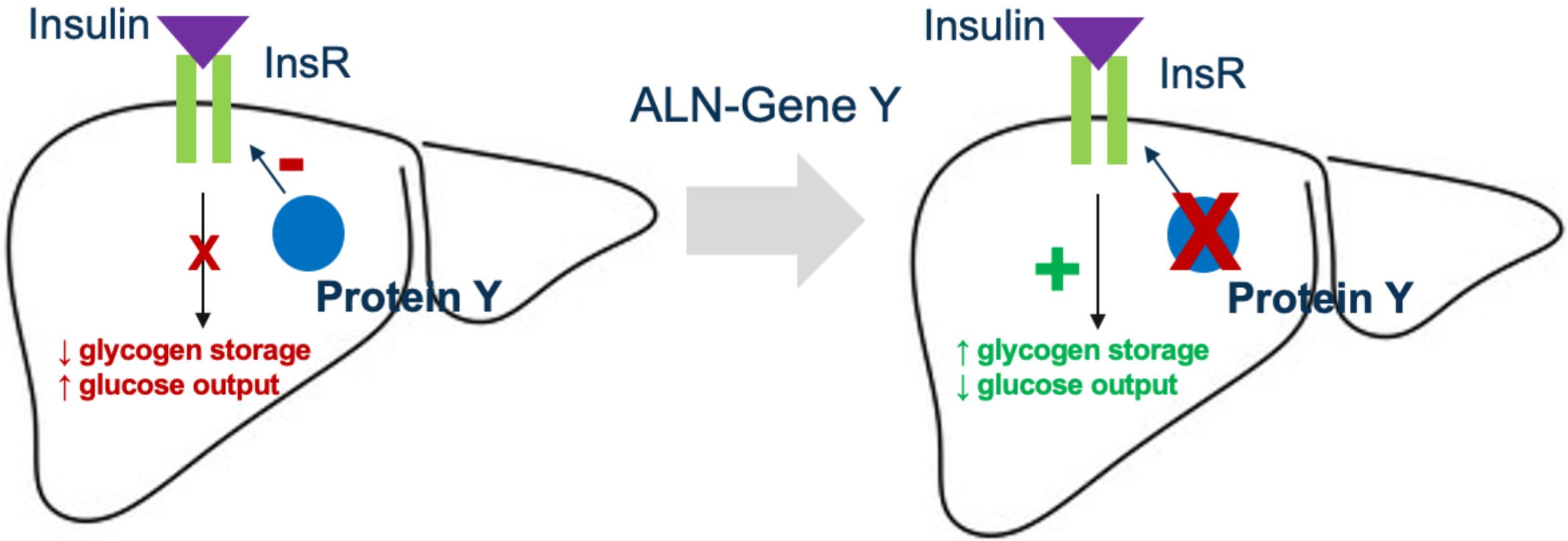
Addressing Unmet Need in Diabetes with RNAi



Standalone agent or synergistic with SGLT2i and/or GLP-1 RAs

Alnylam®

ALN-Gene Y: Genetically Validated Novel Insulin Sensitizer

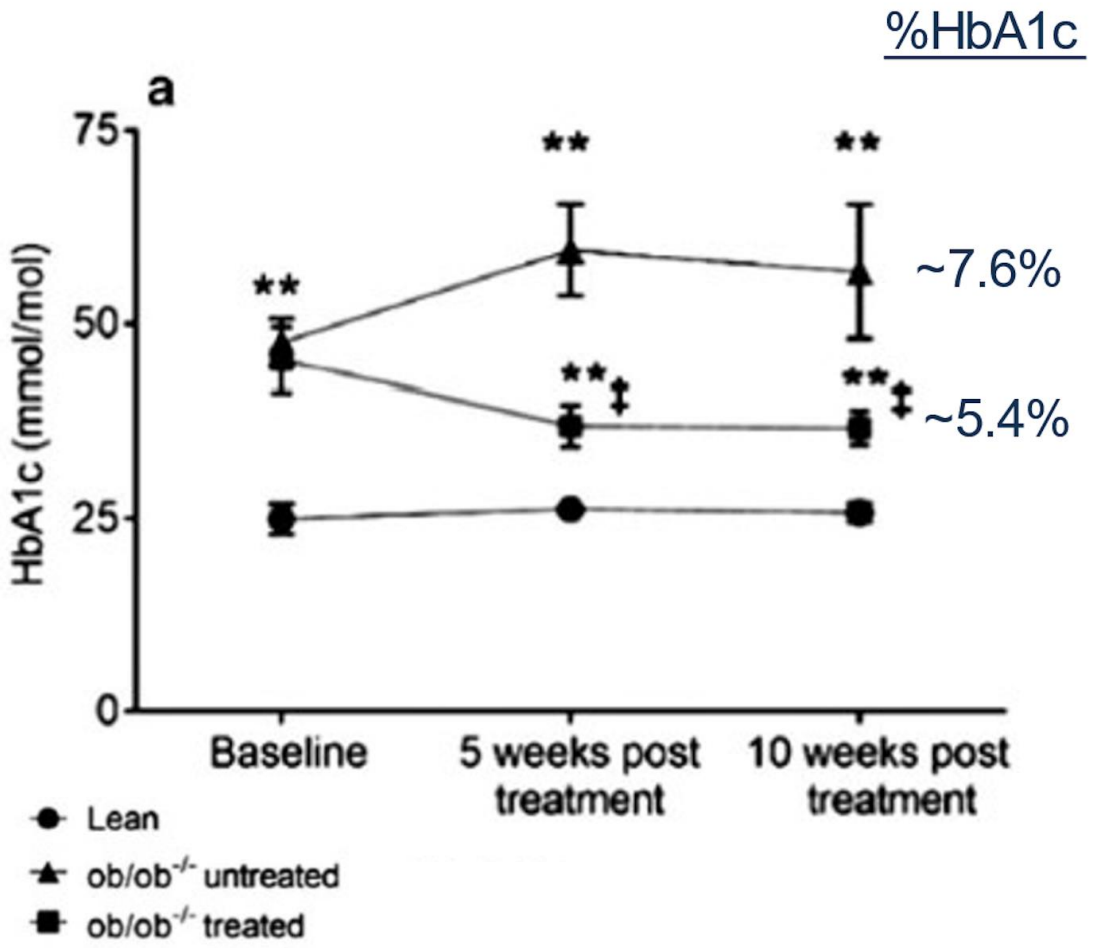


Gene Y genetically validated as lowering risk of T2D and risk of comorbidities such as NASH

Alnylam®

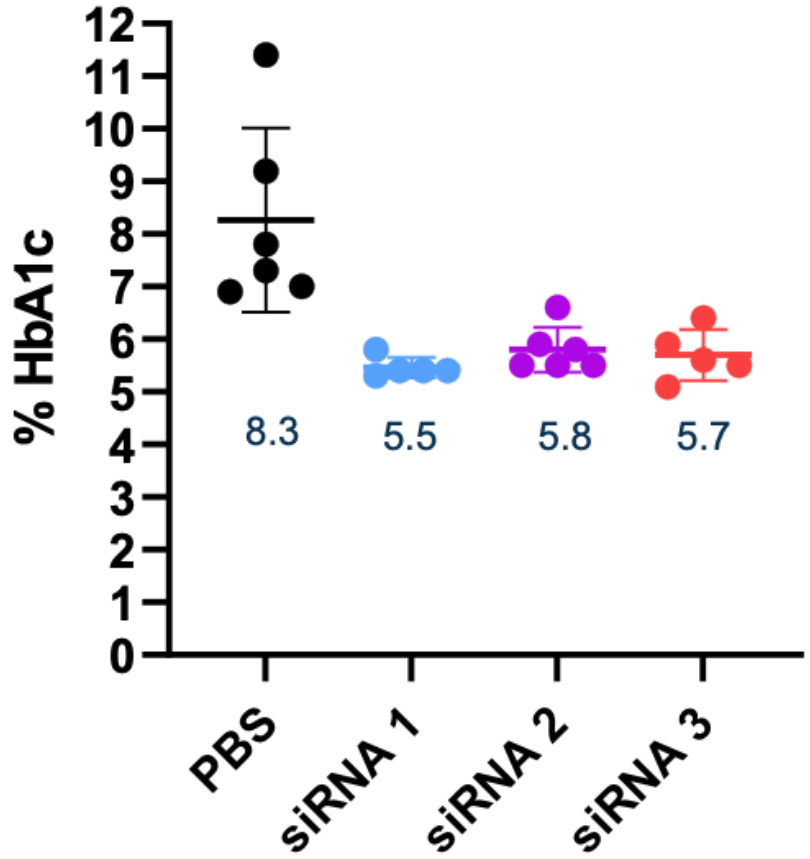
ALN-Gene Y Lowers HbA1c in Ob/Ob Mice to Similar Extent as SGLT2i

Empagliflozin lowers HbA1c in ob/ob mice[1]



siRNAs against Gene Y lower HbA1c to similar extent to Empagliflozin

Ob/Ob mice dosed with siRNA 1mg/kg every 2 weeks for 2 months



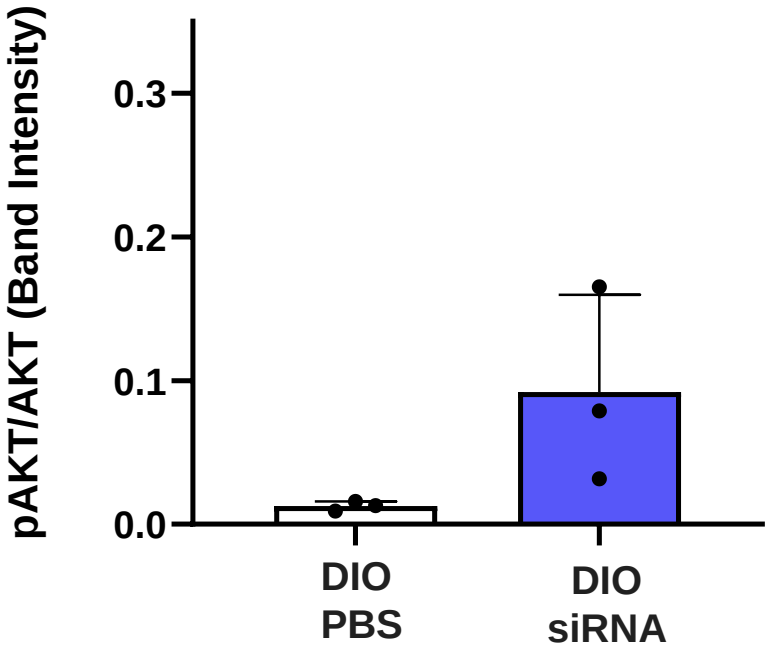
Similar HbA1c lowering but distinct/synergistic mechanisms

1. Adingupu et al., Cardiovasc Diabetol. 2019; 18(1):16

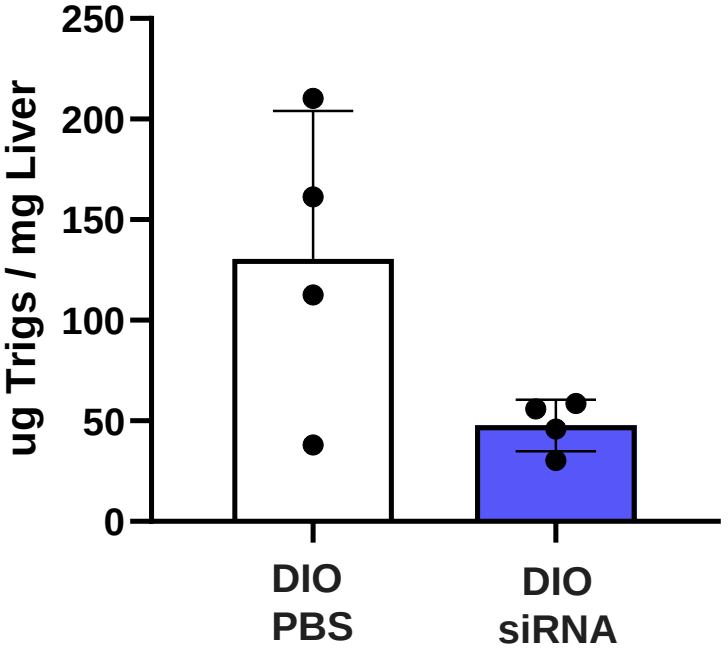
Alnylam®

Silencing Gene Y Increases Insulin Sensitivity, Lowers Liver Fat, and Does Not Cause Weight Gain in Obese Mice

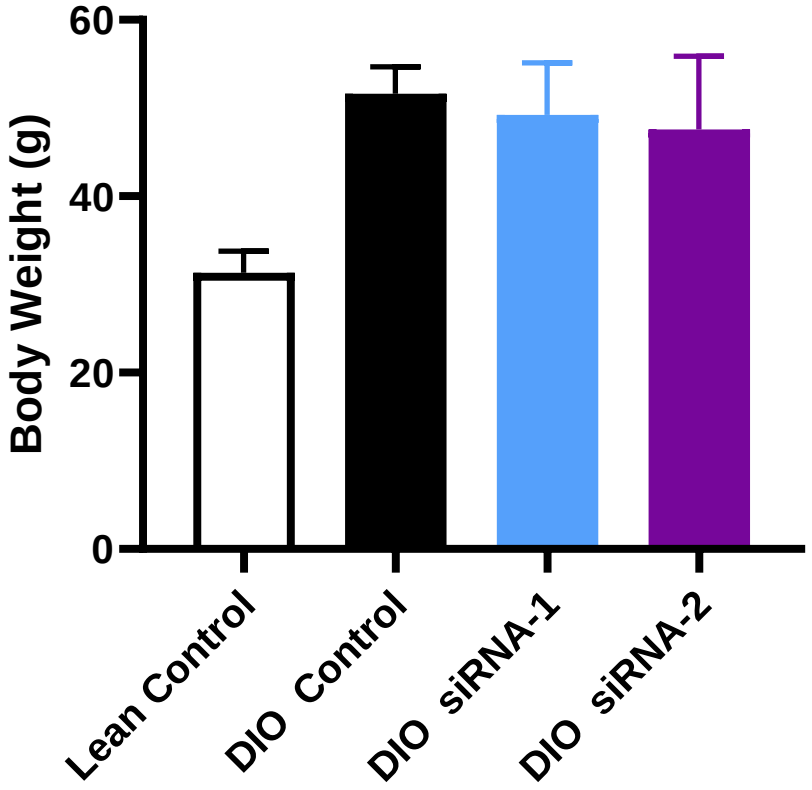
Liver Insulin Sensitivity



Fasted Hepatic Triglyceride Levels



ALN-Gene Y does not cause weight gain in DIO mice



DIO: Diet-induced obese

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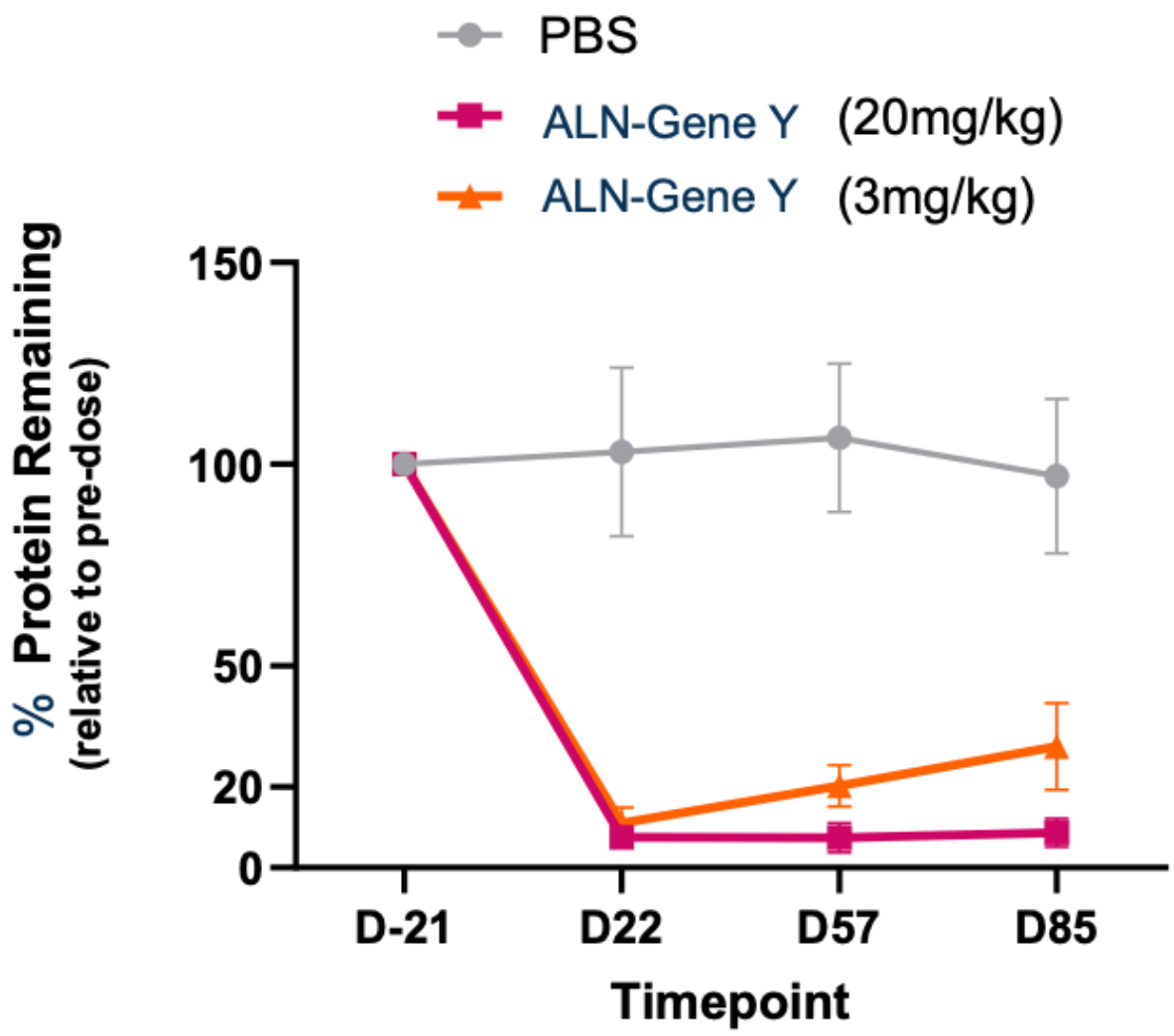
ALN-Gene Y Results in Deep and Durable Silencing in NHPs

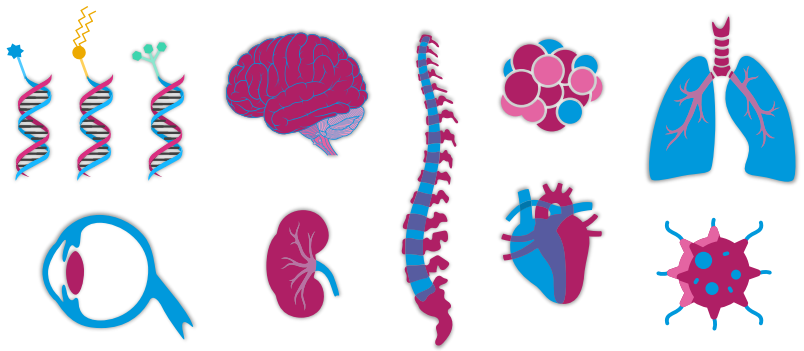


ALN-Gene Y IND expected in **2024**

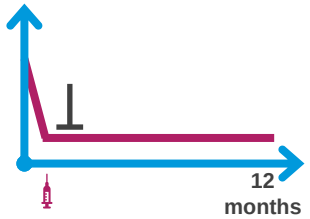
Alnylam

Multiple Sources of Sustainable Innovation Drive Robust Pipeline

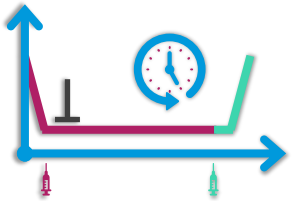
Extrahepatic Delivery



Platform Designs



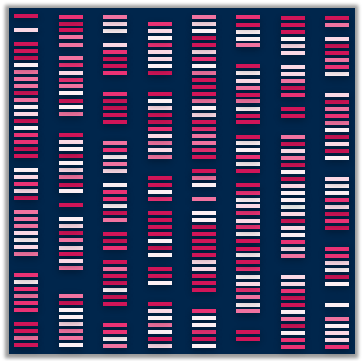
IKARIA™



Reversir™

GEMINI™

Human Genetics

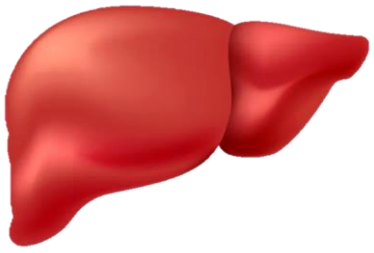


+ Our Future Health

discoverme

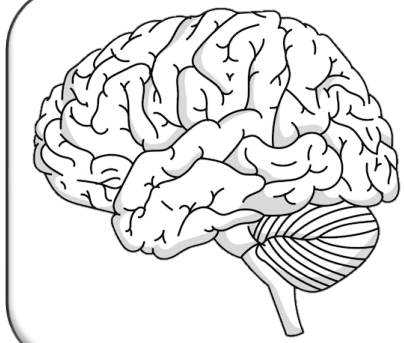
biobank uk

By end of 2025



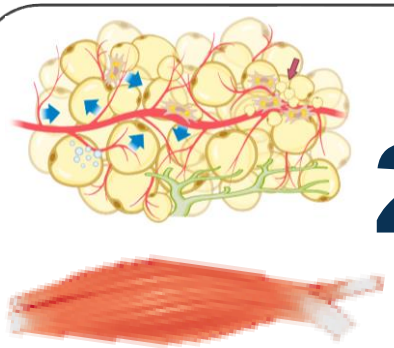
5 new **liver** INDs

10+ including partnered programs



2 new **CNS** INDs

3+ including partnered programs



2 **new tissues** with INDs

Establishing New Frontiers in the CNS with RNAi

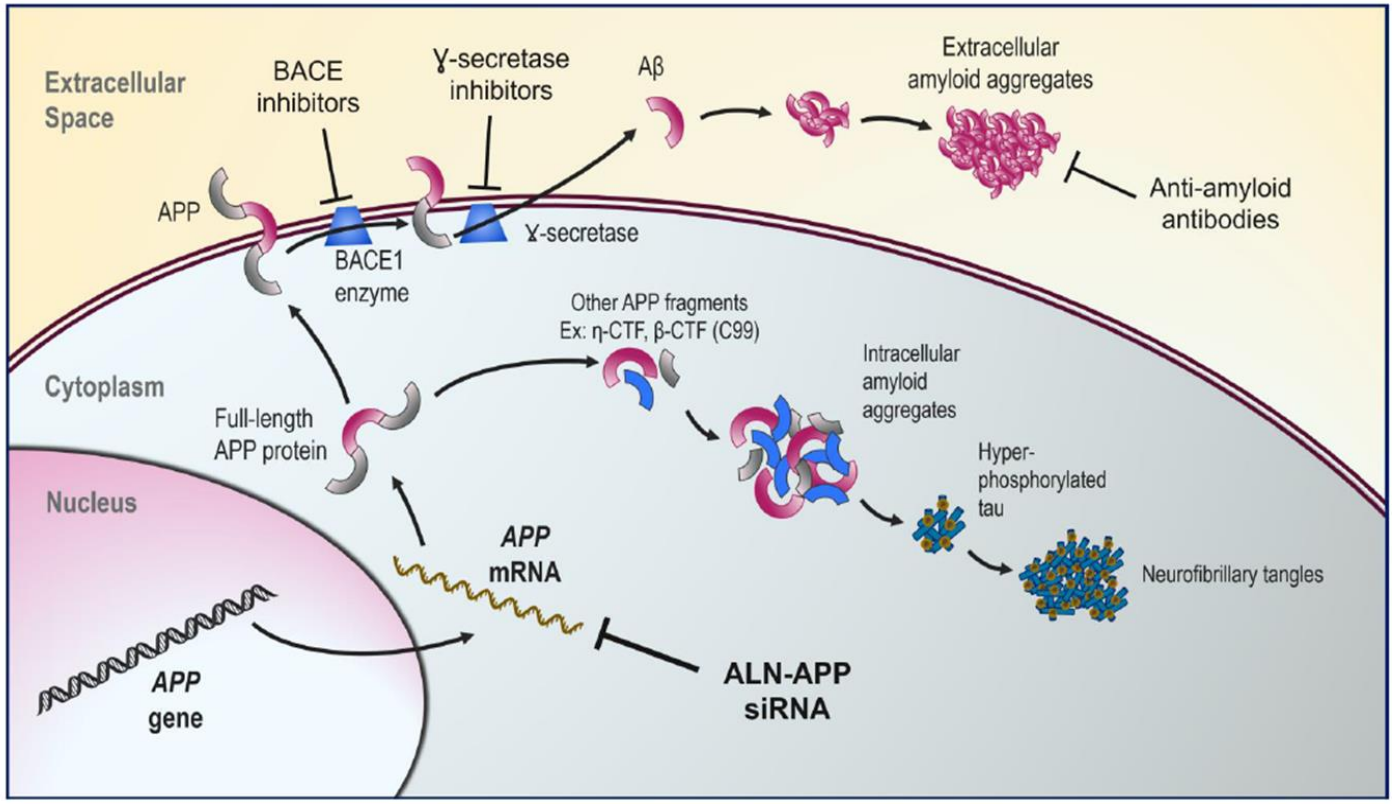
Kirk Brown, Ph.D.
VP, CNS Research

ALN-APP Therapeutic Hypothesis

An Investigational RNAi Therapeutic for Patients with Alzheimer's Disease

- Amyloid precursor protein (APP) is a ***genetically validated target*** for both Alzheimer's disease (AD) and Cerebral Amyloid Angiopathy (CAA)

- ALN-APP reduces ***all downstream Aβ species***.
  - Reduces substrate for brain amyloid deposition
  - May enable ***natural clearance***
  - ***Lowers intracellular Aβ*** and may reduce neuronal dysfunction

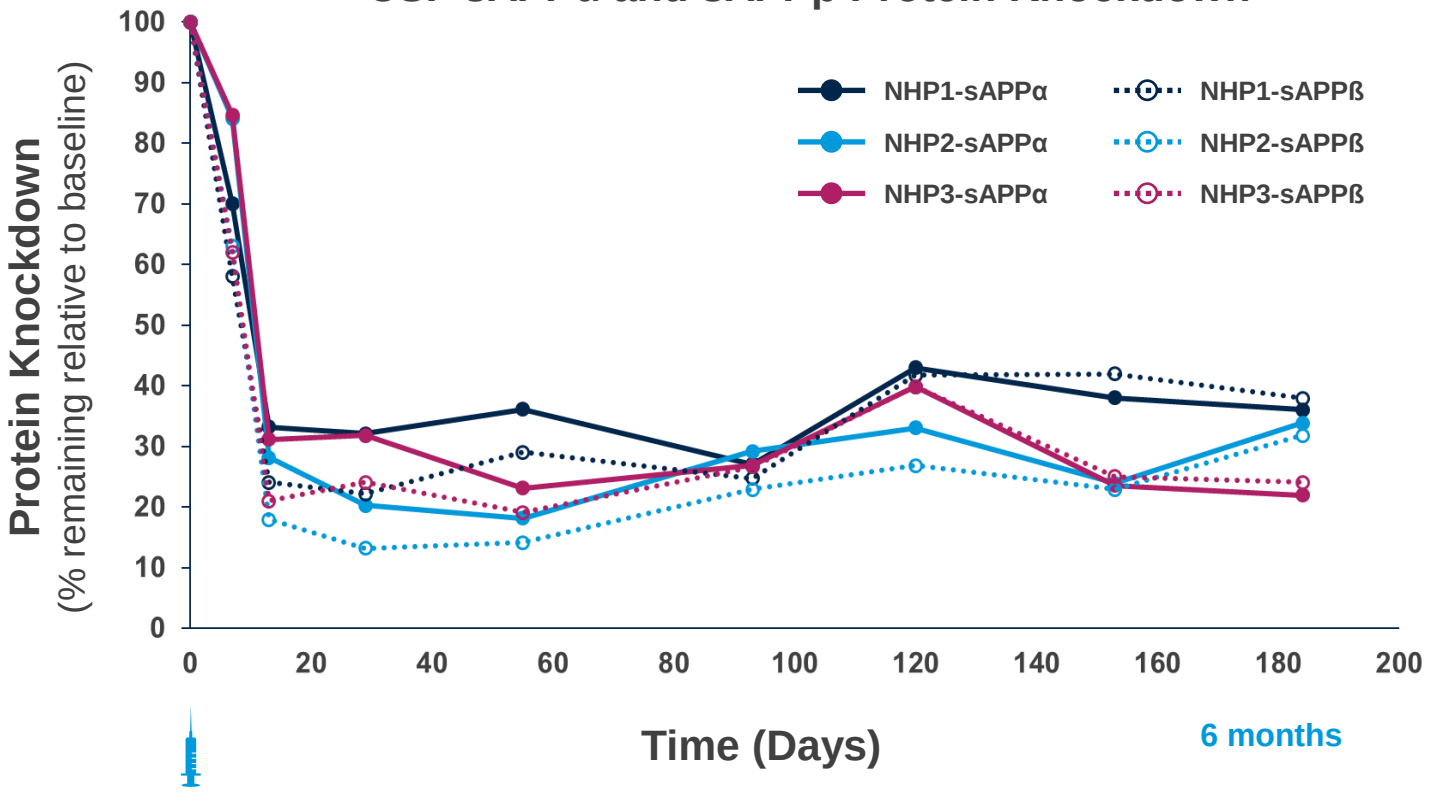


Aβ, amyloid beta; APP, amyloid precursor protein; BACE, beta-secretase; CNS, central nervous system; CTF, c-terminal fragment; mRNA, messenger ribonucleic acid; RISC, ribonucleic acid-induced silencing complex; siRNA, small interfering ribonucleic acid.

Potent, Durable Reduction of sAPPα and sAPPβ in CNS of NHPs

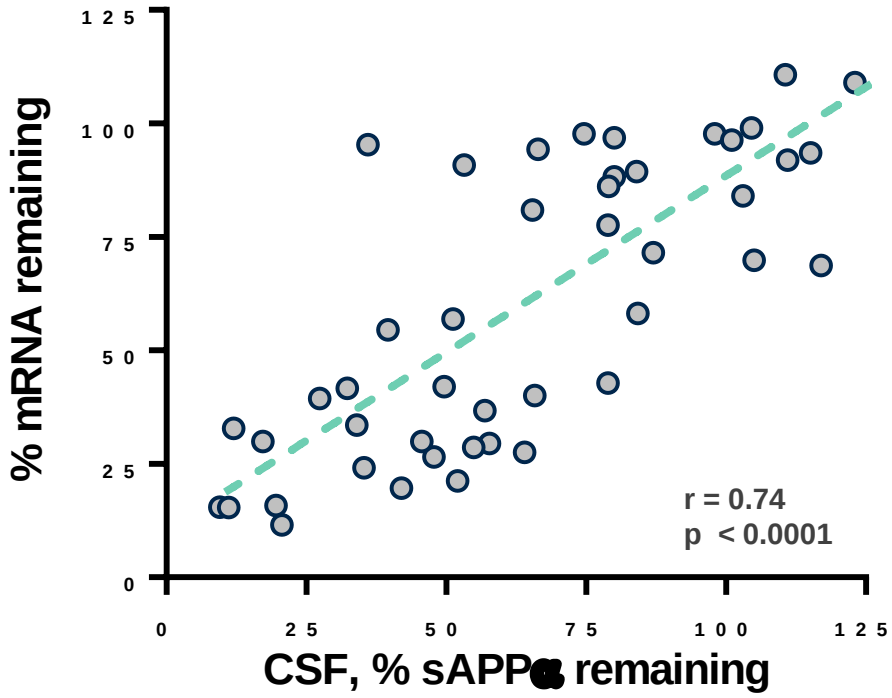
CSF sAPP Knockdown with Single Intrathecal 60 mg Dose of siRNA targeting *APP* mRNA

CSF sAPPα and sAPPβ Protein Knockdown



- >50% APP reduction
- Well-tolerated out to 6 months
- Durability of effect consistent with infrequent IT dosing

CSF sAPPα and Tissue Knockdown Correlation



- Strong correlation between CSF biomarker and tissue knockdown

APP, amyloid precursor protein; CNS, central nervous system; CSF, cerebrospinal fluid; IT, intrathecal; mRNA, messenger RNA; NHP, non-human primate; RNA, ribonucleic acid; sAPP, soluble APP; siRNA, small interfering RNA.

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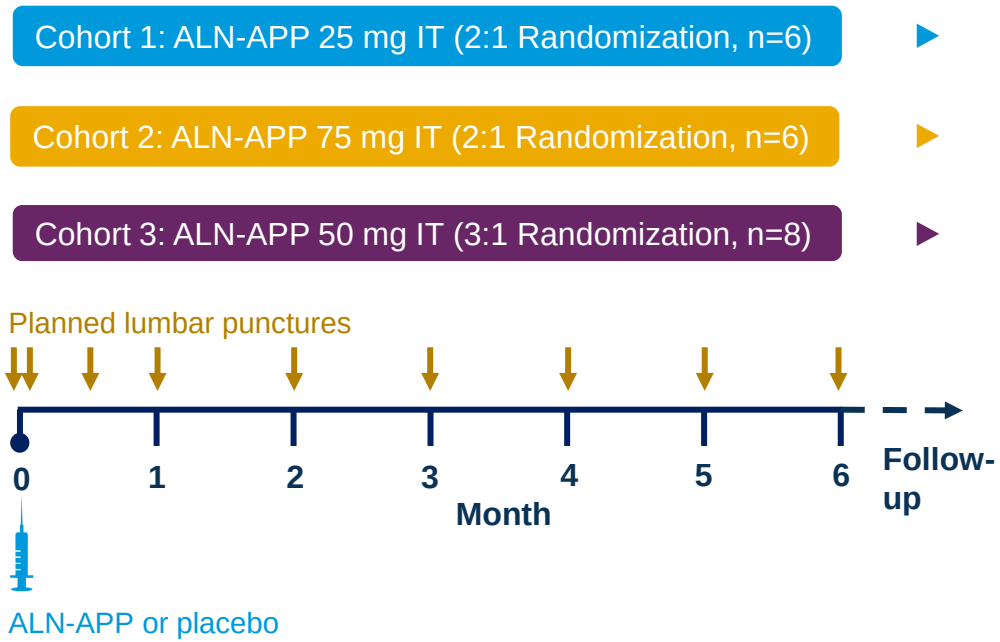
ALN-APP Phase 1 Study Design

Part A, Randomized, Placebo-Controlled, Single-Ascending Dose Study

Patient Population

- Symptom onset <65 years
- Clinical diagnosis of MCI or mild dementia
- Clinical Dementia Rating® global score of 0.5 or 1.0



Primary Endpoint

- Safety and tolerability

Secondary Endpoints

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

Exploratory Endpoints

- Change from baseline in biomarkers of disease
  - CSF Aβ42 and Aβ40

- Additional cohorts being studied in Part A; Part B multi-dose, open-label study initiated in UK, Netherlands and Canada. Part B in US remains on partial clinical hold.

As of September 20, 2023. Cohorts 1, 2, and 3 have a mean time from randomization of 14.8, 9.9, and 6.6 months, respectively.

Aβ, amyloid beta; Aβ40, amyloid beta peptide length 40 amino acids; Aβ42, amyloid beta peptide length 42 amino acids; CSF, cerebrospinal fluid; IT, intrathecally; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; PD, pharmacodynamic; PET, positron emission tomography; PK, pharmacokinetic; sAPP, soluble amyloid precursor protein.

ALN-APP Phase 1 Blinded Safety Summary

Pooled Adverse Event (AE) Summary for Cohorts 1–3[a]

n (%)	ALN-APP 25mg or PBO (N=6, PY=4.1)	ALN-APP 50mg or PBO (N=8, PY=2.8)	ALN-APP 75mg or PBO (N=6, PY=3.6)
At least one mild AE	5 (83.3)	6 (75.0)	4 (66.7)
At least one moderate AE	4 (66.7)	4 (50.0)	3 (50.0)
At least one serious AE	0	0	0
Death	0	0	0
At least one AE related to LP	4 (66.7)	6 (75.0)	2 (33.3)

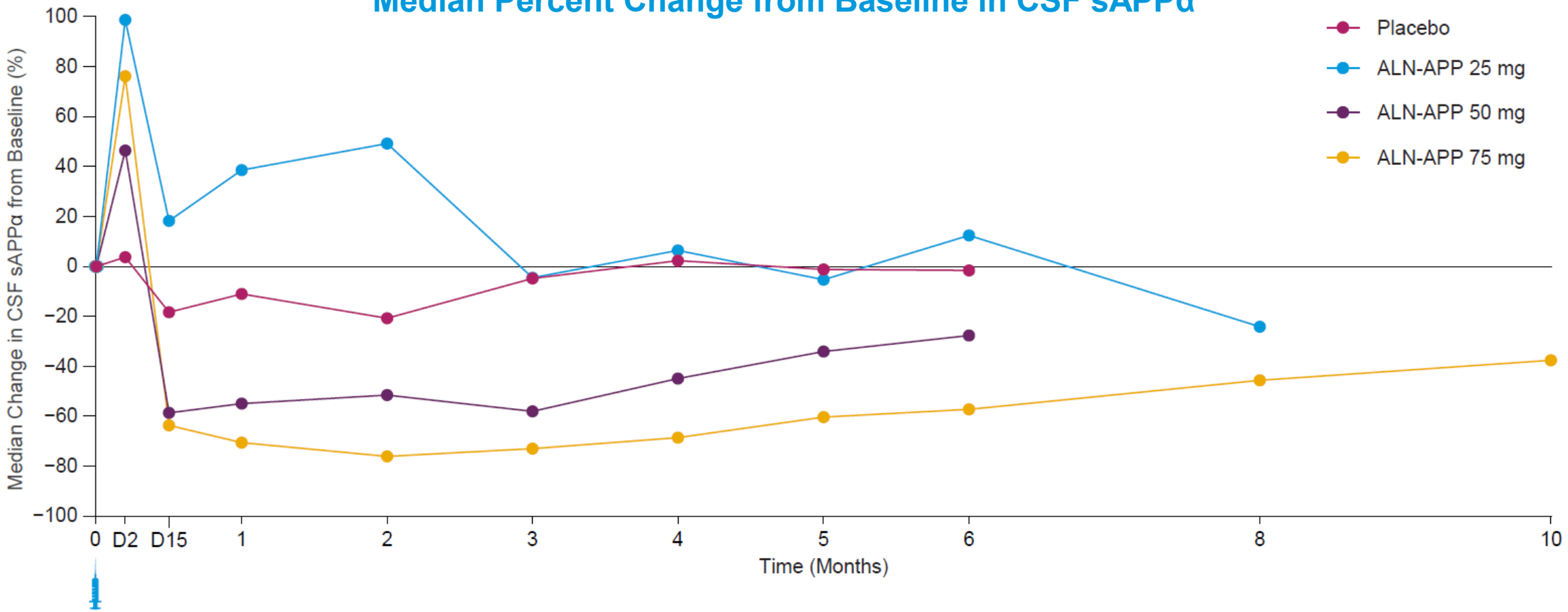
- All AEs mild or moderate in severity
- No deaths, SUSARs, or treatment or study discontinuations occurred

AE, adverse event; LP, lumbar puncture; PBO, placebo; PY, patient years; SUSAR, suspected unexpected serious adverse reaction.
[a]Data shown as of June 29, 2023.

Rapid and Durable Reductions in CSF sAPPα

- Peak mean (±SEM) reduction in sAPPα was 69% (±9.6) for 75 mg dose occurring at Month 2, with maximum individual reduction of 84% observed
- Reduction in sAPPα was sustained, with 31% (±7.6) mean reduction at Month 6 after single 50 mg dose, and 56% (±7.5) and 33% (±6.1) mean reduction at Months 6 and 10, respectively, after single 75 mg dose

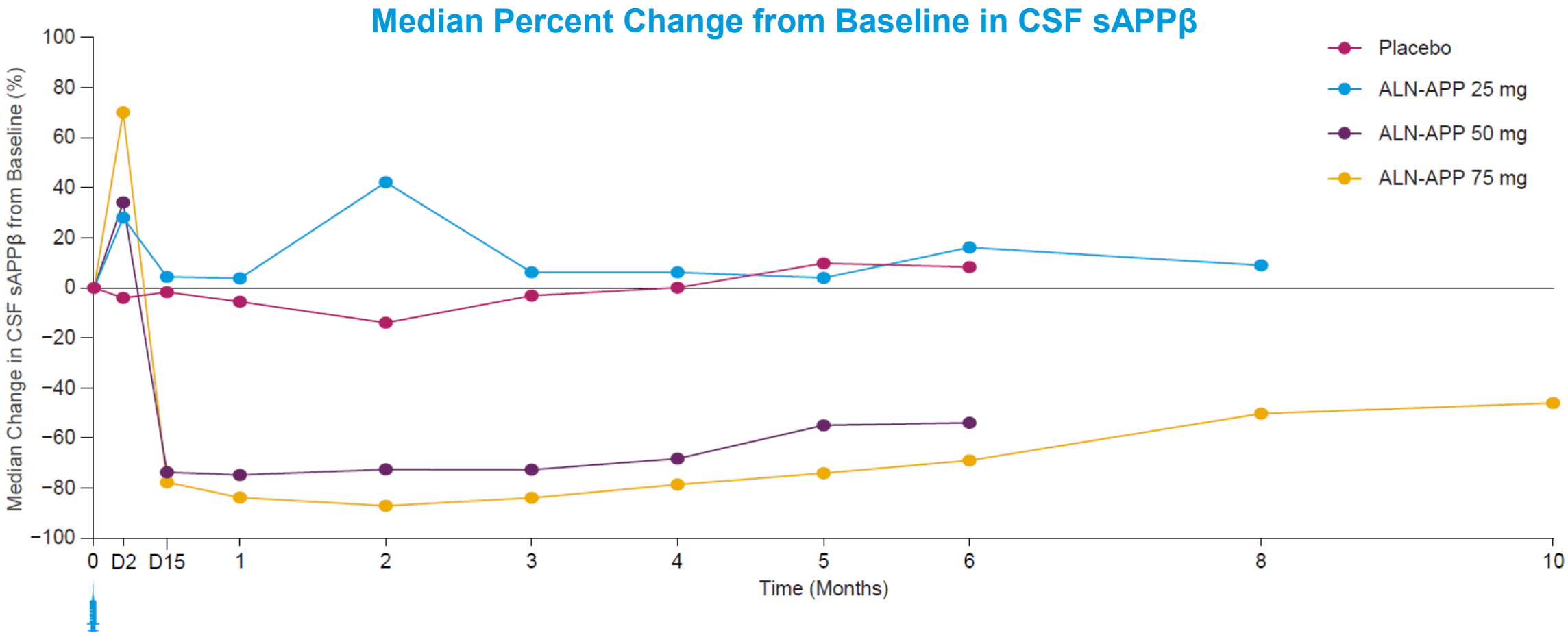
Median Percent Change from Baseline in CSF sAPPα



Data shown as of Oct 6, 2023. Timepoints with an n of ≤2 are not plotted.
CSF, cerebrospinal fluid; D, Day; sAPP, soluble amyloid precursor protein; SEM, standard error of the mean.

Rapid and Durable Reductions in CSF sAPPβ

- Peak mean (±SEM) reduction in sAPPβ was 82% (±6.3) for 75 mg dose occurring at Month 2, with maximum individual reduction of 90% observed
- Reduction in sAPPβ sustained, with 48% (±5.5) mean reduction at Month 6 after single 50 mg dose, and 65% (±9.2) and 39% (±11.5) mean reduction at Months 6 and 10, respectively, after single 75 mg dose

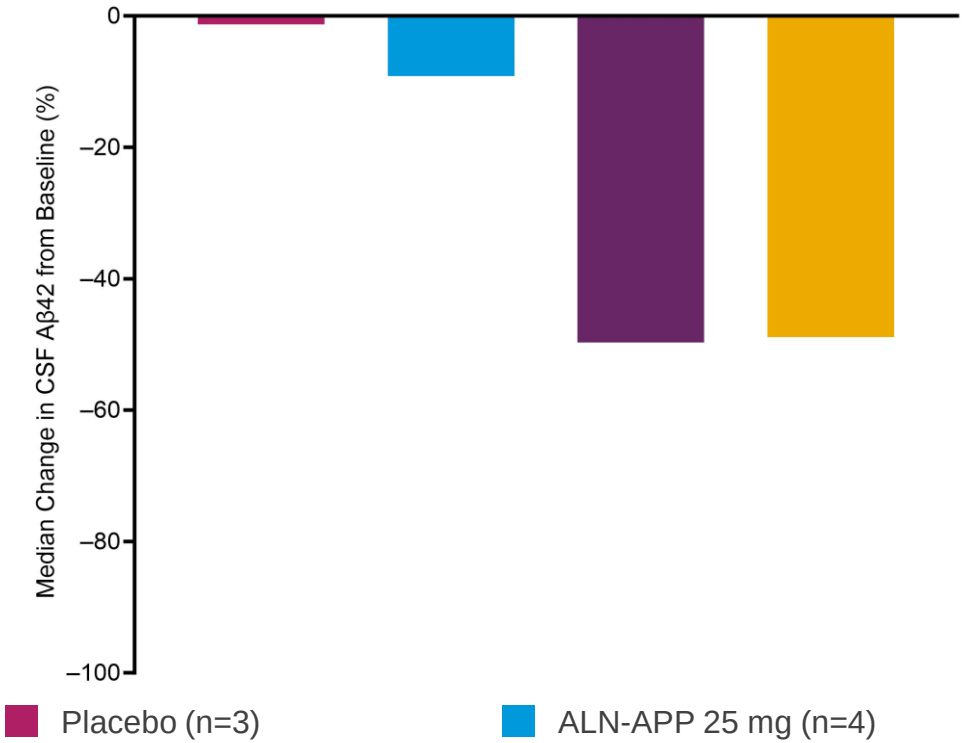


Data shown as of Oct 6, 2023. Timepoints with an n of ≤2 are not plotted.
CSF, cerebrospinal fluid; D, Day; sAPP, soluble amyloid precursor protein; SEM, standard error of the mean.

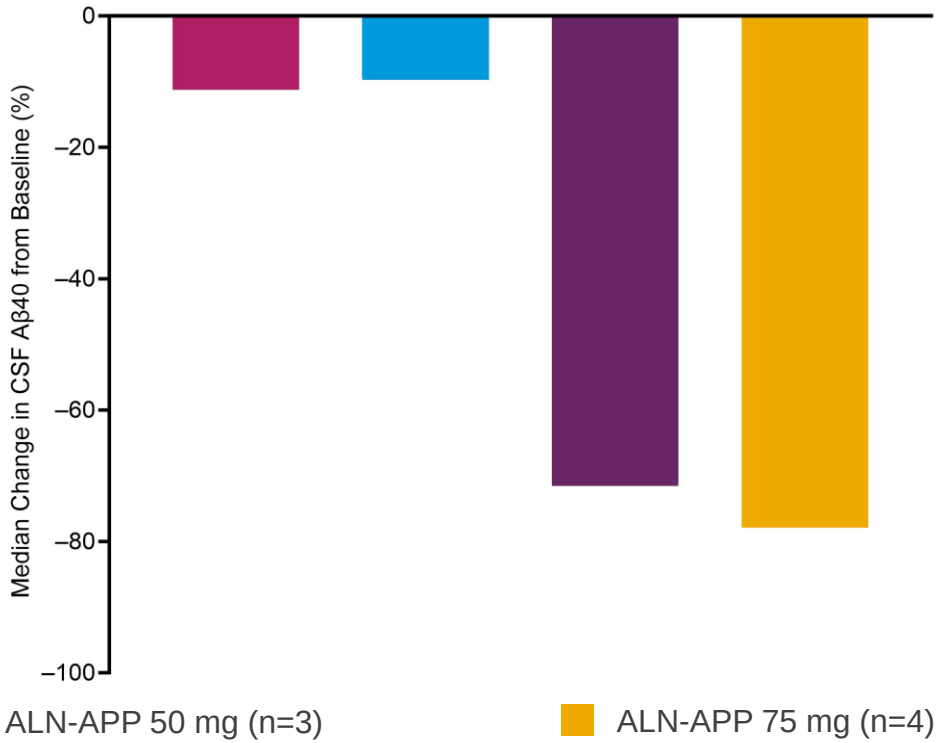
Marked Reductions in CSF Aβ42 and Aβ40 at Month 2

- At Month 2, reductions in CSF Aβ42 and Aβ40 were achieved after single dose of ALN-APP
  - Mean (±SEM) reduction in CSF Aβ42 was 51.9% (±6.8) in 50 mg, and 48.9% (±7.7) in 75 mg cohort
  - Mean (±SEM) reduction in CSF Aβ40 was 69.8% (±7.0) in 50 mg, and 70.6% (±9.3) in 75 mg cohort

Median Percent Change from Baseline in CSF Aβ42



Median Percent Change from Baseline in CSF Aβ40



Placebo (n=3) | ALN-APP 25 mg (n=4) | ALN-APP 50 mg (n=3) | ALN-APP 75 mg (n=4)

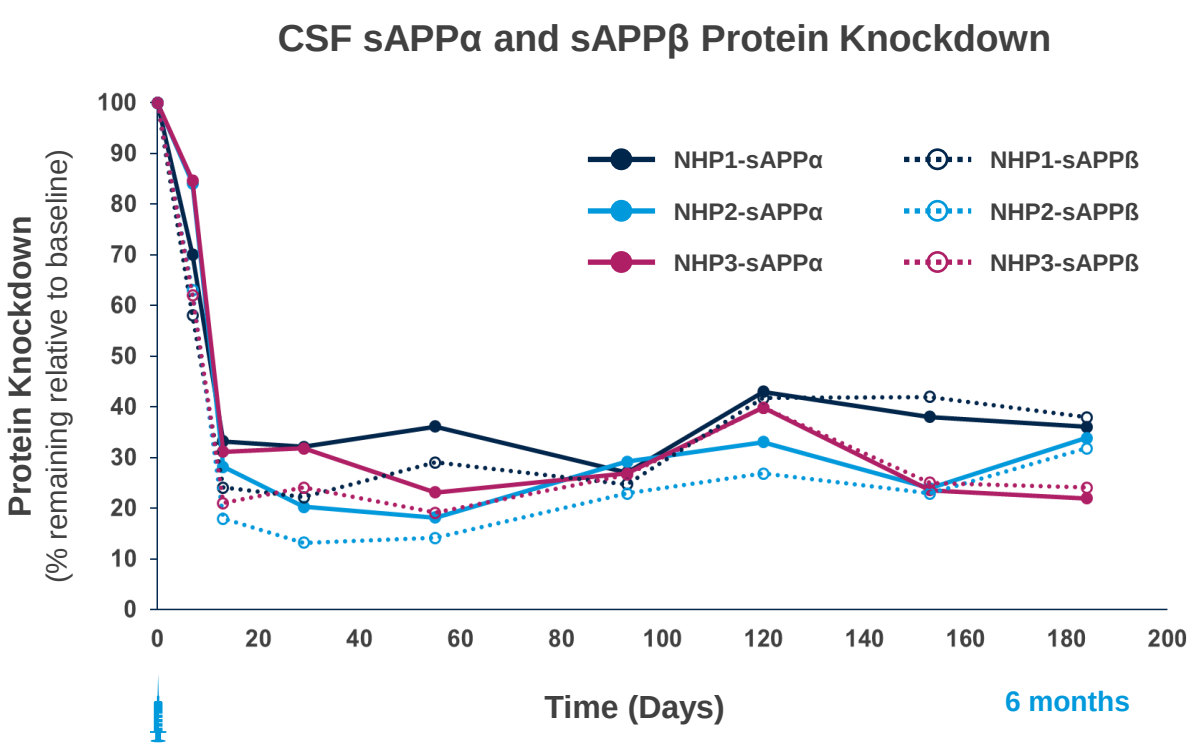
- CSF safety biomarkers, routine lab assessments, and preliminary data for exploratory biomarker neurofilament light chain all continued to show no significant abnormalities

Data shown as of August 17, 2023.
Data are not shown for later timepoints owing to the limited number of patients with data from Month 3.
Aβ40, amyloid beta peptide length 40 amino acids; Aβ42, amyloid beta peptide length 42 amino acids; CSF, cerebrospinal fluid; SEM, standard error of the mean.

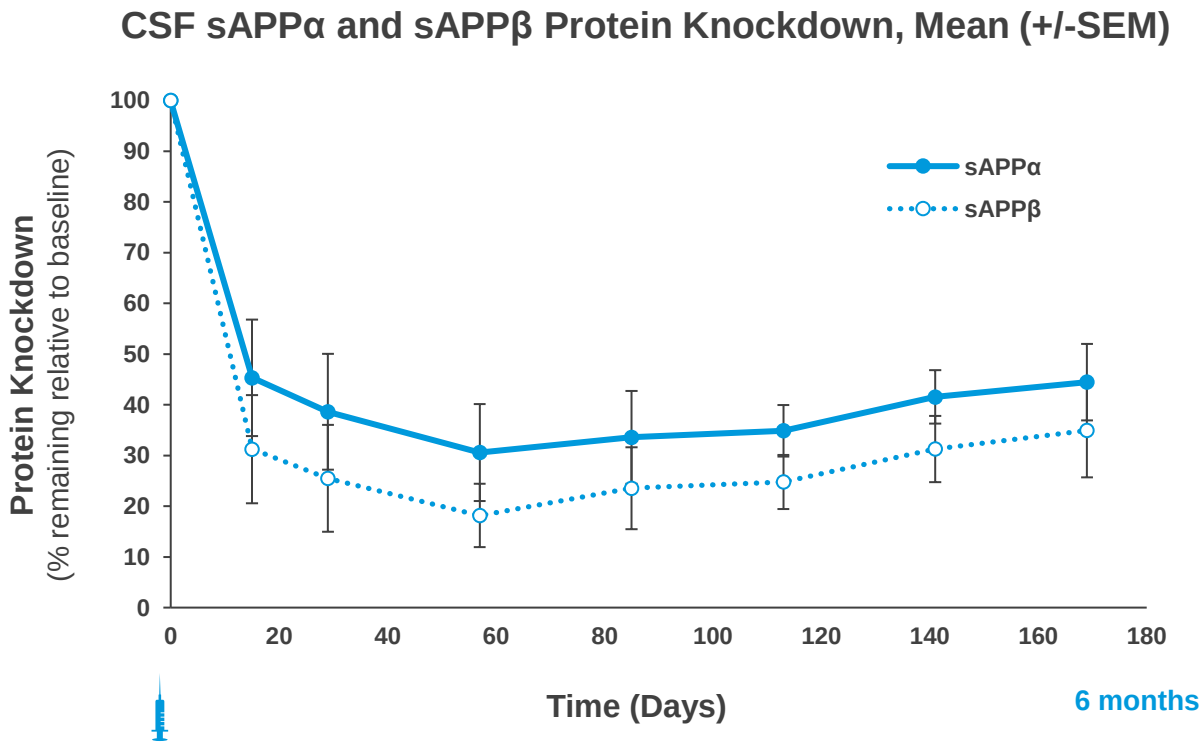
Alnylam®

Translation of CNS Platform from NHP to Human

NHP, 60 mg (600mg HED)



Human, Phase 1 Cohort 2, 75 mg



HED, Human Equivalent Dose

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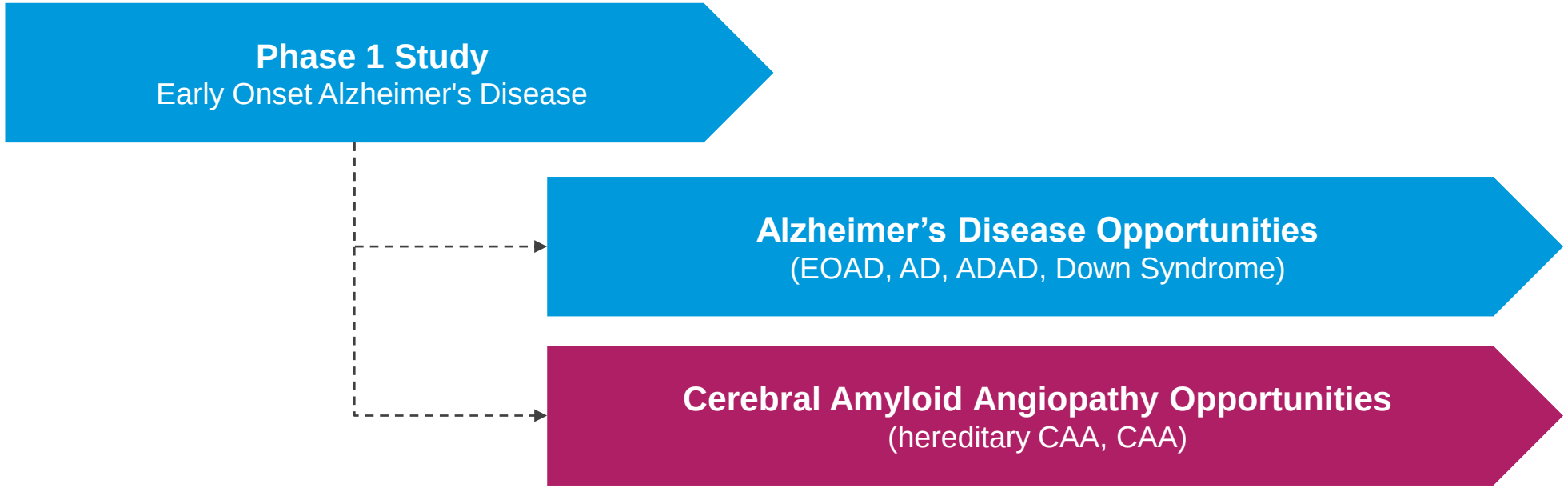
Next Steps with ALN-APP

Phase 1 Data Unlock Development Opportunities in Both AD and CAA



Multiple options for development and commercialization for ALN-APP

- Multiple genetically validated diseases with large populations and high unmet need
- Opportunities to adapt based on program learnings and evolving disease landscape

Alnylam®

Cerebral amyloid angiopathy: an unmet need

David Werring
Professor of Clinical Neurology
UCL Institute of Neurology,
National Hospital for Neurology and Neurosurgery
Queen Square, London

Declarations of Interest

- Grant funding from the Stroke Association and British Heart Foundation
- Honoraria (speaking) from Bayer (talks or debates on anticoagulants, intracerebral haemorrhage, atrial fibrillation, dementia)
- Honoraria (chairing) from Alexion and NovoNordisk
- Consultancy fees from Bayer, NovoNordisk and Alnylam
- Local PI ENRICH-AF trial
- CI OPTIMAS
- CI PROHIBIT-ICH

Talk structure

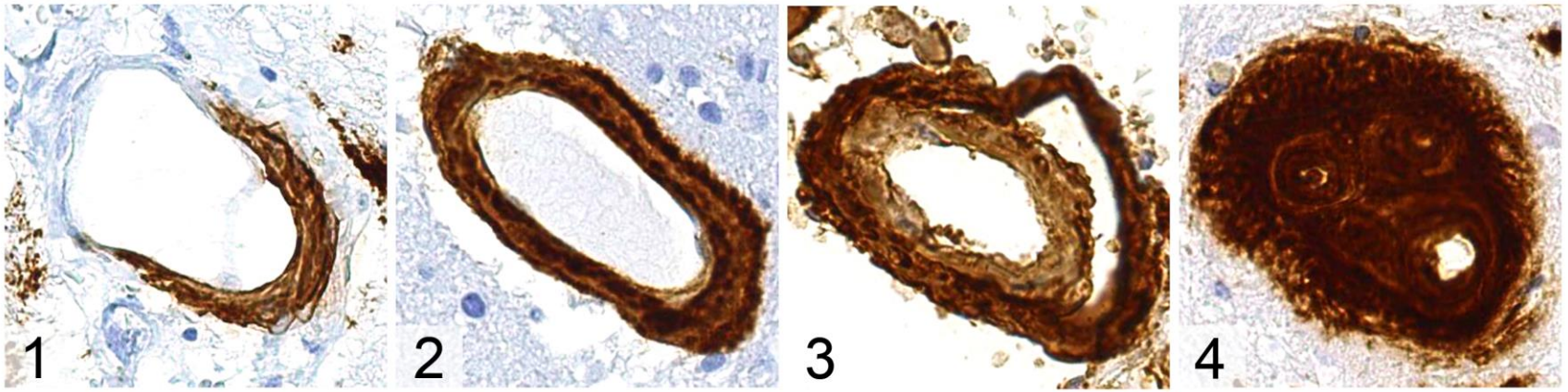
- What is CAA?
- Epidemiology of CAA
- Diagnosis of CAA
- Clinical syndromes associated with CAA
  - Intracerebral haemorrhage
  - Transient focal neurological episodes (TFNE)
  - Cognitive decline
- Management
- Markers of disease progression
- Summary

Talk structure

- What is CAA?
- Epidemiology of CAA
- Diagnosis of CAA
- Clinical syndromes associated with CAA
  - Intracerebral haemorrhage
  - Transient focal neurological episodes (TFNE)
  - Cognitive decline
- Management
- Markers of disease progression
- Summary

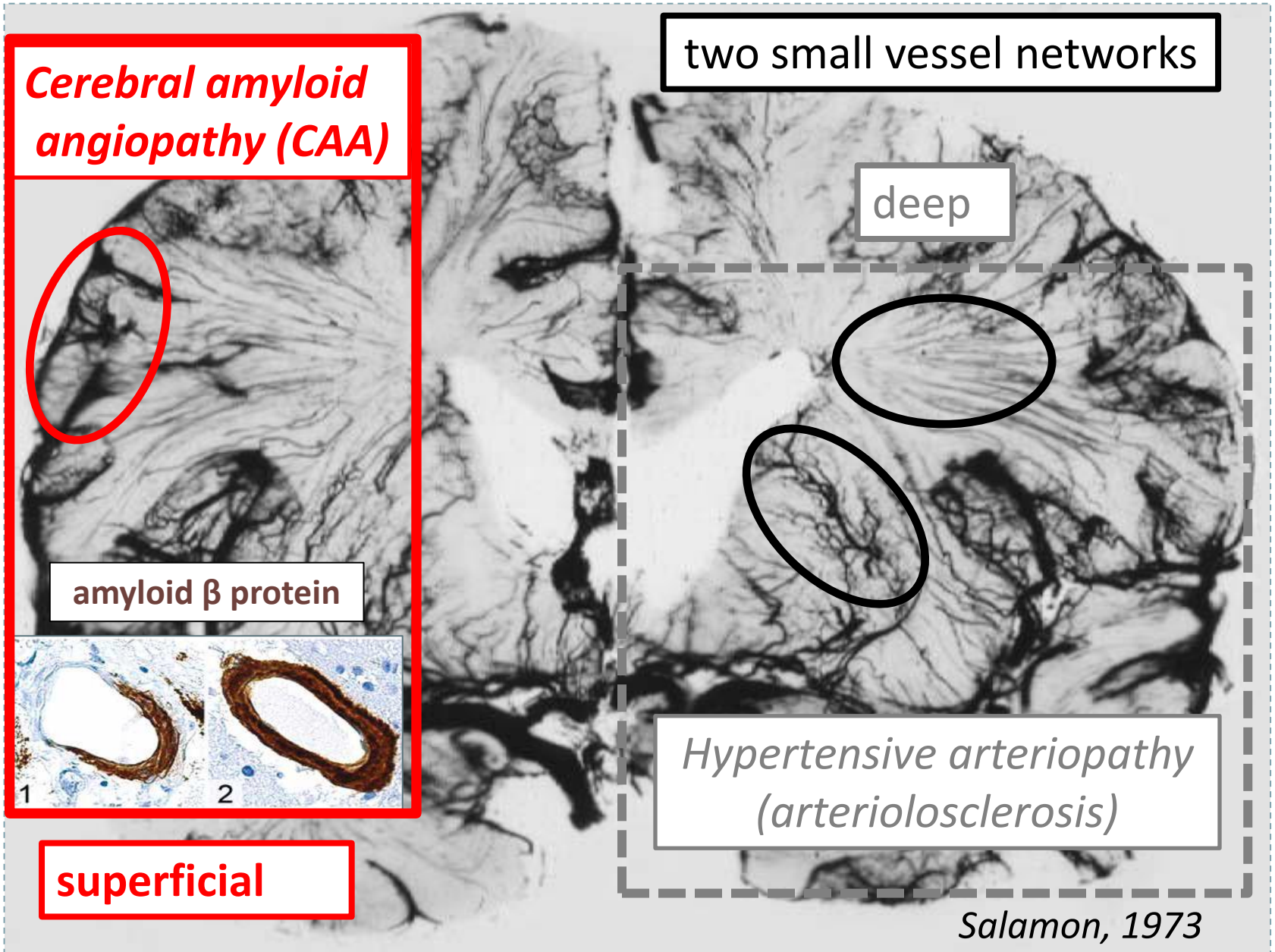
What is CAA?

CAA = deposition of beta-amyloid in leptomeningeal and cortical arterioles and capillaries

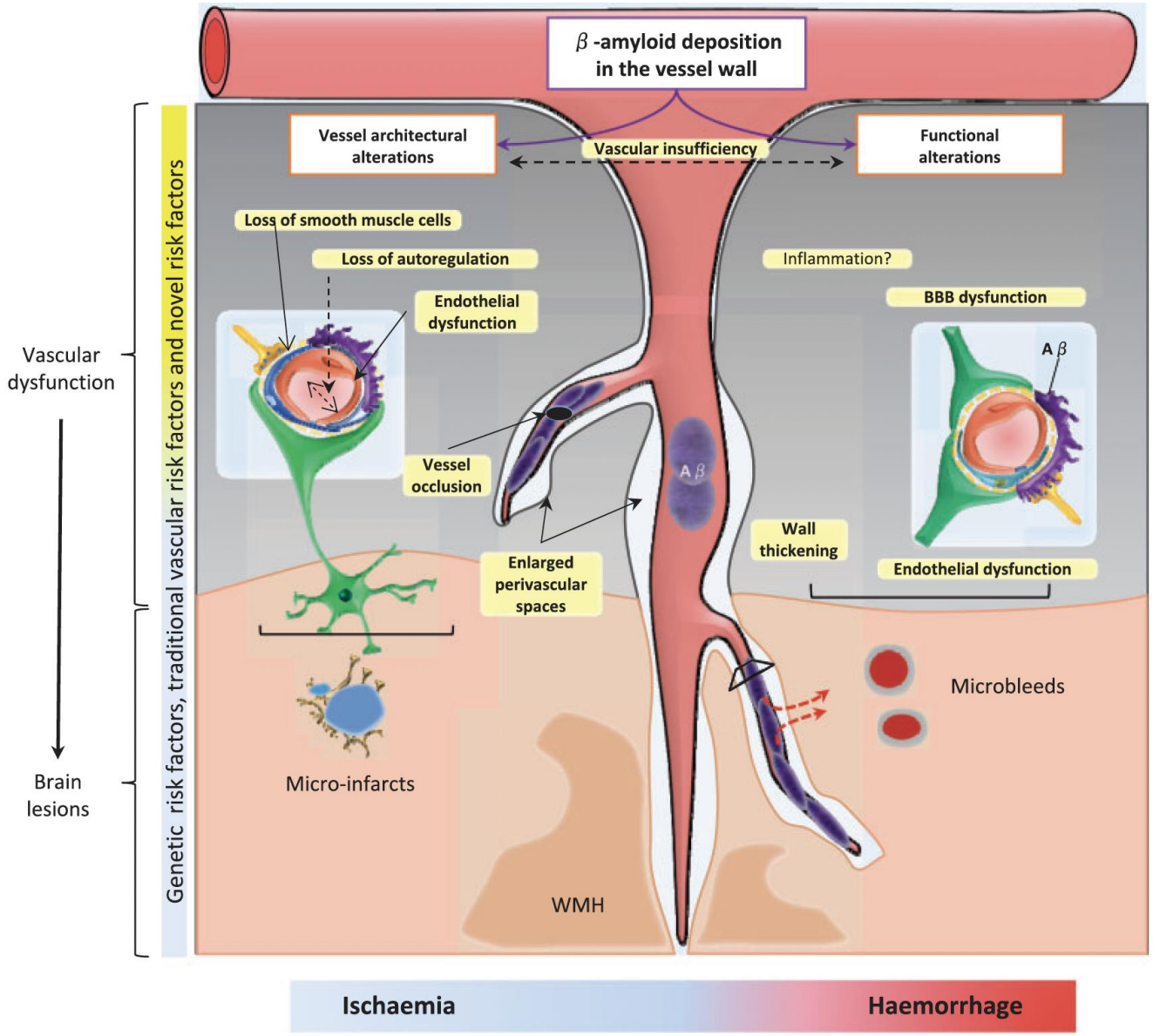


Progressive stages of CAA (Vonsattel grading system) courtesy Dr Z Jaunmuktane

Banerjee and Werring ACNR 2016


Cerebral amyloid angiopathy (CAA)
amyloid β protein
1
2
superficial
two small vessel networks
deep
Hypertensive arteriopathy (arteriolosclerosis)
Salamon, 1973

Pathophysiology



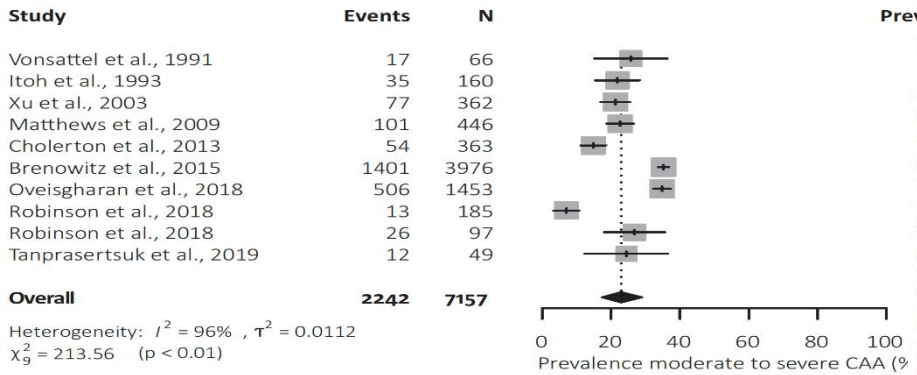
Brain 2011: 134; 2376–2386.

Talk structure

- What is CAA?
- Epidemiology of CAA
- Diagnosis of CAA
- Clinical syndromes associated with CAA
  - Intracerebral haemorrhage
  - Transient focal neurological episodes (TFNE)
  - Cognitive decline
- Management
- Markers of disease progression
- Summary

Prevalence of CAA

General population ~20%

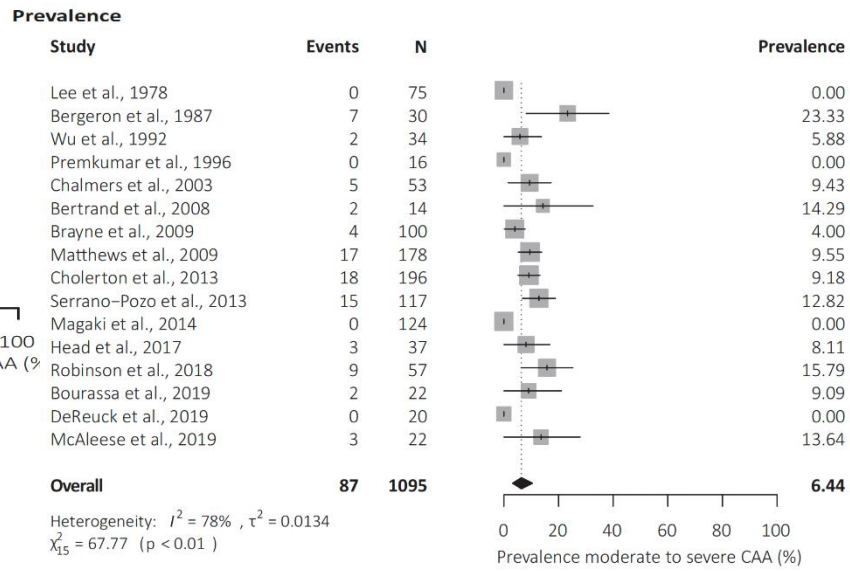


Study	Events	N
Vonsattel et al., 1991	17	66
Itoh et al., 1993	35	160
Xu et al., 2003	77	362
Matthews et al., 2009	101	446
Cholerton et al., 2013	54	363
Brenowitz et al., 2015	1401	3976
Oveisgharan et al., 2018	506	1453
Robinson et al., 2018	13	185
Robinson et al., 2018	26	97
Tanprasertsuk et al., 2019	12	49
Overall	**2242**	**7157**

Heterogeneity: $I^2 = 96\%$, $\tau^2 = 0.0112$
$\chi^2_9 = 213.56$ ($p < 0.01$)

0 20 40 60 80 100
Prevalence moderate to severe CAA (%

Cognitively normal elderly ~6%



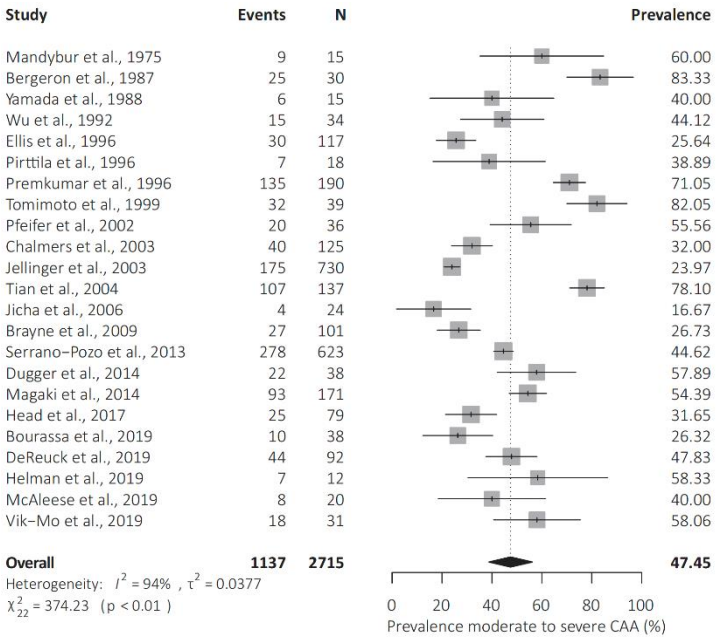
Prevalence

Study	Events	N	Prevalence
Lee et al., 1978	0	75	0.00
Bergeron et al., 1987	7	30	23.33
Wu et al., 1992	2	34	5.88
Premkumar et al., 1996	0	16	0.00
Chalmers et al., 2003	5	53	9.43
Bertrand et al., 2008	2	14	14.29
Brayne et al., 2009	4	100	4.00
Matthews et al., 2009	17	178	9.55
Cholerton et al., 2013	18	196	9.18
Serrano-Pozo et al., 2013	15	117	12.82
Magaki et al., 2014	0	124	0.00
Head et al., 2017	3	37	8.11
Robinson et al., 2018	9	57	15.79
Bourassa et al., 2019	2	22	9.09
DeReuck et al., 2019	0	20	0.00
McAleese et al., 2019	3	22	13.64
Overall	**87**	**1095**	**6.44**

Heterogeneity: $I^2 = 78\%$, $\tau^2 = 0.0134$
$\chi^2_{15} = 67.77$ ($p < 0.01$)

0 20 40 60 80 100
Prevalence moderate to severe CAA (%)

Alzheimer's disease ~50%

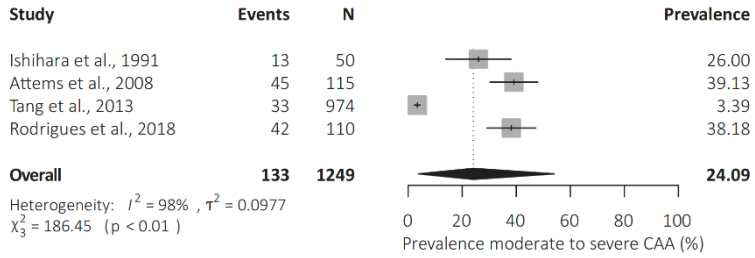


Study	Events	N	Prevalence
Mandybur et al., 1975	9	15	60.00
Bergeron et al., 1987	25	30	83.33
Yamada et al., 1988	6	15	40.00
Wu et al., 1992	15	34	44.12
Ellis et al., 1996	30	117	25.64
Pirttila et al., 1996	7	18	38.89
Premkumar et al., 1996	135	190	71.05
Tomimoto et al., 1999	32	39	82.05
Pfeifer et al., 2002	20	36	55.56
Chalmers et al., 2003	40	125	32.00
Jellinger et al., 2003	175	730	23.97
Tian et al., 2004	107	137	78.10
Jicha et al., 2006	4	24	16.67
Brayne et al., 2009	27	101	26.73
Serrano-Pozo et al., 2013	278	623	44.62
Dugger et al., 2014	22	38	57.89
Magaki et al., 2014	93	171	54.39
Head et al., 2017	25	79	31.65
Bourassa et al., 2019	10	38	26.32
DeReuck et al., 2019	44	92	47.83
Helman et al., 2019	7	12	58.33
McAleese et al., 2019	8	20	40.00
Vik-Mo et al., 2019	18	31	58.06
Overall	**1137**	**2715**	**47.45**

Heterogeneity: $I^2 = 94\%$, $\tau^2 = 0.0377$
$\chi^2_{22} = 374.23$ ($p < 0.01$)

0 20 40 60 80 100
Prevalence moderate to severe CAA (%)

Intracerebral haemorrhage ~25%



Study	Events	N	Prevalence
Ishihara et al., 1991	13	50	26.00
Attems et al., 2008	45	115	39.13
Tang et al., 2013	33	974	3.39
Rodrigues et al., 2018	42	110	38.18
Overall	**133**	**1249**	**24.09**

Heterogeneity: $I^2 = 98\%$, $\tau^2 = 0.0977$
$\chi^2_3 = 186.45$ ($p < 0.01$)

0 20 40 60 80 100
Prevalence moderate to severe CAA (%)

Jäke,…Verbeek DOI: 10.1002/alz.12366

(based on neuropathological examination)

Talk structure

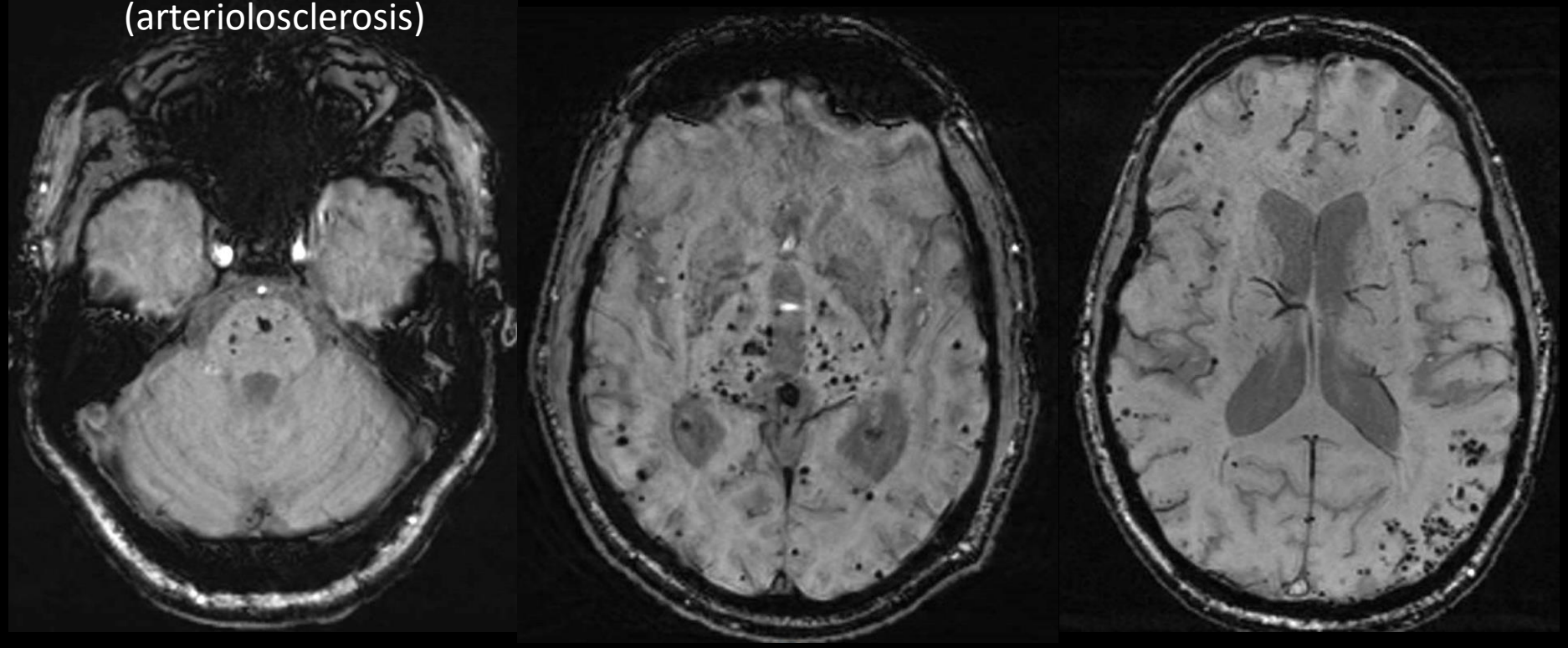
- What is CAA?
- Epidemiology of CAA
- Diagnosis of CAA
- Clinical syndromes associated with CAA
  - Intracerebral haemorrhage
  - Transient focal neurological episodes (TFNE)
  - Cognitive decline
- Management
- Markers of disease progression
- Summary

CMB topography and small vessel disease subtypes

Deep perforator arteriopathy (arteriolosclerosis)

Mixed arteriopathy

Cerebral amyloid angiopathy

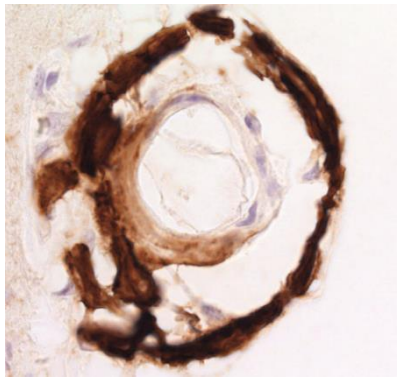


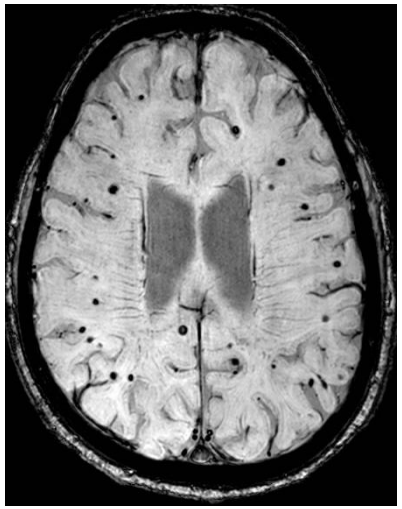
Deep

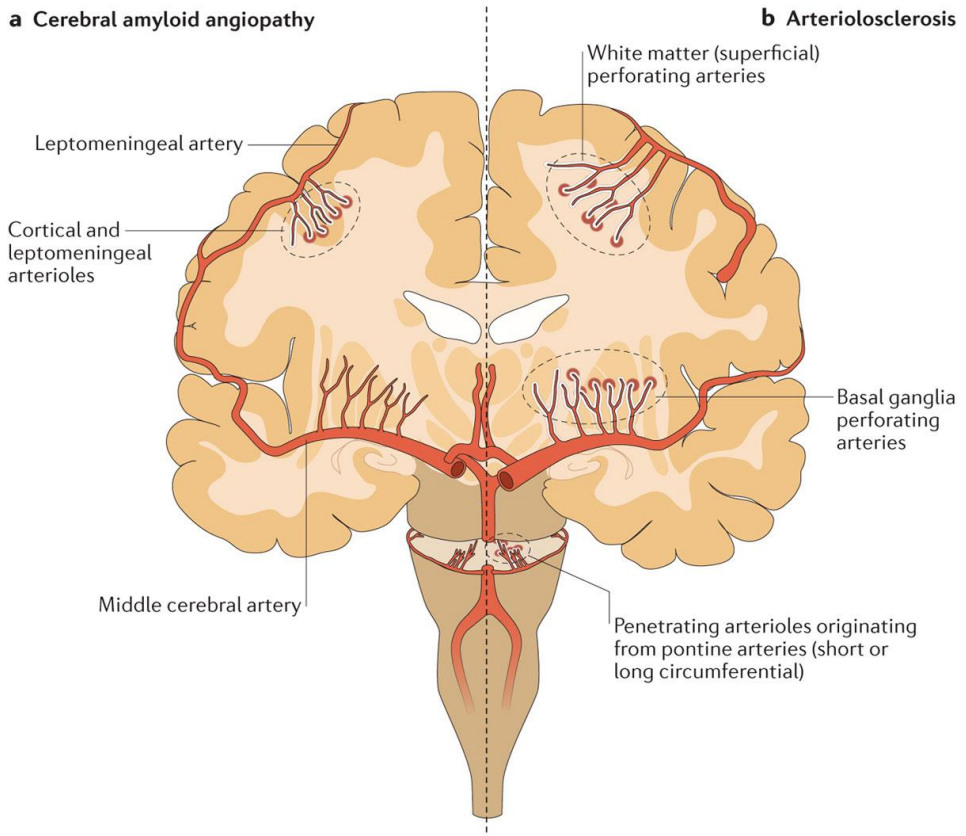
Deep and lobar (mixed)

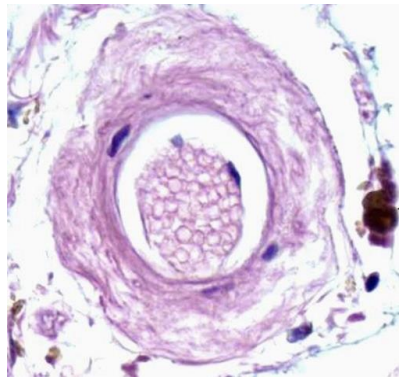
Strictly lobar

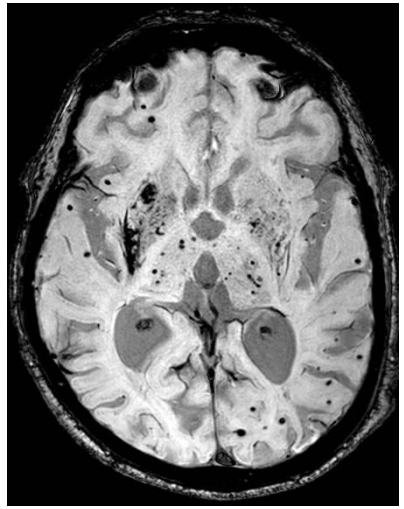
Strictly lobar cerebral microbleeds on MRI have good diagnostic accuracy for CAA







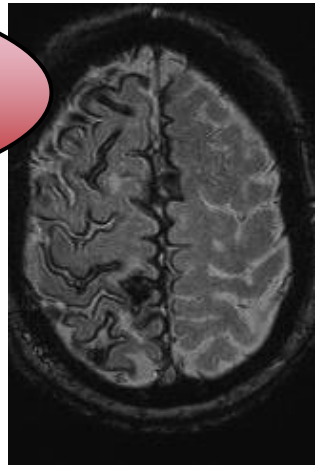




Nature Reviews Neurology 12, 680–682 (2016)

Boston criteria v1.0 and modified (v1.5)

modifed criteria include cortical superficial siderosis



Definite CAA

- Full postmortem examination demonstrating severe CAA

Probable CAA with supporting pathology

- Clinical data and pathological tissue (evacuated hematoma or cortical biopsy) with CAA

Probable CAA*

- Clinical data and MRI or CT demonstrating **multiple haemorrhages** (ICH, CMB) restricted to lobar, cortical, or cortical–subcortical regions (cerebellar hemorrhage allowed), OR single lobar, cortical, or cortical–subcortical hemorrhage **AND cSS (focal or disseminated)**

Possible CAA*

- Clinical data and MRI or CT demonstrating single lobar, cortical, or cortical–subcortical ICH, CMB, **OR cSS (focal or disseminated)**

**age ≥55 years, no other cause of haemorrhage*

Pathological validation of Boston Criteria

Setting	CAA Pathology+Subjects (ICH+/ICH–)	CAA Pathology–Subjects (ICH+/ICH–)	Sensitivity	Specificity
MRI-neuropathology studies				
Hospital-based[15]	11 (11/0)	4 (4/0)	72.7%	100%
Hospital-based[10]	38 (27/11)	22 (22/0)	57.9% (71.1%*)	95.5% (95.5%*)
Hospital-based[16]	14 (9/5)	10 (10/0)	76.9%	87.5%
Hospital-based[17]	33 (0/33)	22 (0/22)	42.4%	90.9%
Population-based[17]	22 (0/22)	25 (0/25)	4.5%	88.0%

with ICH

without ICH

**modified Boston criteria*

- Note the much lower sensitivity in non-ICH populations
- Do not include newer imaging biomarkers of CAA

Neurology 2001; 56: 537–539.
Neurology 2010; 74: 1346–1350.
Neurology 2014; 82: 57–62.
Alzheimers Dement 2015; 11: 1480–1488.
Int J Stroke 2019, Vol. 14(9) 956–971
Stroke 2018;49:491-497.

The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI–neuropathology diagnostic accuracy study

Andreas Charidimou, Gregoire Boulouis, Matthew P Frosch, Jean-Claude Baron, Marco Pasi, Jean Francois Albucher, Gargi Banerjee, Carmen Barbato, Fabrice Bonneville, Sebastian Brandner, Lionel Calviere, François Caparros, Barbara Casolla, Charlotte Cordonnier, Marie-Bernadette Delisle, Vincent Deramecourt, Martin Dichgans, Elif Gokcal, Jochen Herms, Mar Hernandez-Guillamon, Hans Rolf Jäger, Zane Jaunmuktane, Jennifer Linn, Sergi Martinez-Ramirez, Elena Martínez-Sáez, Christian Mawrin, Joan Montaner, Solene Moulin, Jean-Marc Olivot, Fabrizio Piazza, Laurent Puy, Nicolas Raposo, Mark A Rodrigues, Sigrun Roeber, Jose Rafael Romero, Neshika Samarasekera, Julie A Schneider, Stefanie Schreiber, Frank Schreiber, Corentin Schwall, Colin Smith, Levente Szalardy, Pascale Varlet, Alain Viguier, Joanna M Wardlaw, Andrew Warren, Frank A Wollenweber, Marialuisa Zedde, Mark A van Buchem, M Edip Gurol, Anand Viswanathan, Rustam Al-Shahi Salman, Eric E Smith, David J Werring, Steven M Greenberg

Lancet Neurol 2022; 21: 714–25.

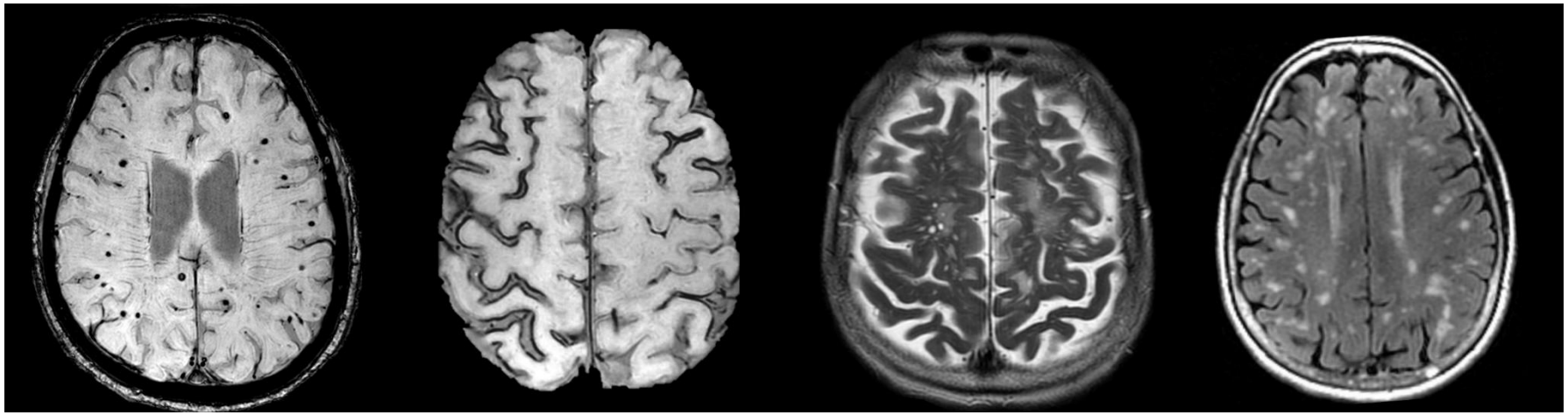
Provisional Boston v2.0 criteria

New v2.0 criteria include white matter features

Probable CAA

- ≥2 strictly lobar hemorrhagic lesions in any combination:
  - ICH, CMBs, **cSS/cSAH foci**

  OR
- 1 strictly lobar hemorrhagic lesion + **1 WM feature (Severe CSO-PVS or multispot WMH pattern)**



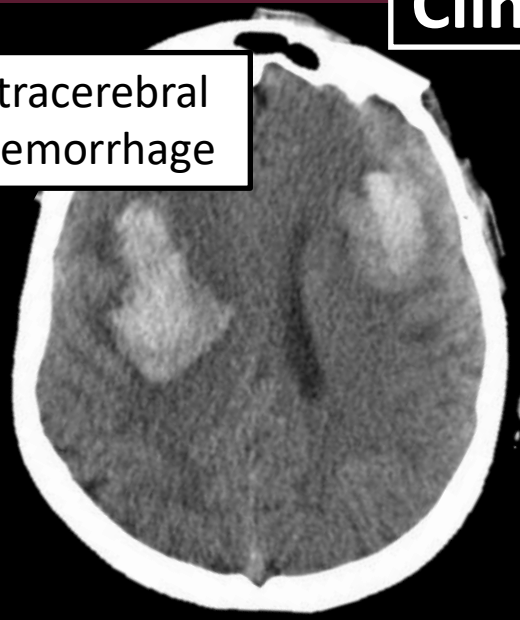
Int J Stroke 2019;14:956

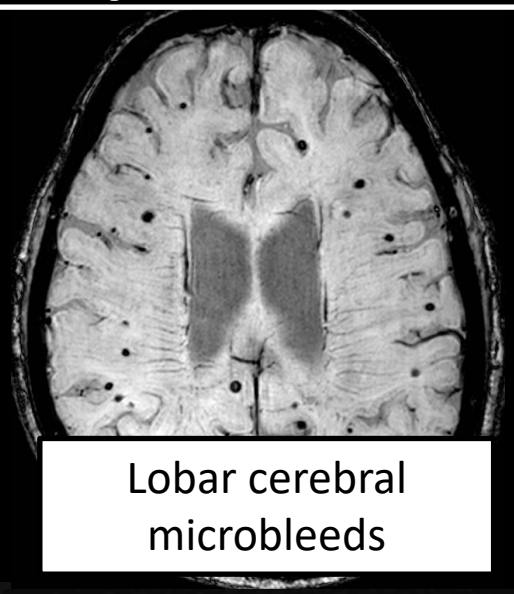
Talk structure

- What is CAA?
- Epidemiology of CAA
- Diagnosis of CAA
- Clinical syndromes associated with CAA
  - Intracerebral haemorrhage
  - Transient focal neurological episodes (TFNE)
  - Cognitive decline
- Management
- Markers of disease progression
- Summary

Clinical spectrum of CAA

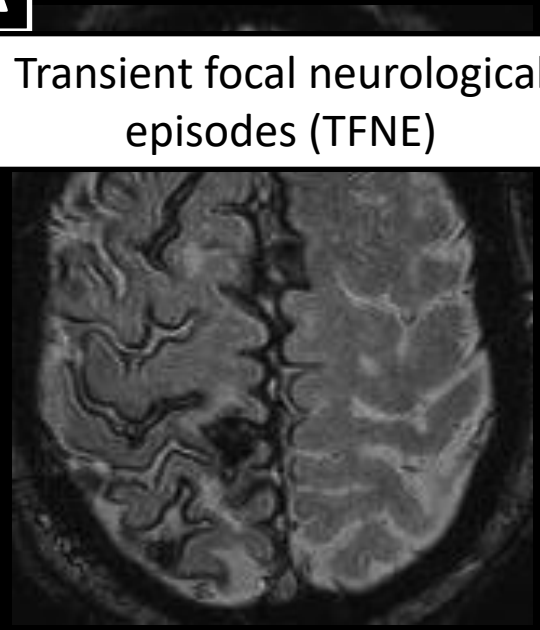
Intracerebral haemorrhage

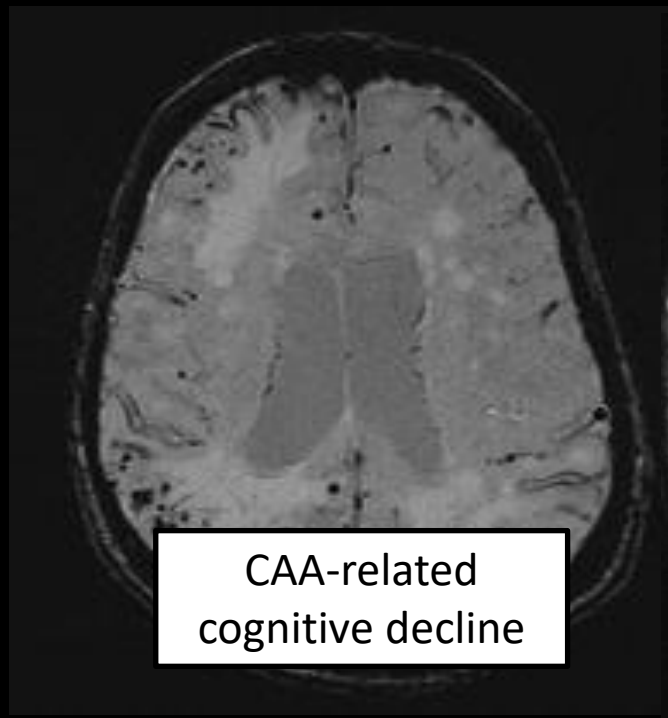




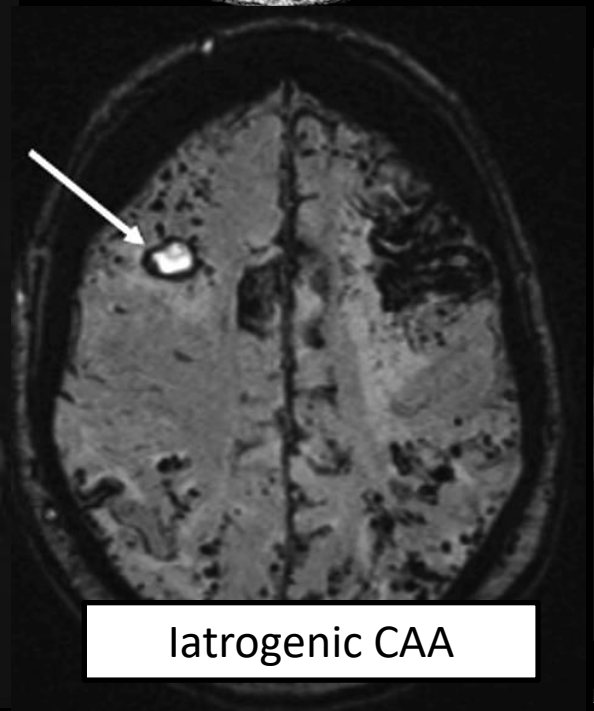
Lobar cerebral microbleeds

Transient focal neurological episodes (TFNE)

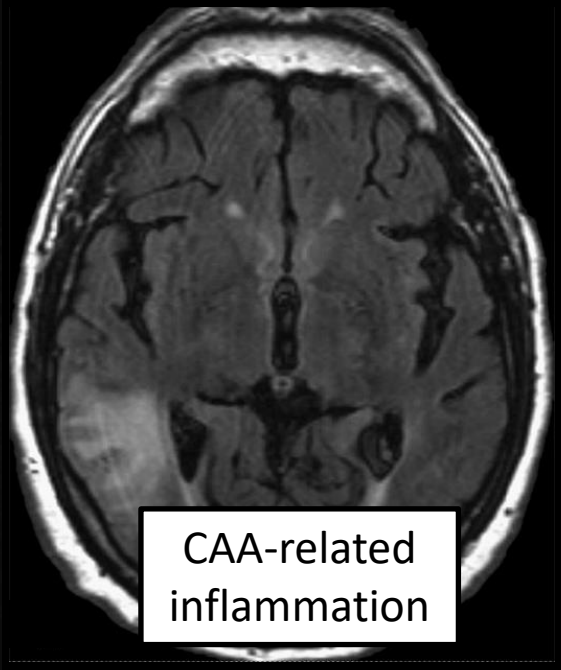




CAA-related cognitive decline



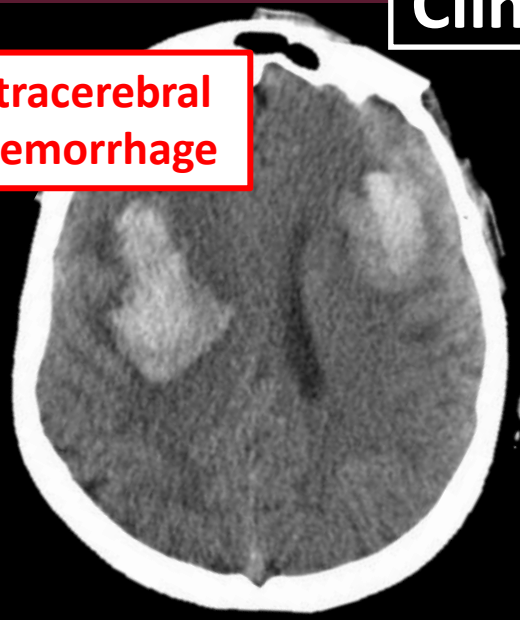
Iatrogenic CAA

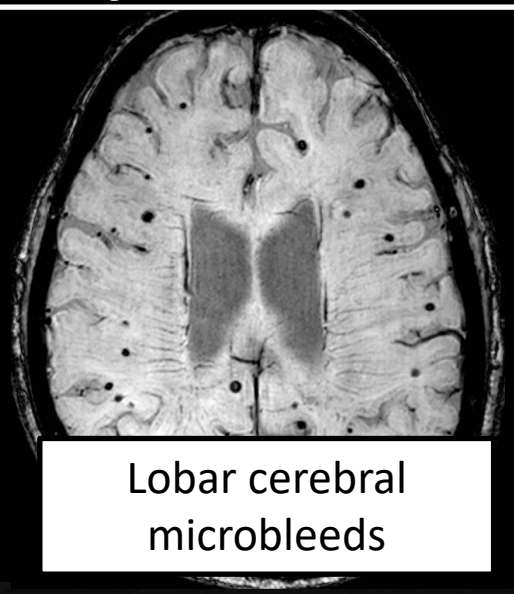


CAA-related inflammation

Clinical spectrum of CAA

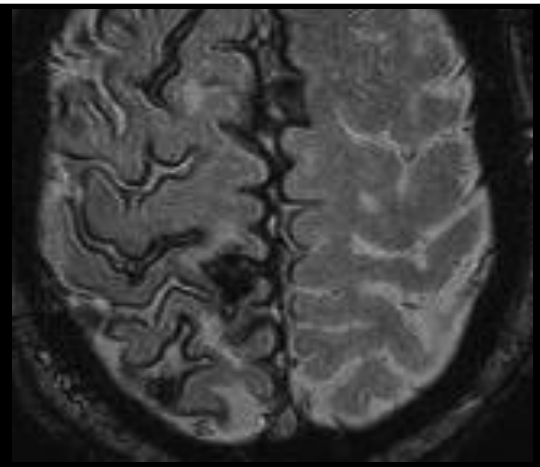
Intracerebral haemorrhage

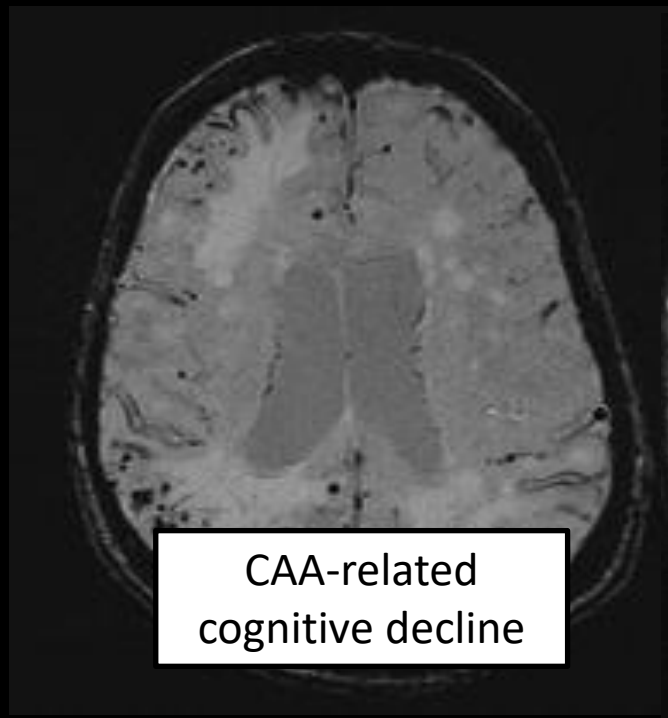




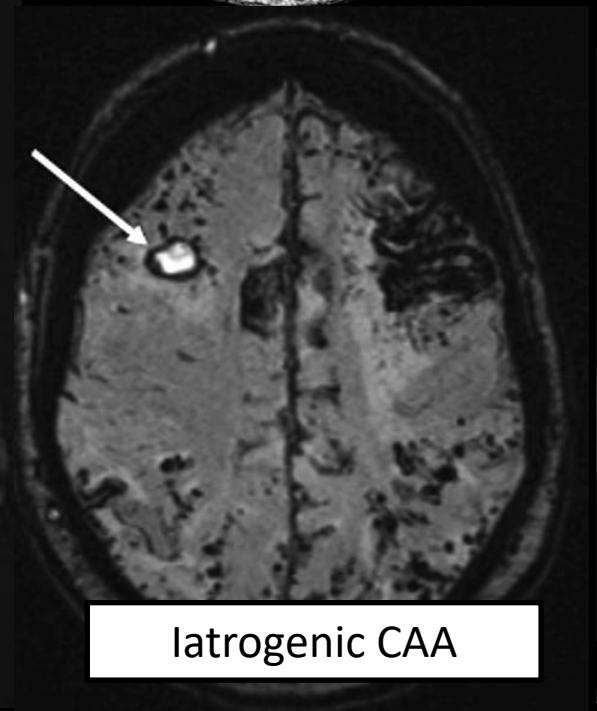
Lobar cerebral microbleeds

Transient focal neurological episodes (TFNE)

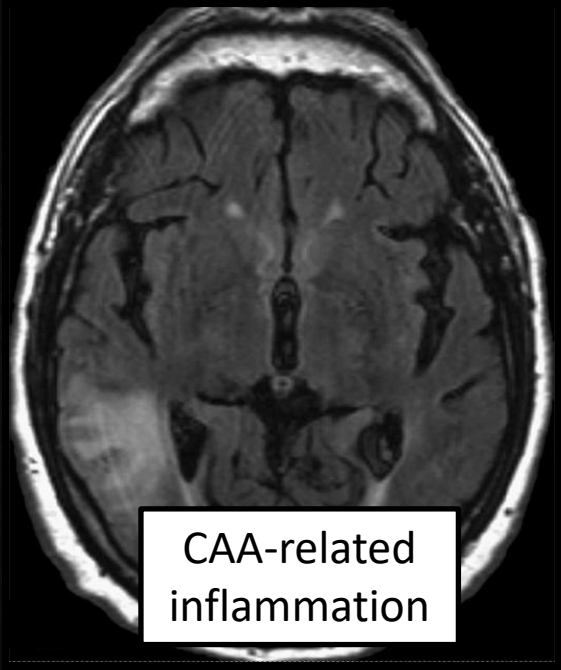




CAA-related cognitive decline



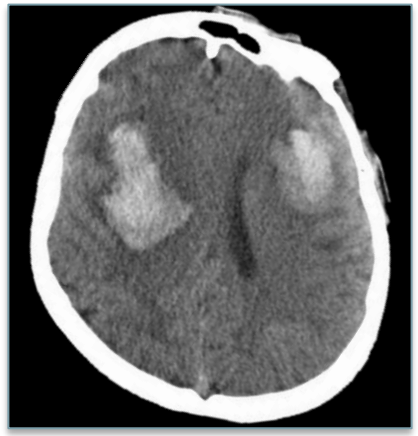
Iatrogenic CAA

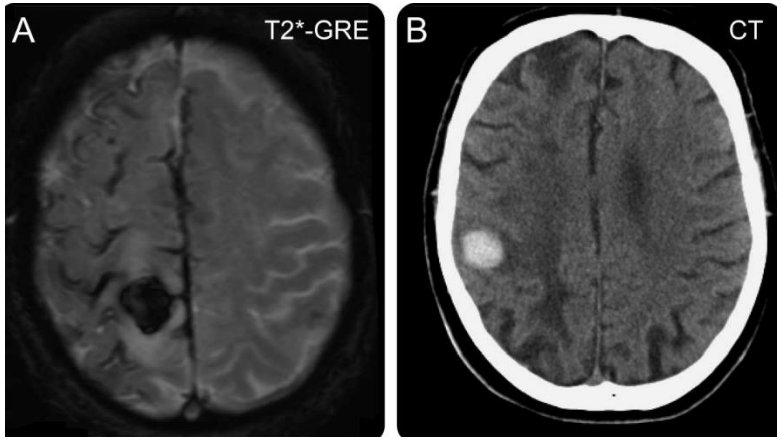


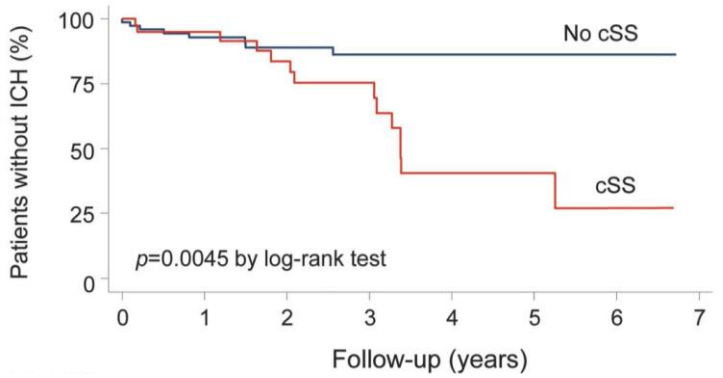
CAA-related inflammation

CAA and intracerebral haemorrhage

- ~20% of spontaneous lobar ICH
- High early recurrence risk (spatial and temporal clustering?)
- Can be multiple, synchronous
- Initial ICH may be mild, with radiological-clinical mismatch
- May be minor trauma
- Can be diagnosed on clinico-radiological (Boston) criteria based on strictly lobar bleeding
- **Cortical superficial siderosis** is the strongest bleeding predictor (not microbleeds)



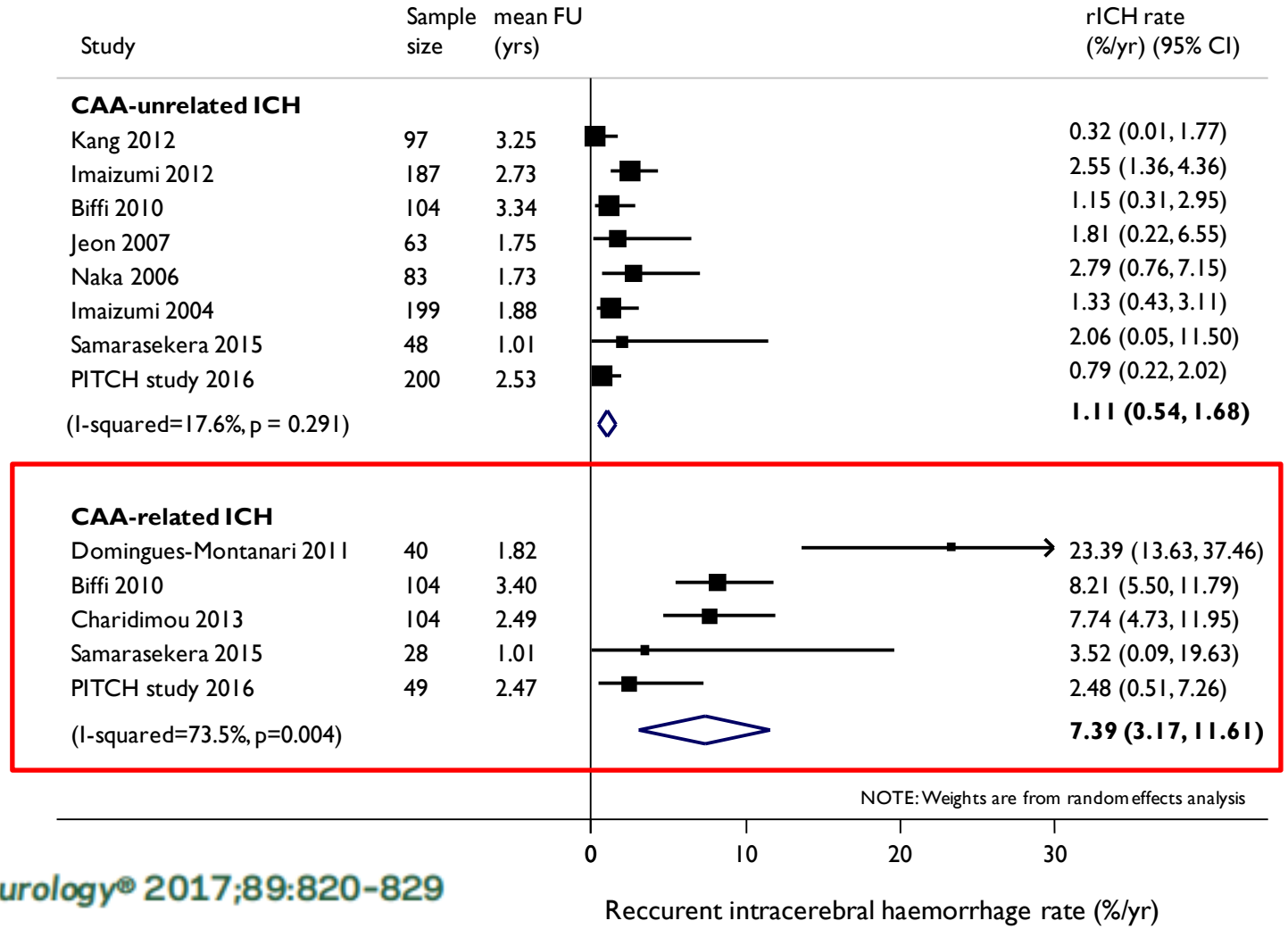




CAA-ICH has a high recurrence risk

Brain hemorrhage recurrence, small vessel disease type, and cerebral microbleeds

A meta-analysis

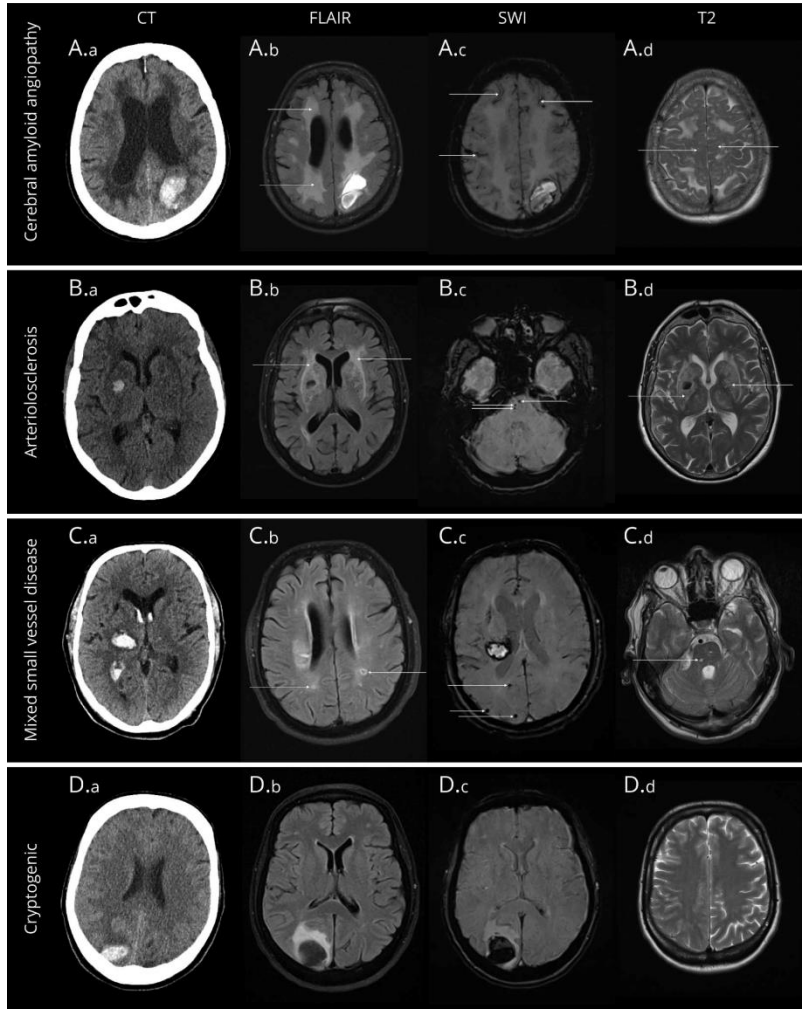


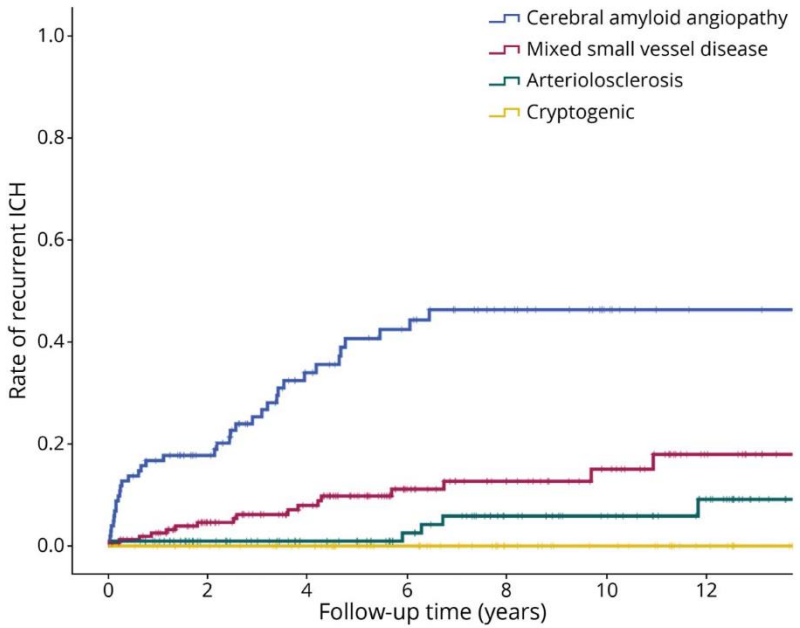
Neurology® 2017;89:820-829

CAA has a high recurrence risk

RESEARCH ARTICLE OPEN ACCESS

Association of the Presence and Pattern of MRI Markers of Cerebral Small Vessel Disease With Recurrent Intracerebral Hemorrhage

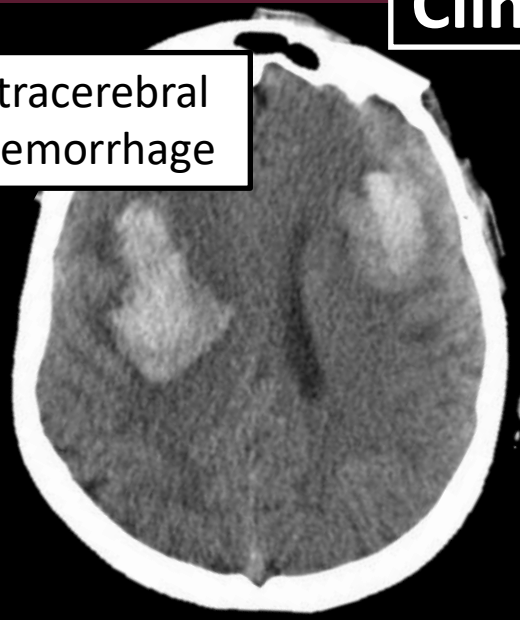


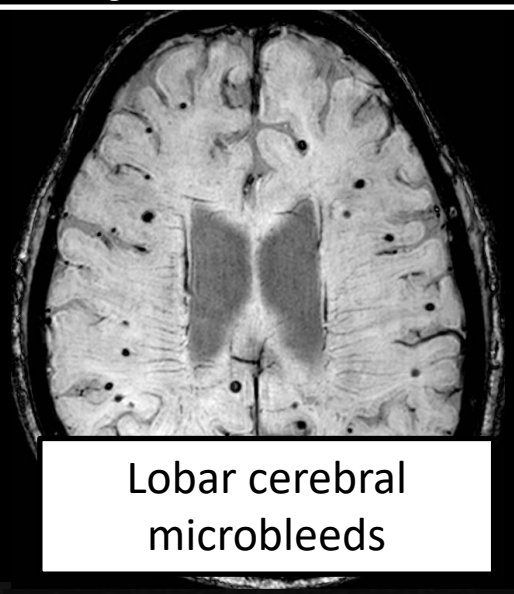


doi:10.1212/WNL.0000000000207510

Clinical spectrum of CAA

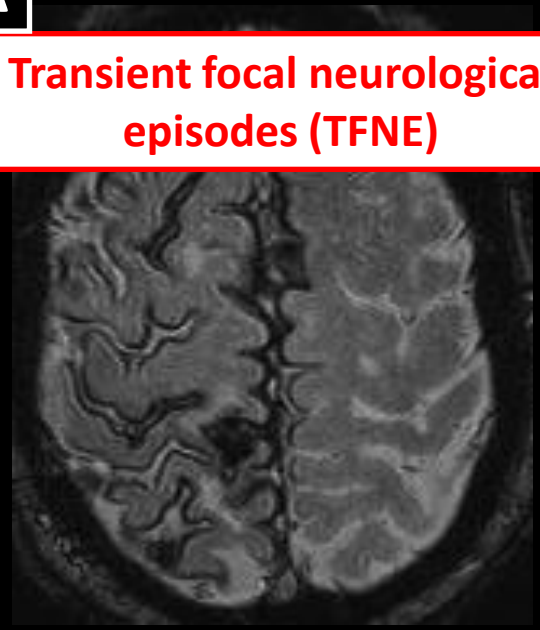
Intracerebral haemorrhage

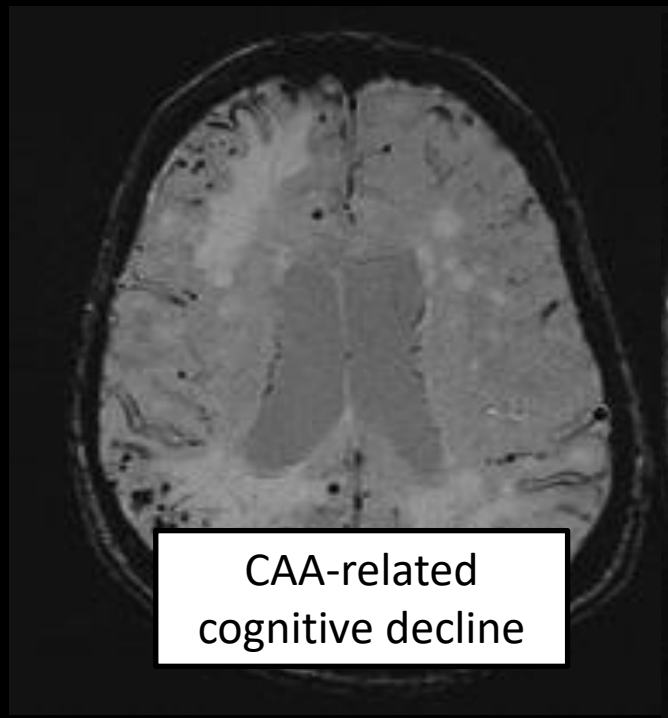




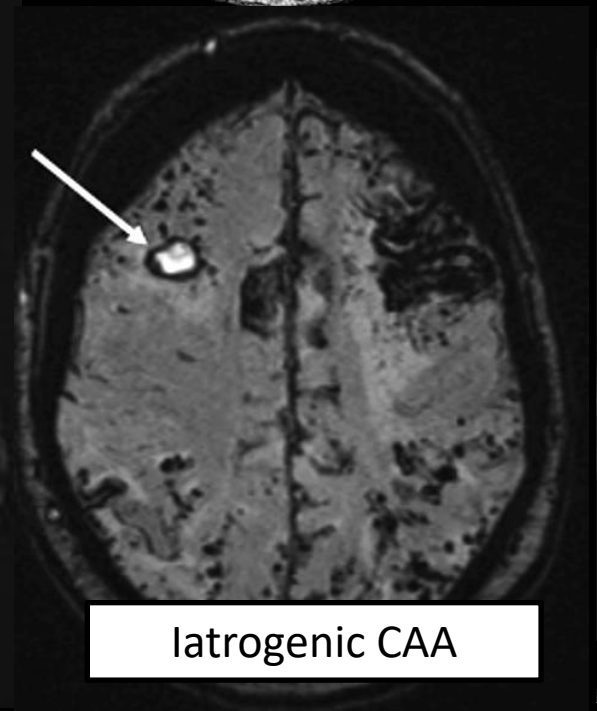
Lobar cerebral microbleeds

Transient focal neurological episodes (TFNE)

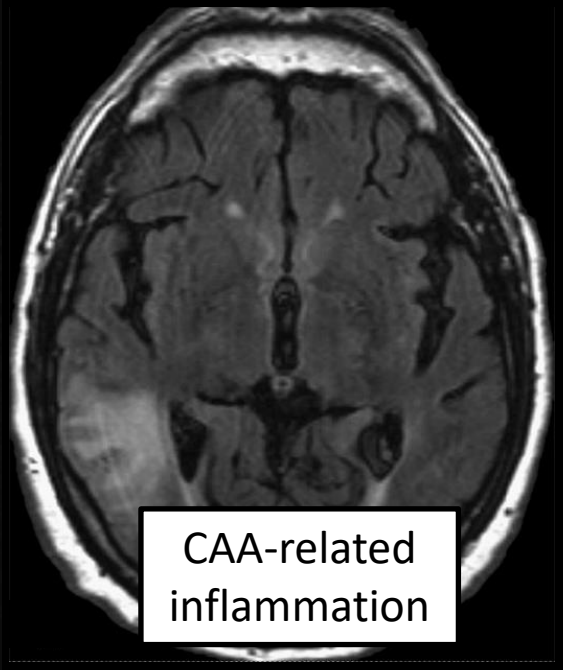




CAA-related cognitive decline



Iatrogenic CAA

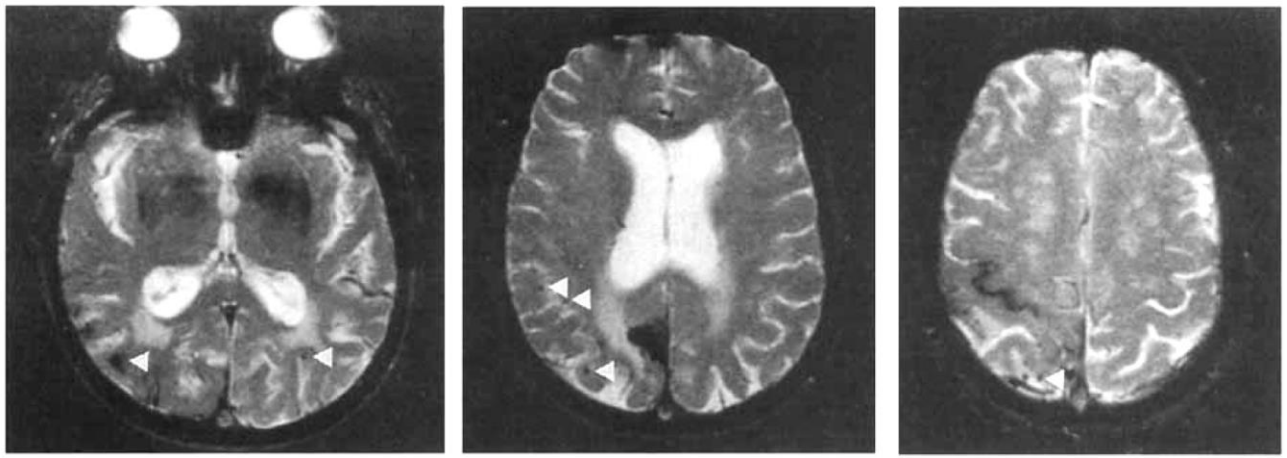


CAA-related inflammation

The clinical spectrum of cerebral amyloid angiopathy:
Presentations without lobar hemorrhage

S.M. Greenberg, MD, PhD; J.P.G. Vonsattel, MD; J.W. Stakes, MD; M. Gruber, MD; and S.P. Finklestein, MD

1/73/M	Episodes of numbness and weakness spreading from L hand to arm and face
2/82/F	Episodes of paresthesias spreading from L shoulder to hand
4/77/F	Episodes of spreading paresthesias on L side; mild memory loss, progressive over 3 years
7/57/M	Episodes of numbness and weakness spreading from R fingers to arm, trunk, leg, and face;



These cases raise practical concerns about the safety of prophylactic anticoagulation in elderly patients with recurrent neurologic symptoms

NEUROLOGY 1993;43:2073-2079

The clinical spectrum of cerebral amyloid angiopathy:
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1/73/M Episodes of numbness

- characteristic spread of symptoms into contiguous body areas
- small haemorrhagic lesions or subsequent large ICH in cortical locations corresponding to the neurological symptoms

progressive over 3 years

7/57/M Episodes of numbness and weakness spreading from R fingers to arm, trunk, leg, and face;

These cases raise practical concerns about the safety of prophylactic anticoagulation in elderly patients with recurrent neurologic symptoms

NEUROLOGY 1993;43:2073-2079

Clinical presentation

Spectrum of Transient Focal Neurological Episodes in Cerebral Amyloid Angiopathy

Multicentre Magnetic Resonance Imaging Cohort Study and Meta-Analysis

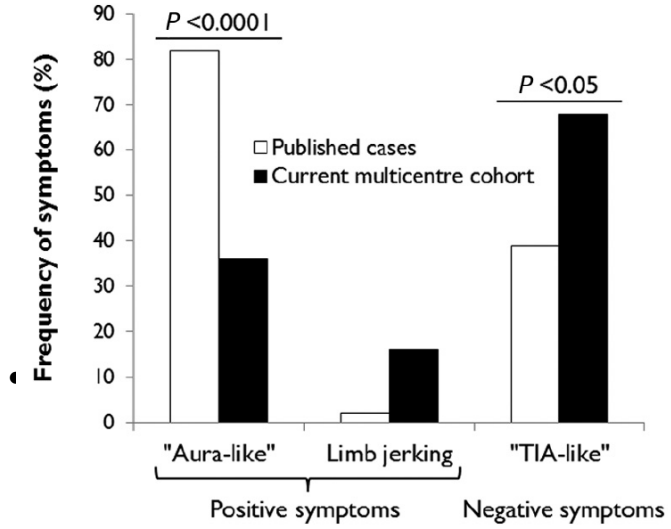
Andreas Charidimou, MSc; Andre Peeters, Zoe Fox, PhD; Simone M. Gregoire, MD; Yves Vandermeeren, PhD; Patrice Laloux, PhD; Hans R. Jäger, PhD; Jean-Claude Baron, PhD; David J. Werring, PhD

- 25/172 patients (14.5%; 95% CI 9.6%–20.7%) had TFNE
- The commonest positive symptoms are transient paraesthesias in the mouth or hand (32%), usually with a gradual spread to contiguous body parts
- Negative symptoms included focal weakness and dysphasia
- Usually multiple episodes, nearly always stereotyped
- Duration <6 minutes in 44% of patients, <30 minutes in 70%, and ≤3 hours in 96%.
- Note: often mixed positive and negative symptoms

Stroke. 2012 Sep;43(9):2324-30.

High risk of intracerebral haemorrhage after CAA-TFNEs

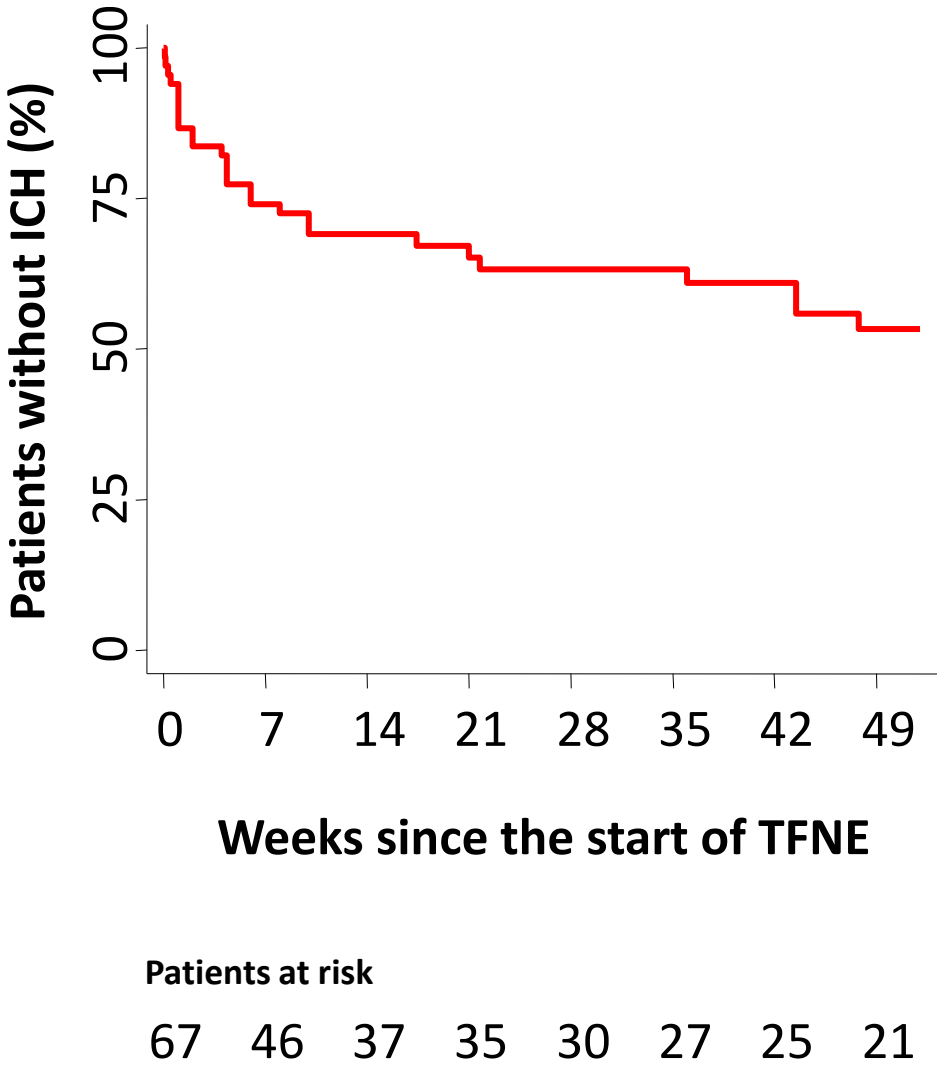
- **Negative (TIA-like)** symptoms common



nth ICH

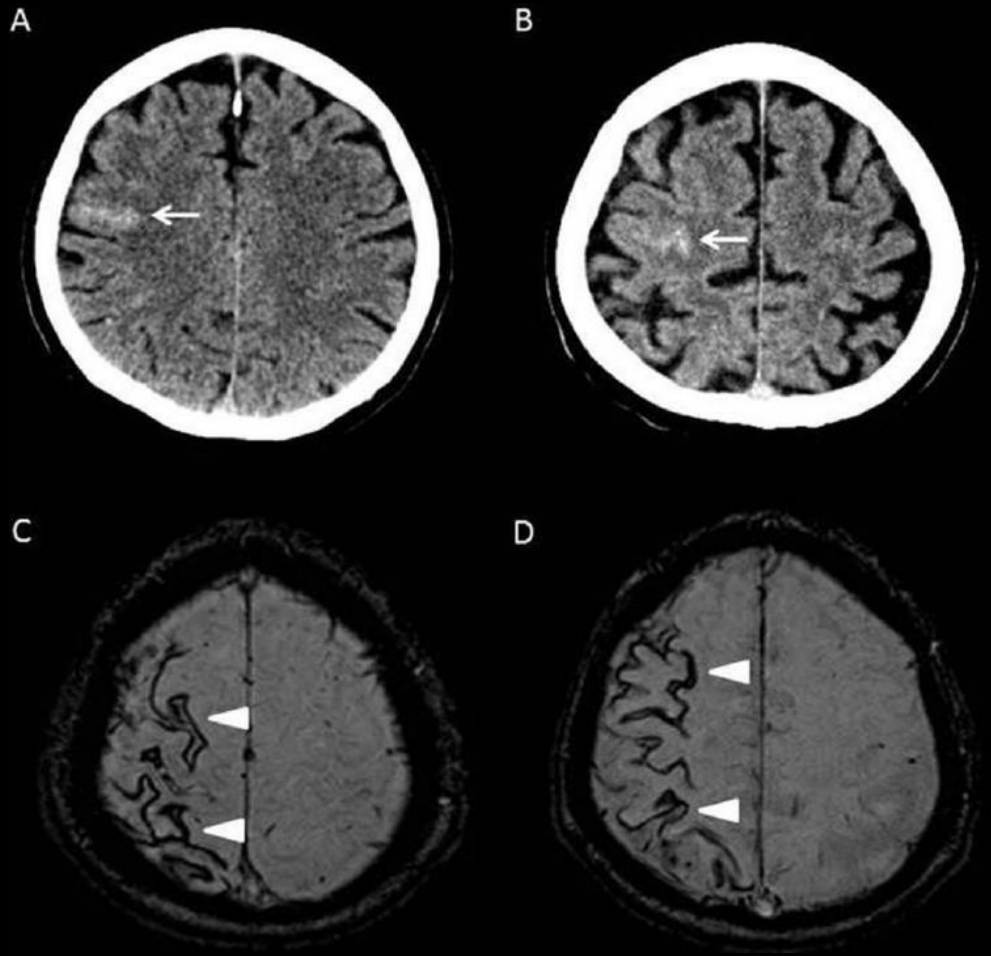
to

Time to symptomatic ICH from start of TFNEs



Stroke. 2012 Sep;43(9):2324-30.

Neuroimaging in CAA-TFNE

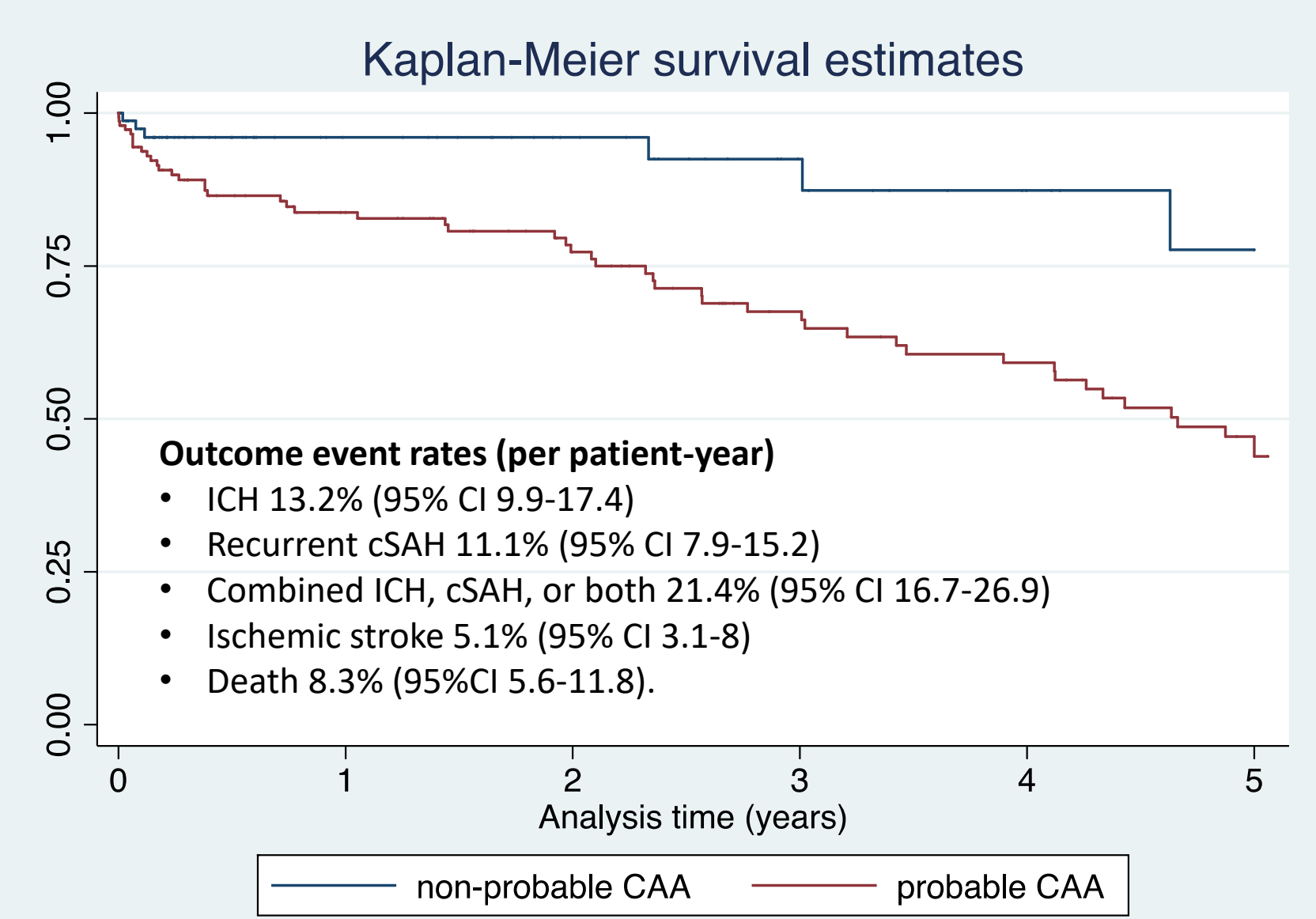


- 76-year-old patient who presented with migratory left-sided sensory symptoms consistent with CAA-associated TFNE.
- Acute CT (A) shows a hyperdense area in keeping with an acute cSAH (arrow).
- Repeat CT (B) after a further episode 3 months later demonstrated another acute cSAH nearby (arrow).
- Subsequent SWI MRI (C and D) showed widespread disseminated cSS affecting the right hemisphere (arrowheads).

- **CAA-TFNE are closely associated with cSAH or cSS**
- **Most patients with CAA-TFNE have one or both of cSAH or cSS**
- **Disseminated cSS is common**

J Neurol Neurosurg Psychiatry 2017;0:1–13. doi:10.1136/jnnp-2016-314697

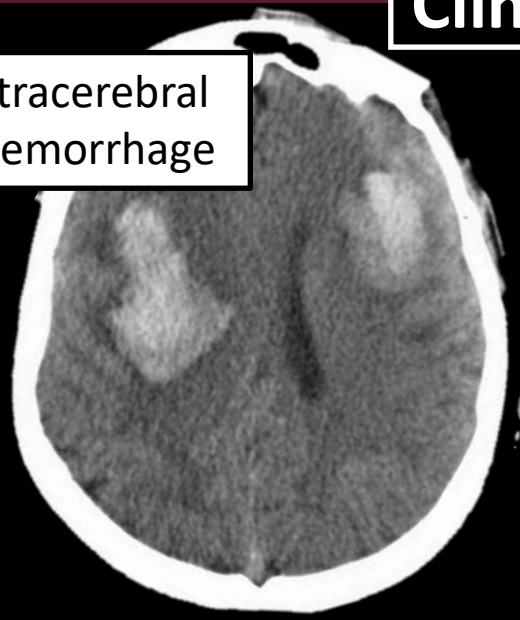
Convexity SAH prognosis, collaborative pooled analysis, n=190

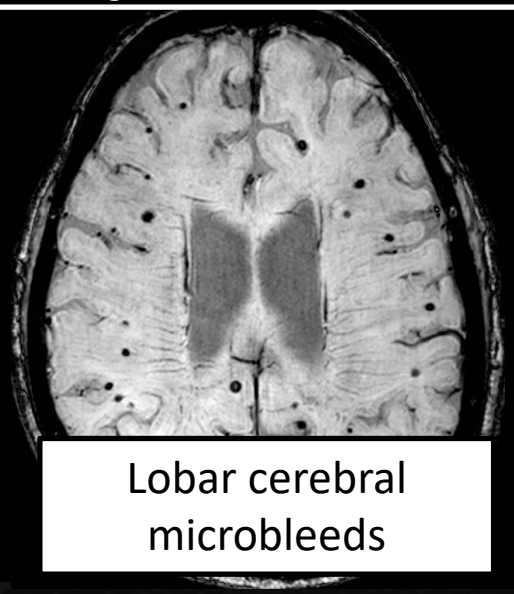


Hostettler et al. J Neurol 2021

Clinical spectrum of CAA

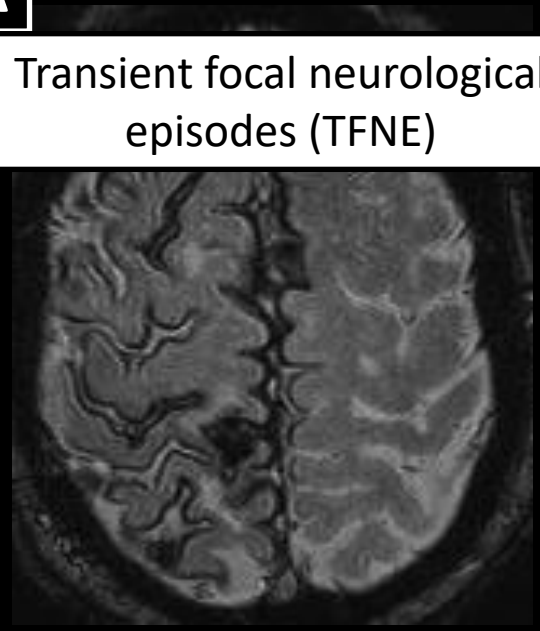
Intracerebral haemorrhage

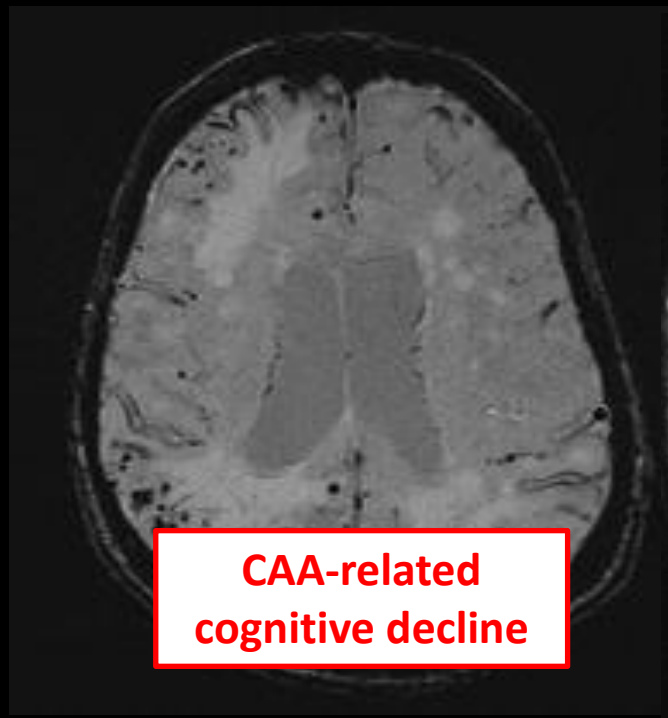




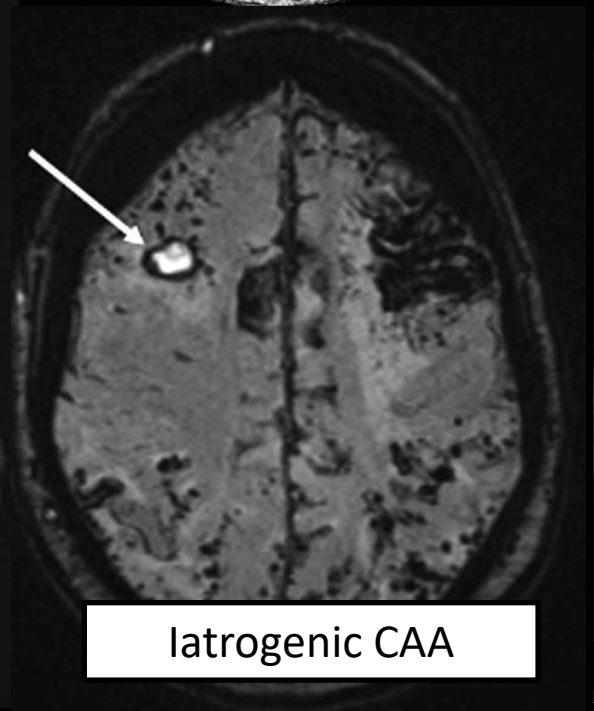
Lobar cerebral microbleeds

Transient focal neurological episodes (TFNE)

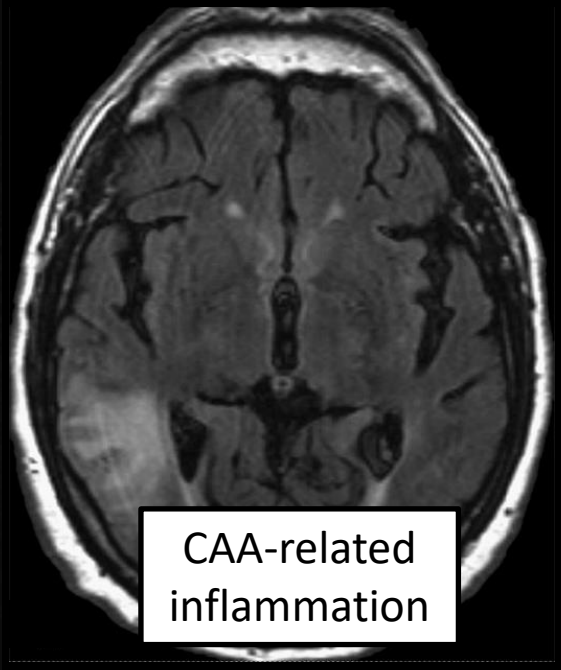




CAA-related cognitive decline

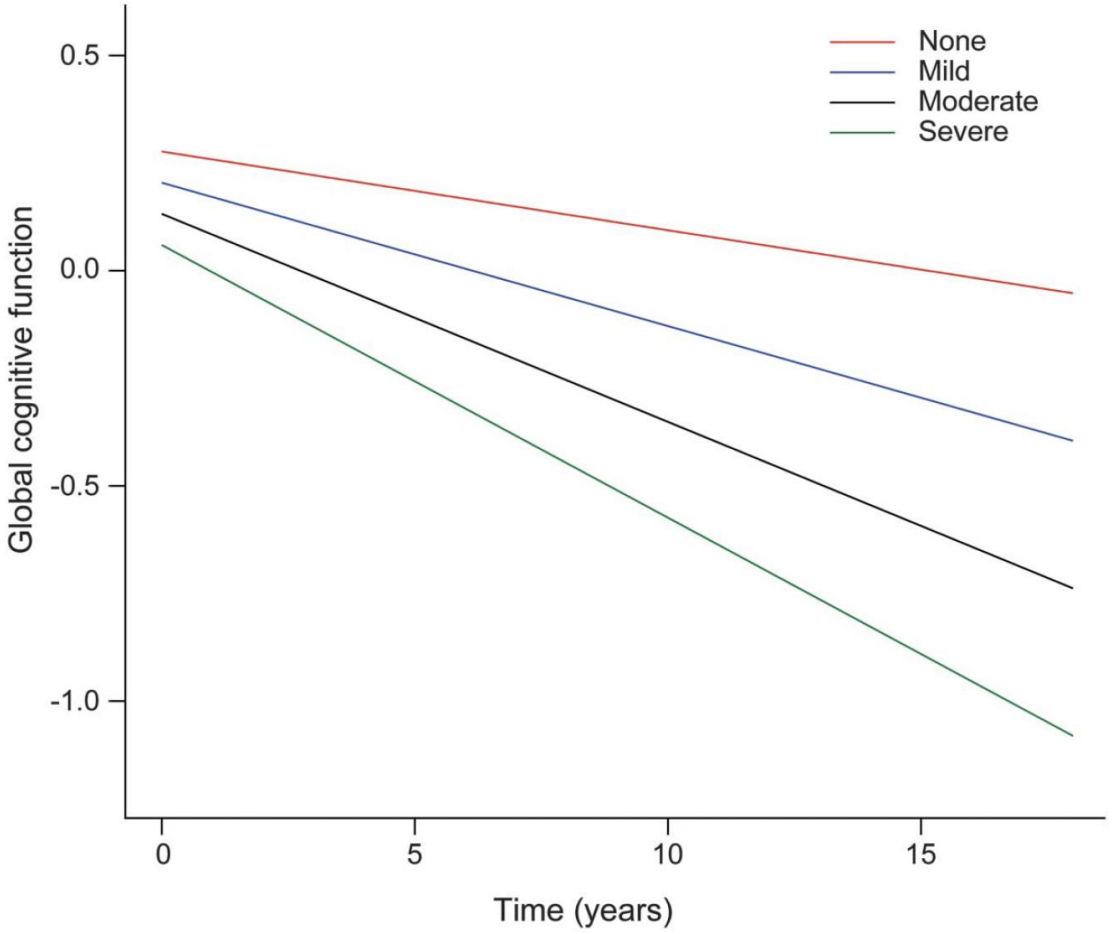


Iatrogenic CAA



CAA-related inflammation

Independent effect of CAA on cognitive progression



adjusted for age, sex, education, AD pathology, macro- and microscopic infarcts, and Lewy bodies.

- Data from 1100 older persons
- Cognitive data collected over 19 years
- Faster rates of decline in global cognition, perceptual speed, episodic and semantic memory.

Neurology 2015;85:1930–1936

Talk structure

- What is CAA?
- Epidemiology of CAA
- Diagnosis of CAA
- Clinical syndromes associated with CAA
  - Intracerebral haemorrhage
  - Transient focal neurological episodes (TFNE)
  - Cognitive decline
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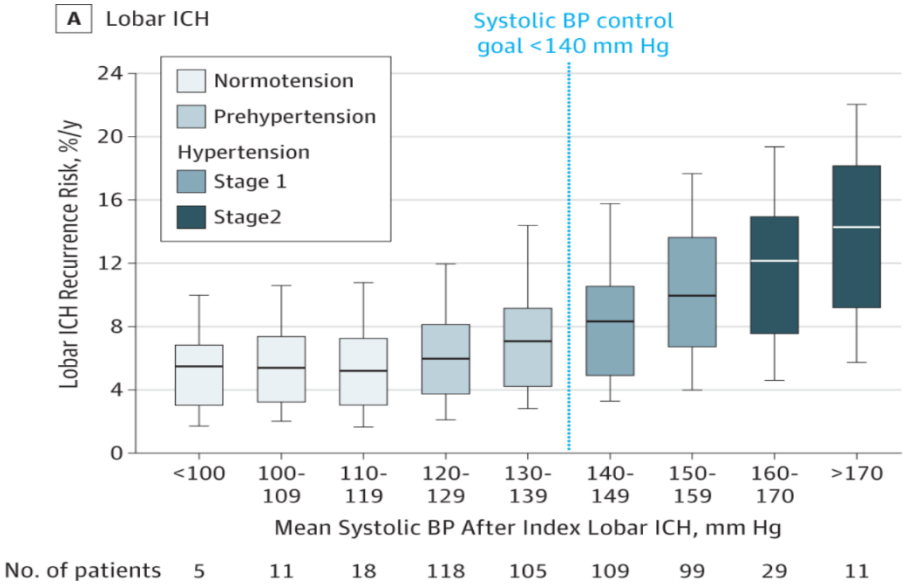
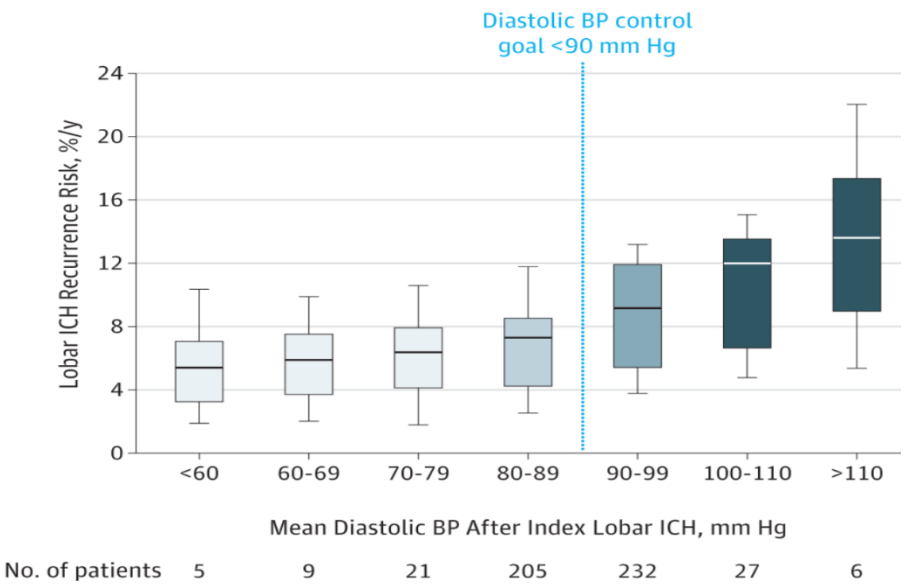
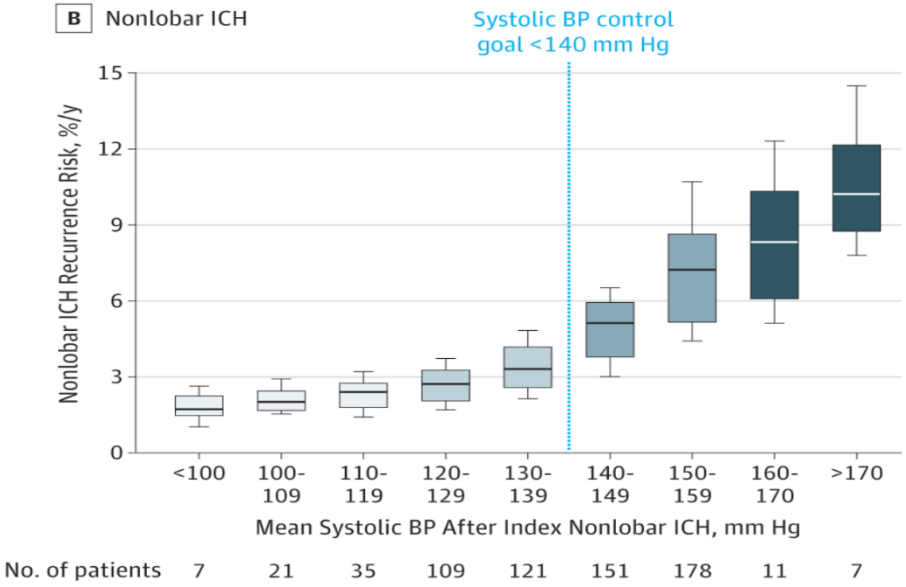
Acute treatment of CAA-ICH

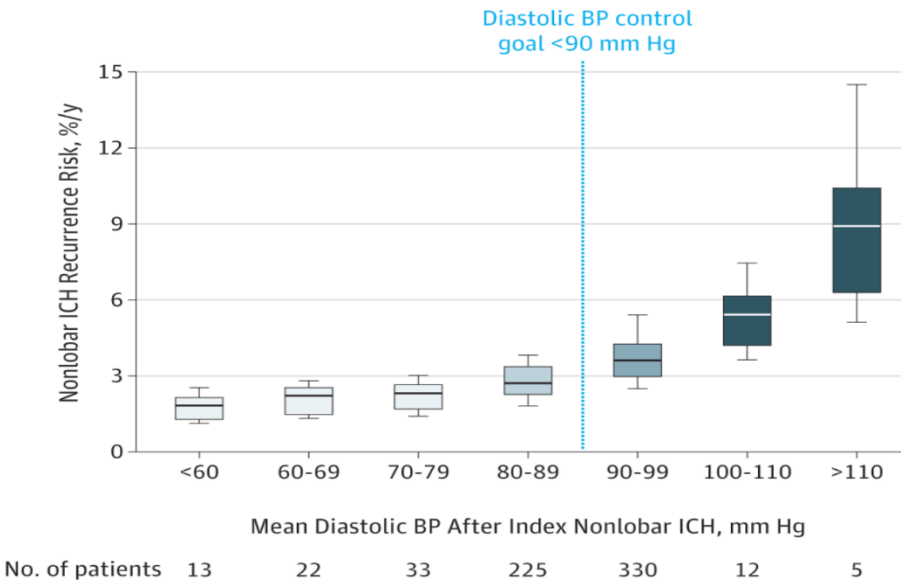
- As for any acute ICH
- Stroke unit care
- Critical care (HDU / neuro-ITU) for ICH with large volume, IVH, progressive deficit, etc.
- Rapid reversal of OAC (PCC)
- BP control according to INTERACT trials and UK guidelines
- Avoid DNAR orders in the first 48 hours
- Neurosurgical referral pathway - or consider for clinical trials
- Noninvasive surgery looks promising
- TICH-3 in set-up (tranexamic acid; CI Sprigg)

PREVENTION of recurrent ICH: blood pressure control









JAMA. 2015 Sep 1;314(9):904-12.

Anticoagulation in patients with cerebral amyloid angiopathy

EdoxabaN foR IntraCranial Hemorrhage Survivors With Atrial Fibrillation (ENRICH-AF) (ENRICH-AF)

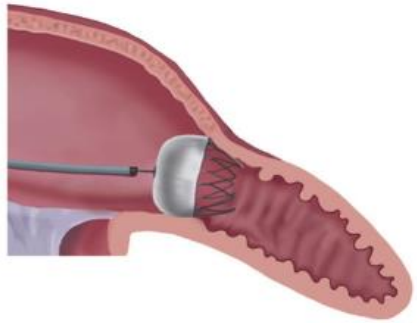
- edoxaban (60/30 mg daily) compared to non-antithrombotic medical therapy (either no antithrombotic therapy or antiplatelet monotherapy) in high-risk atrial fibrillation (CHA2DS2-VASc ≥2) patients with previous intracranial hemorrhage

"…the ENRICH-AF data safety monitoring board (DSMB) recommended that ***participants with lobar intracranial haemorrhage and convexity subarachnoid haemorrhage stop receiving the drug as soon as possible and that no further patients with these intracranial haemorrhage subtypes be enrolled***. The DSMB indicated that these recommendations were based on observations of ***unacceptably high risks of recurrent haemorrhagic stroke among patients with lobar intracerebral haemorrhage and convexity subarachnoid haemorrhage assigned to the edoxaban arm***."

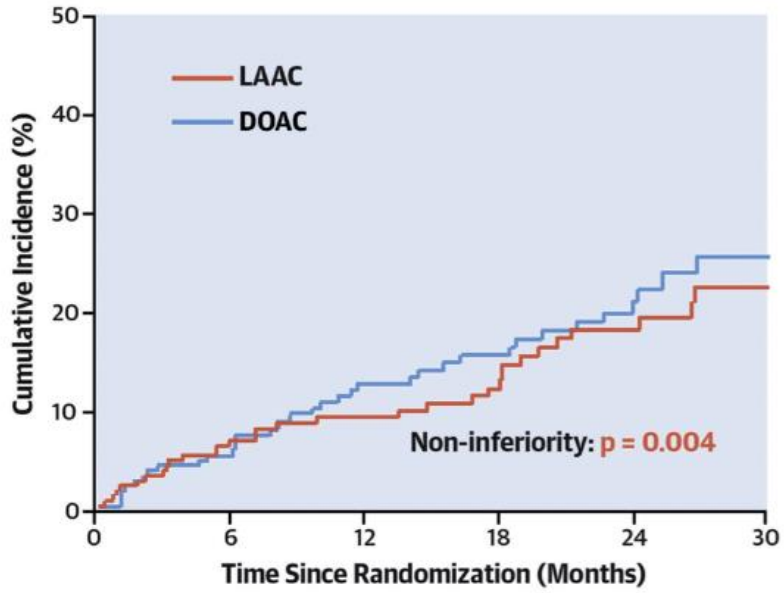
Published in *The Lancet* **Online** October 12, 2023
https://doi.org/10.1016/ S01406736(23)020251

Left atrial appendage occlusion vs DOACs

- 402 High-Risk AF Pts ➡ Randomized
  - CHA_2DS_2-VASc = 4.7 ± 1.5
  - HAS-BLED = 3.1 ± 0.9
- Follow-up: 20.8 ± 10.8 mo (695 pt-year)



Primary Endpoint
Stroke, TIA, SE, CV Death, Bleeding, or Complications



	sHR (95% CI)	p value
Primary Endpoint		
mITT	0.84 (0.53-1.31)	0.44
Per Protocol	0.82 (0.52-1.30)	0.40
On-Treatment	0.79 (0.49-1.25)	0.31
All-Stroke/TIA	1.00 (0.40-2.51)	0.99
CV Death	0.75 (0.34-1.62)	0.46
Major + NMCR Bleeding		
All	0.81 (0.44-1.52)	0.51
Nonprocedural	0.53 (0.26-1.06)	0.07

Osmancik, P. et al. J Am Coll Cardiol. 2020;75(25):3122–35.

LAAC: left atrial appendage closure
miTT: modified intention-to-treat
NMCRB: nonmajor clinically relevant bleeding

Talk structure

- What is CAA?
- Epidemiology of CAA
- Diagnosis of CAA
- Clinical syndromes associated with CAA
  - Intracerebral haemorrhage
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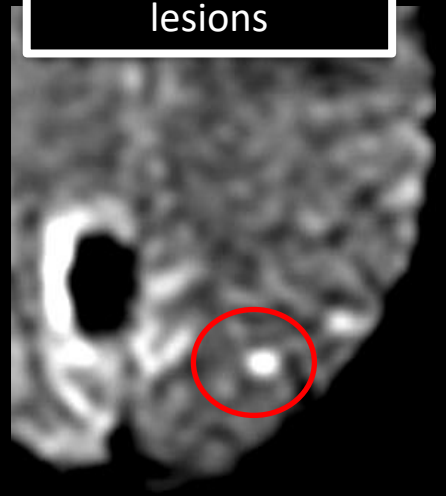
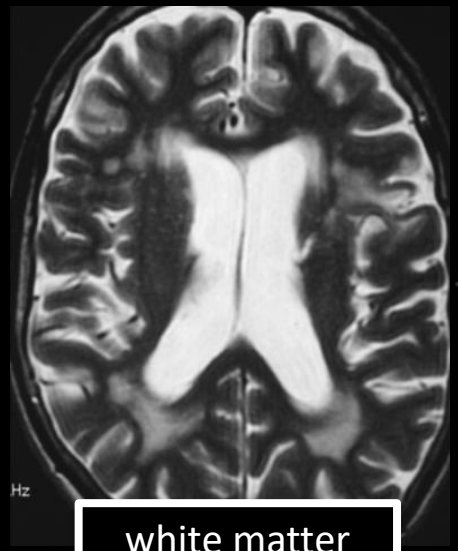
Summary of neuroimaging biomarkers in CAA

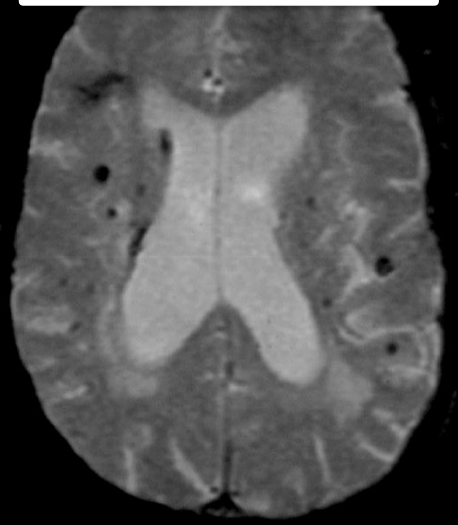
DWI hyperintense lesions



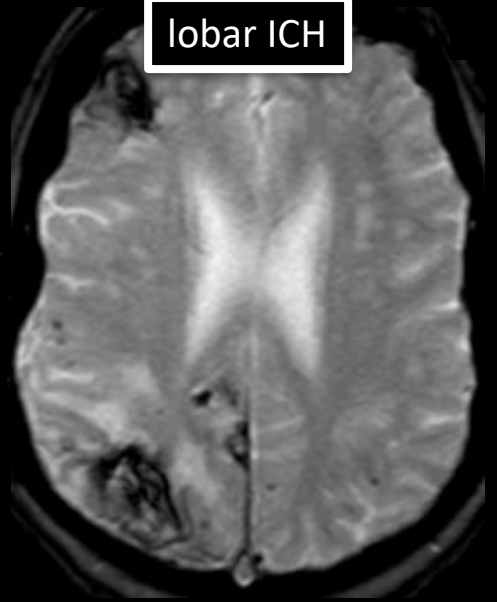


white matter hyperintensities

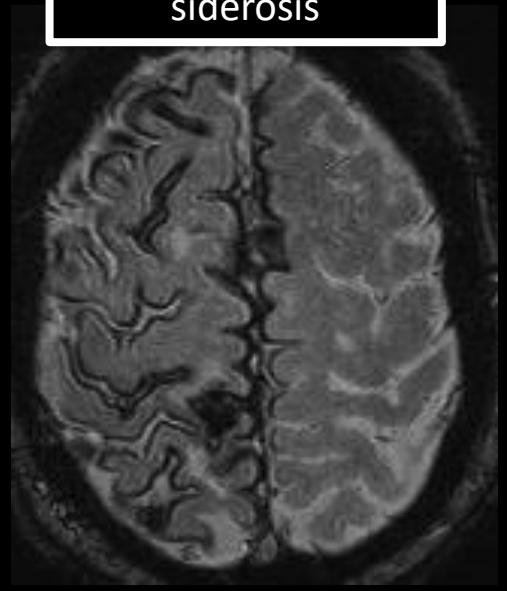
cerebral microbleeds

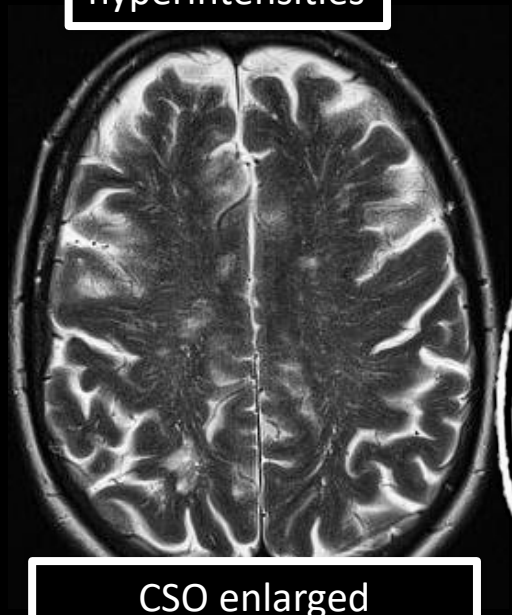


lobar ICH



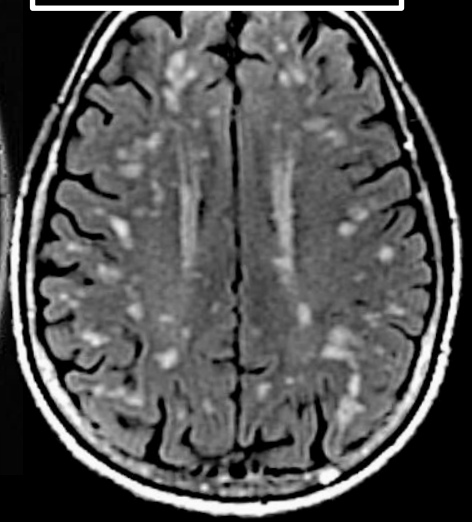
cortical superficial siderosis

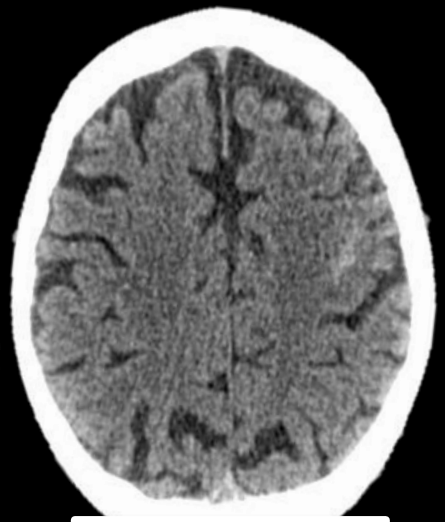




CSO enlarged perivascular spaces

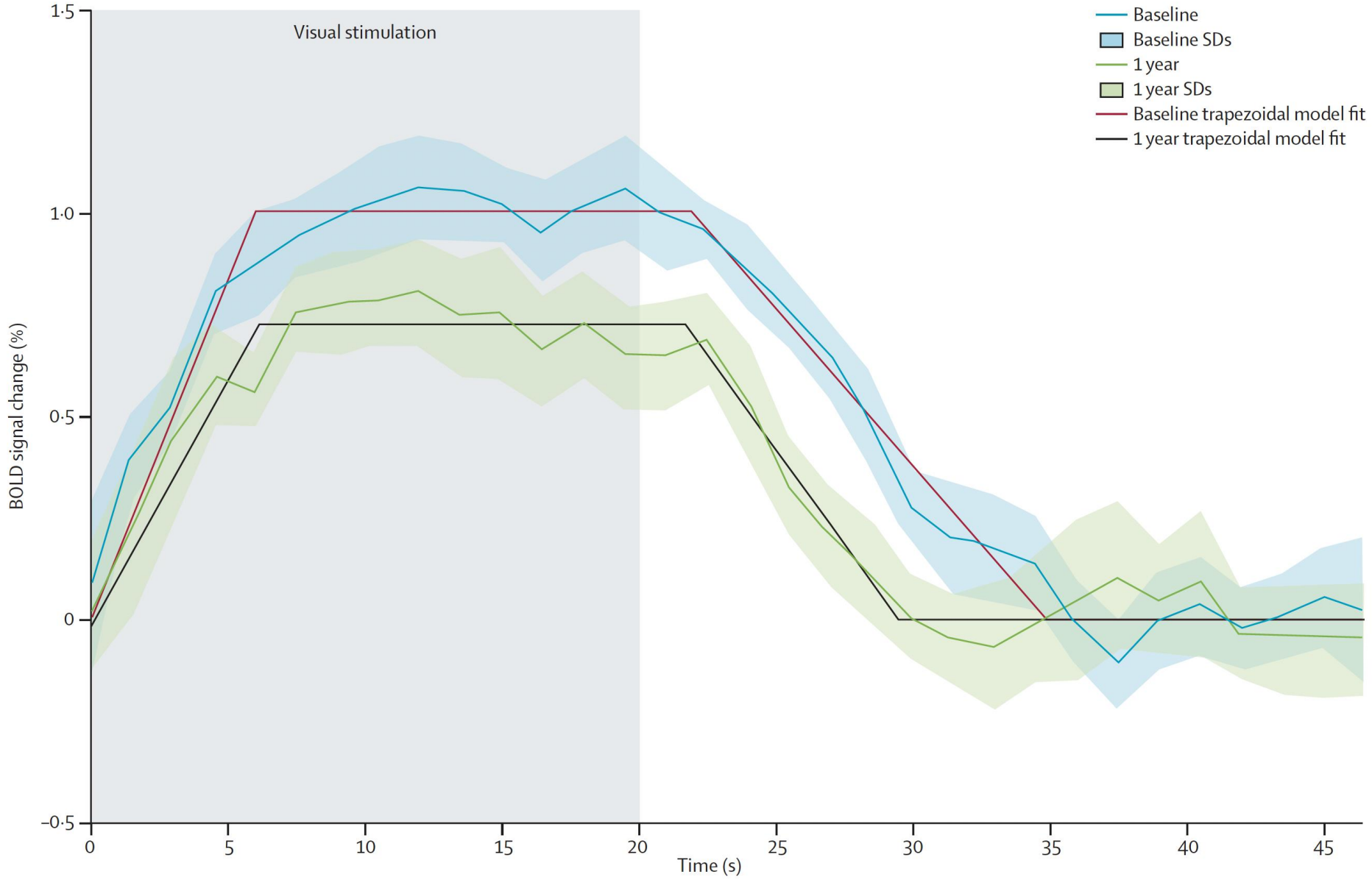
white matter subcortical spots





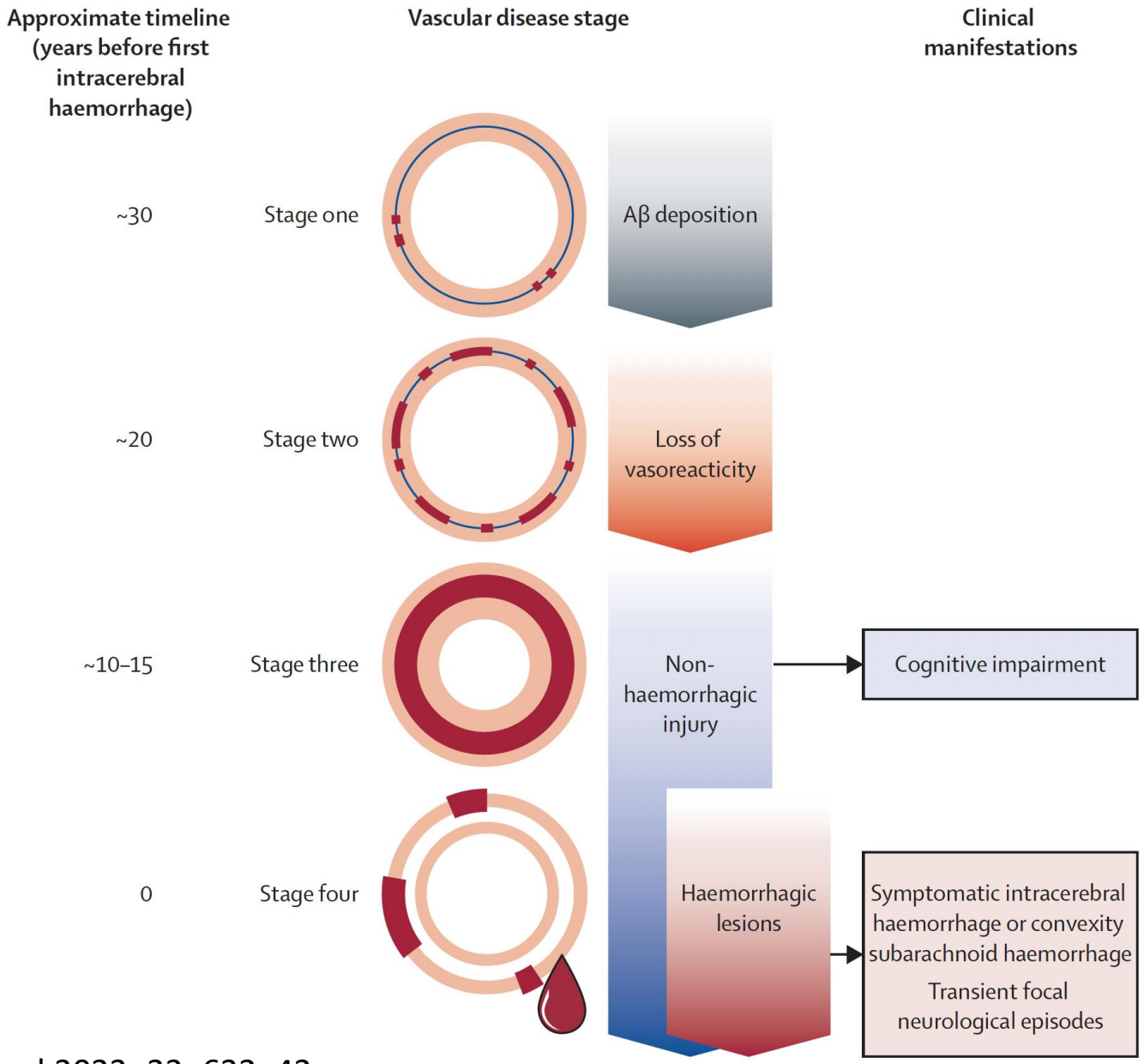
Convexity SAH

Serial fMRI BOLD response to visual stimulation



Lancet Neurol 2014; 13: 419–28.

Timeline of CAA progression



Lancet Neurol 2023; 22: 632–42.

Talk structure

- What is CAA?
- Epidemiology of CAA
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- Clinical syndromes associated with CAA
  - Intracerebral haemorrhage
  - Transient focal neurological episodes (TFNE)
  - Cognitive decline
- Management
- Markers of disease progression
- Summary

Summary

- CAA is common
- CAA is a key cause of ICH, transient focal neurological episodes (TFNE) and cognitive decline
- CAA-ICH has a high risk of recurrence
- A wide range of neuroimaging markers (MRI) are transforming diagnosis and understanding of the disease, including non-haemorrhagic markers in Boston criteria v2.0
- There are no proven interventions to treat acute CAA-ICH or prevent recurrence
- CAA is an unmet healthcare need

Acknowledgements

cromis-2
Clinical Relevance Of Microbleeds In Stroke

Stroke association

British Heart Foundation

PROHIBIT-ICH
Prevention Of Hypertensive Injury to the Brain by Intensive Treatment in IntraCerebral Haemorrhage

OPTIMAS
OPTIMAL TIMING OF ANTICOAGULATION AFTER STROKE

NHS
National Institute for Health Research

University College London Hospitals NHS
NHS Foundation Trust

University College
London Hospitals
Biomedical Research Centre

THE NATIONAL HOSPITAL FOR NEUROLOGY AND NEUROSURGERY

UCL STROKE RESEARCH CENTRE

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Amy Gent

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Zane Jaunmuktane

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Leads: Marilena Marinescu, Azra Banaras

Collaborators

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Niki Sprigg
Keith Muir
John Bamford
Liz Warburton
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Stefan Engelter
David Seiffge
Yusuke Yakishiji
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Andreas Charidimou
Charlotte Cordonnier
Christian Nolte
Peter Rothwell
Jennifer Linn
Meike Vernooij
Joanna Wardlaw
Steve Greenberg
Eric Smith
Roxana Carare

…and many, many others!

Thank you!

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@UCLStrokeRes

https://www.ucl.ac.uk/stroke/

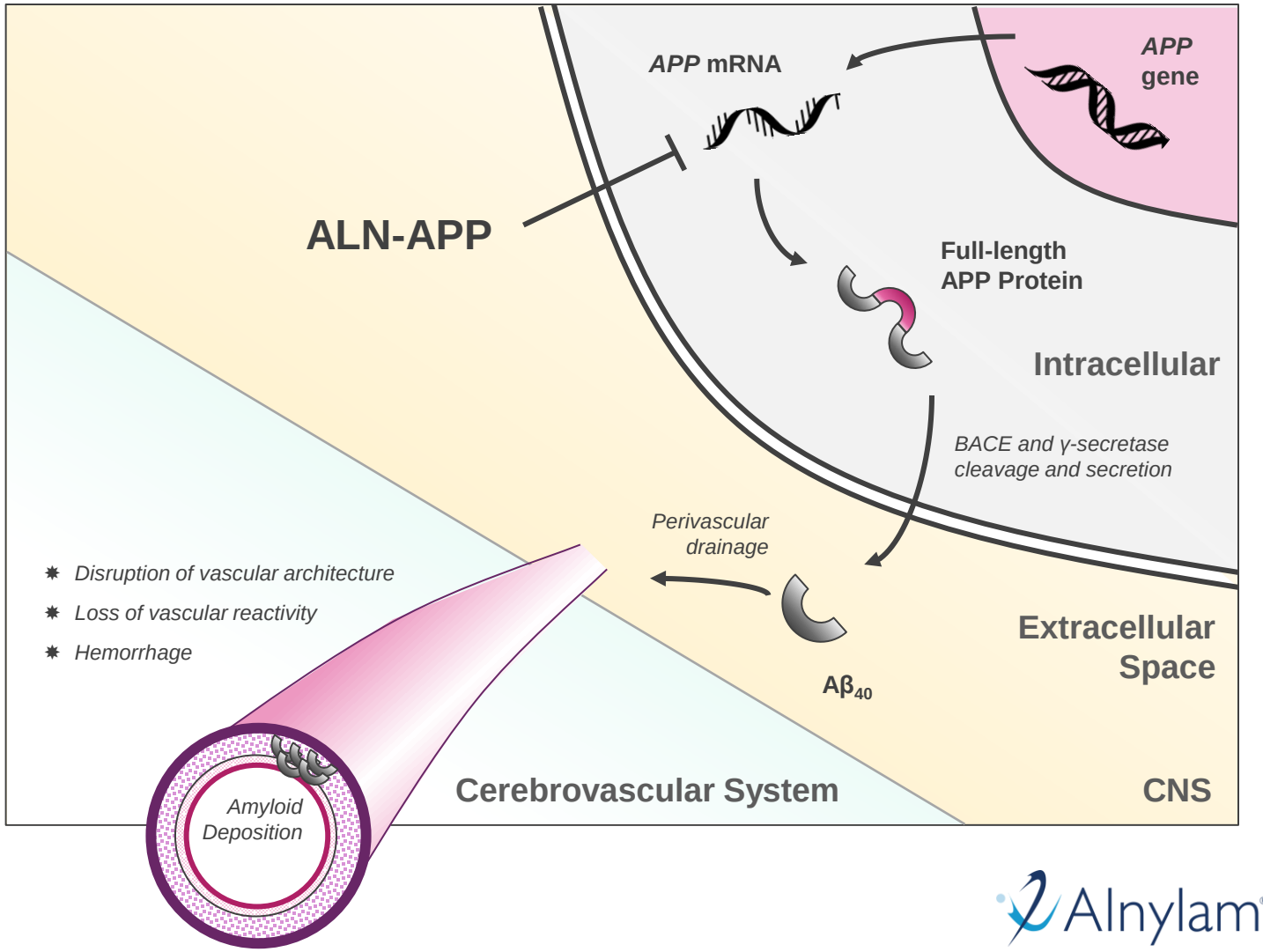
Development of ALN-APP for Cerebral Amyloid Angiopathy

Alnylam®

Therapeutic Hypothesis: Cerebral Amyloid Angiopathy

Reducing Production of Amyloidogenic Protein Fragments

- Target pathogenic protein production at its source ***upstream of amyloid production and deposition***
- Lower ***all Aβ isoforms*** including AB_{40}, the primary component of vascular amyloid deposits
- Enable **natural clearance mechanisms** and reversal of vascular damage



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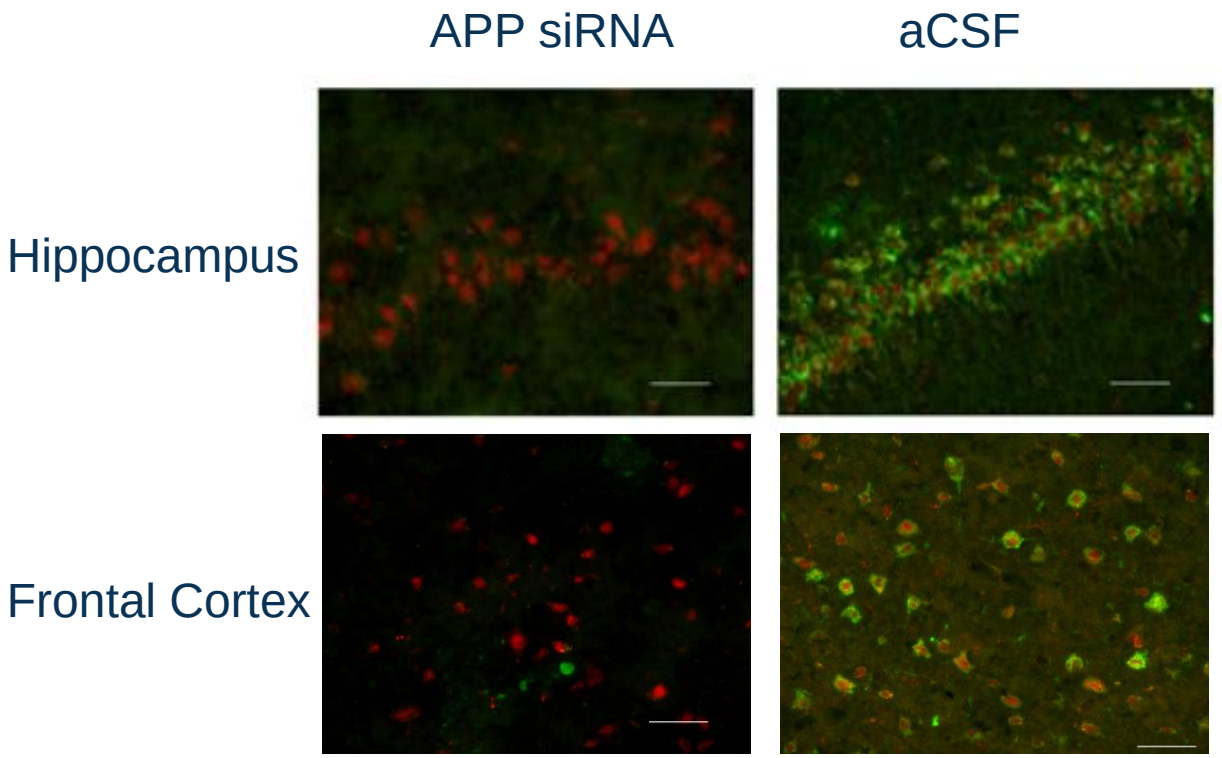
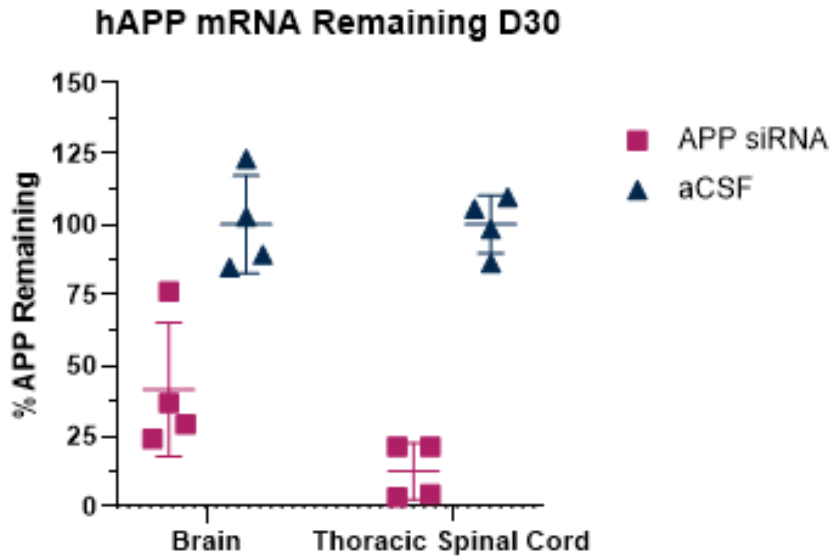
Dosing of APP siRNA in rTg-DI CAA Model Silenced Human APP Protein

Single IT Dose of 0.9 mg in rTg-DI Rat; Day 30 Hippocampus and Frontal Cortex Shown





Antibodies

- NeuN - Red
- hAPP - Green

rTg-DI rat model – Davis et al., American Journal of Pathology 2018. ALNY data on file in collaboration with Van Nostrand Lab at U. of RI.

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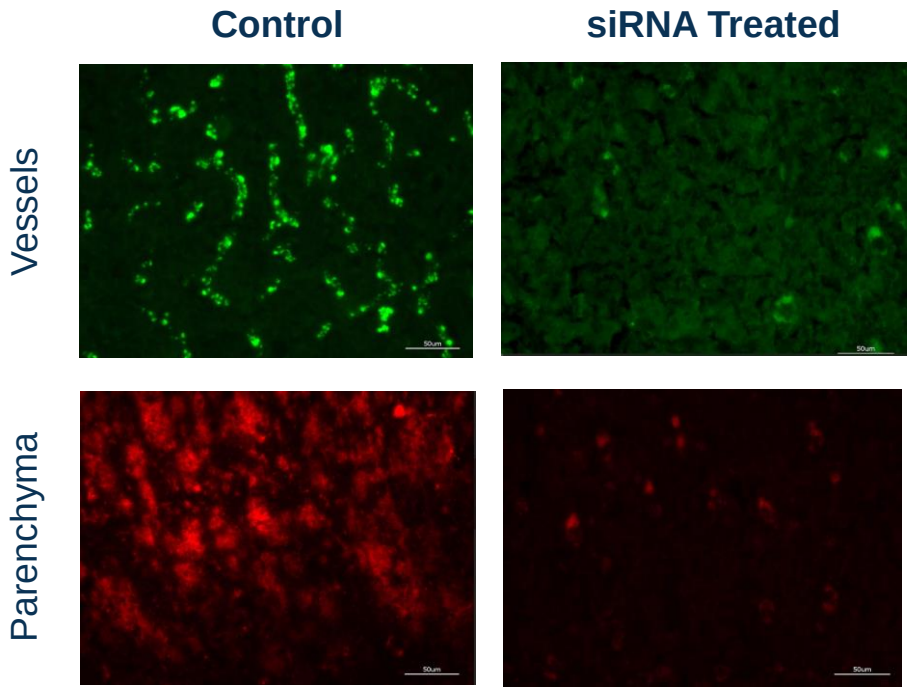
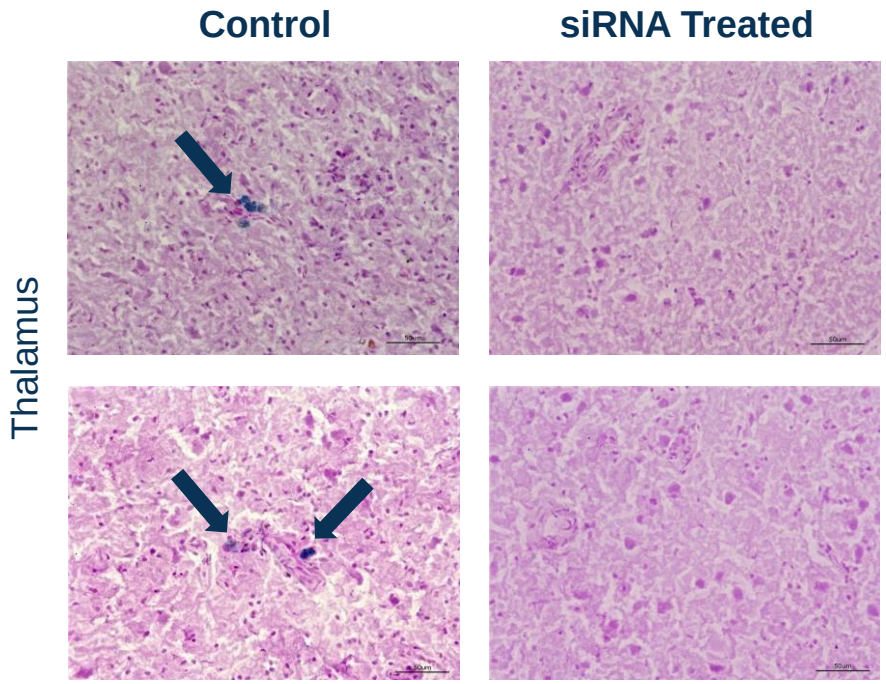
rTg-DI Model Treated with APP-Lowering siRNA Demonstrated Amyloid Clearance at 6 Months

Amyloid Deposition



Vascular amyloid stained with ThS (green); parenchymal amyloid stained with AmyTracker (red)

Microhemorrhages



Microhemorrhages (blue) shown with arrows

Single dose of APP siRNA in CAA animal model resulted in reduced amyloid deposition and fewer microhemorrhages vs control

rTg-DI rat model – Davis et al., American Journal of Pathology 2018. ALNY data on file in collaboration with Van Nostrand Lab at U. of RI.

Expanding Development: Bringing Innovation to CAA

Phase 2 Study in CAA to Begin in 2024, Starting Development in This High Unmet Need Disease

Parallel early development in AD and CAA

Phase 1 EOAD study: platform translation achieved; study ongoing to explore safety and pharmacology of ALN-APP

PART B ENROLLMENT ONGOING

Future AD Studies

Alzheimer's Disease

Cerebral Amyloid Angiopathy

Interventional clinical trial to include patients with both sporadic and Dutch-type cerebral amyloid angiopathy

EXPECTED TO BEGIN 2024

Future CAA Studies

Alnylam®

CNS Pipeline

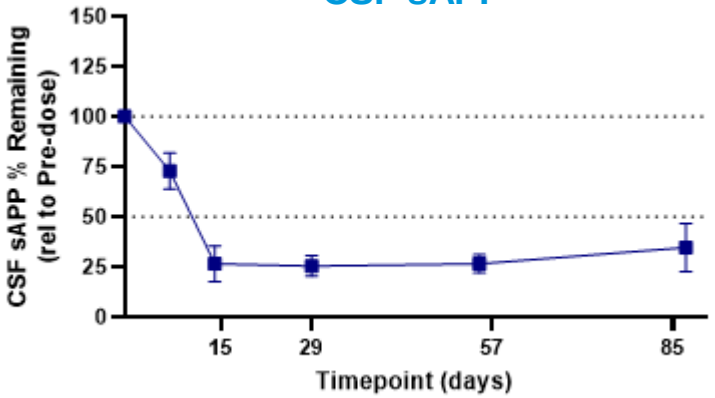
Alnylam®

CNS Platform Expansion

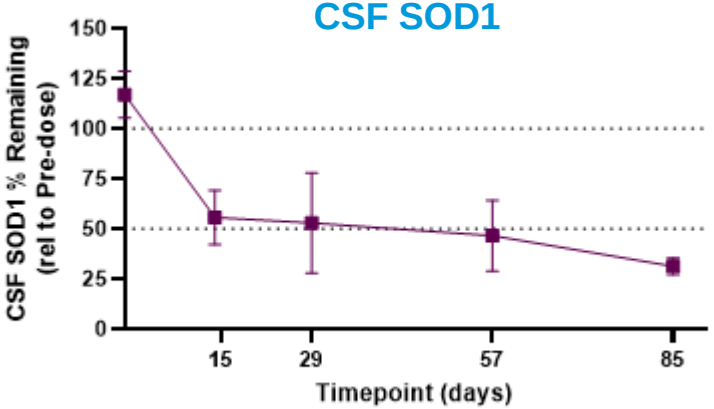
Modular and Reproducible Platform for Silencing CNS Disease Genes in NHP

Targets in Clinical or IND-Enabling Development

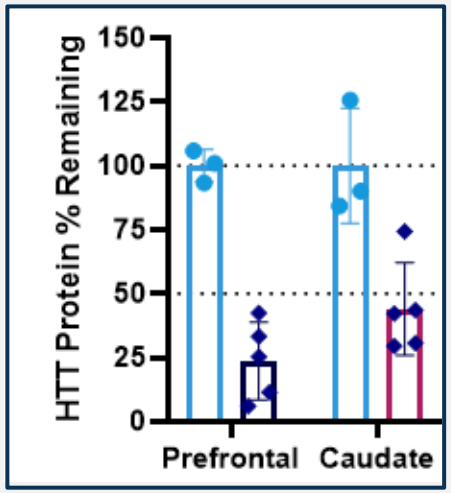
CSF sAPP



CSF SOD1

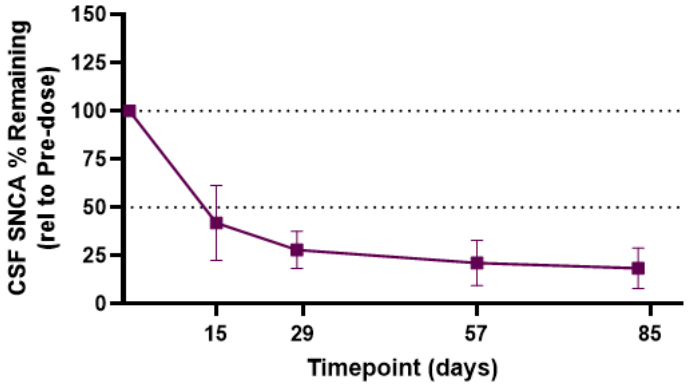


Tissue HTT protein

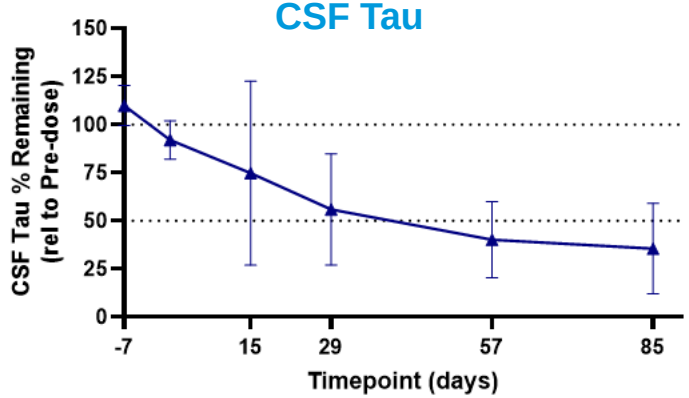


Next Wave of CNS Targets

CSF α synuclein



CSF Tau



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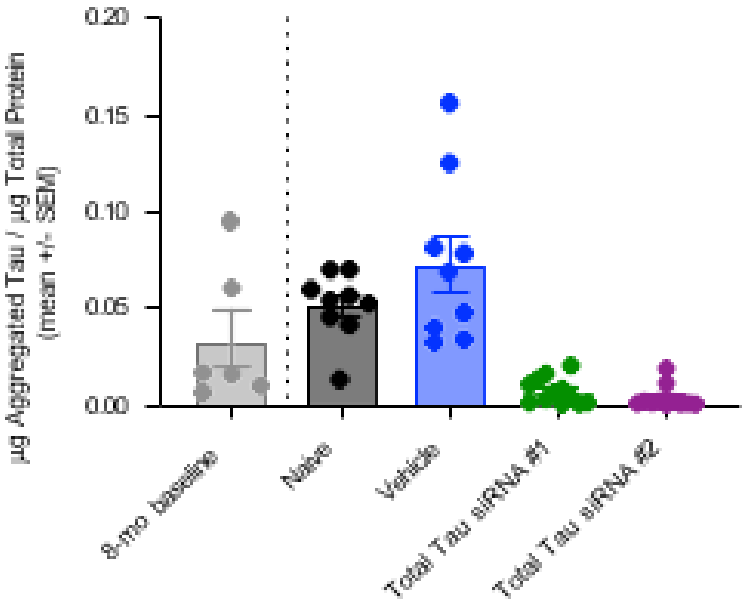
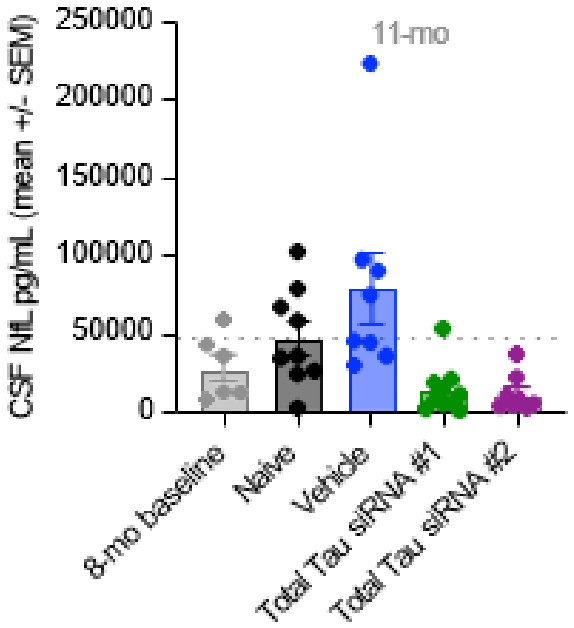
RNAi Knockdown of MAPT Prevents Axonal Damage and Clears Tau Aggregates in P301S Transgenic Mice

- P301S transgenic mice show progressive accumulation of Tau aggregates, increases in NfL in blood and CSF and locomotion impairment with symptoms onset at 6 months

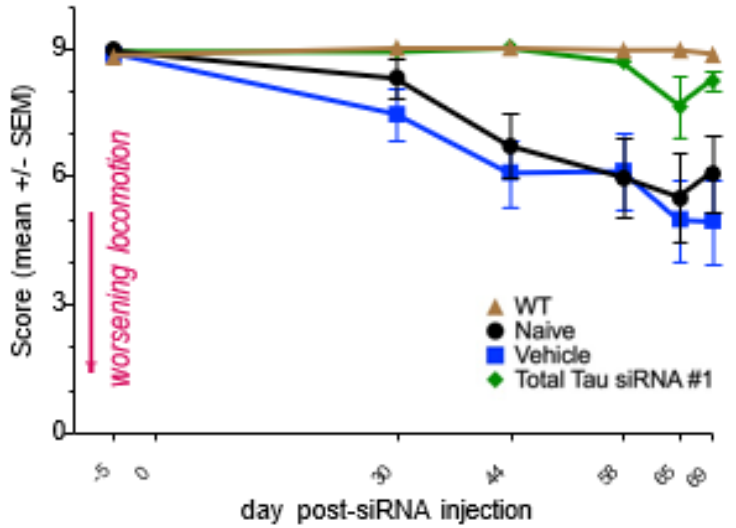
Insoluble Tau ELISA



NfL levels



Movement



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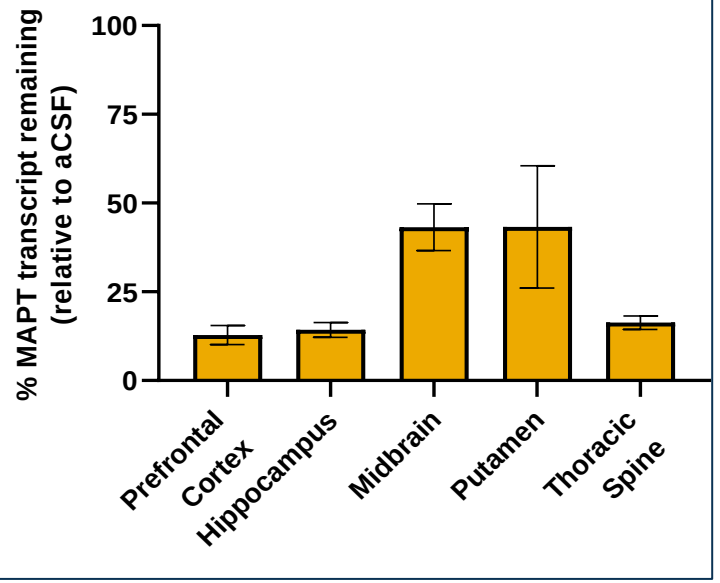
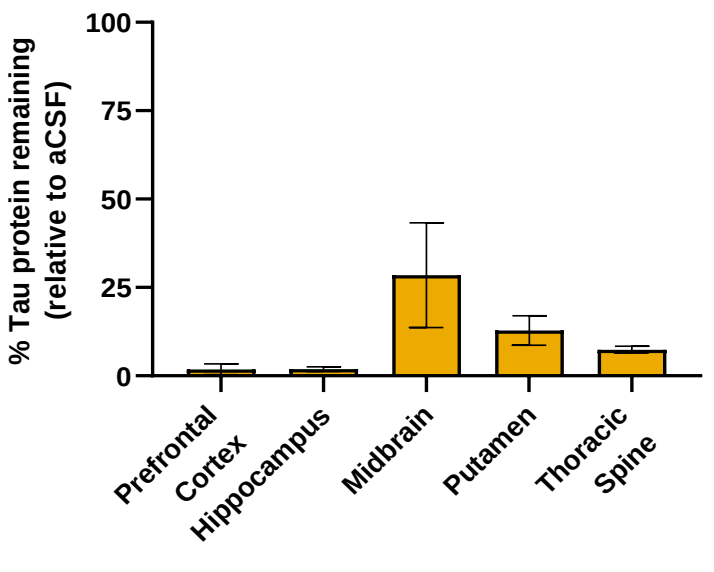
Intrathecal Administration of RNAi Therapeutic Targeting MAPT in NHP

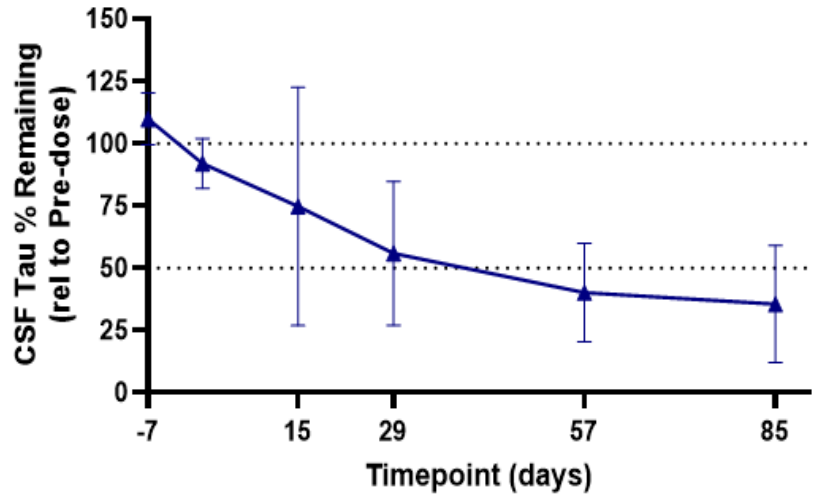
MAPT Transcript in CNS Tissue



Tau Protein in CNS Tissue



Tau Protein in CSF



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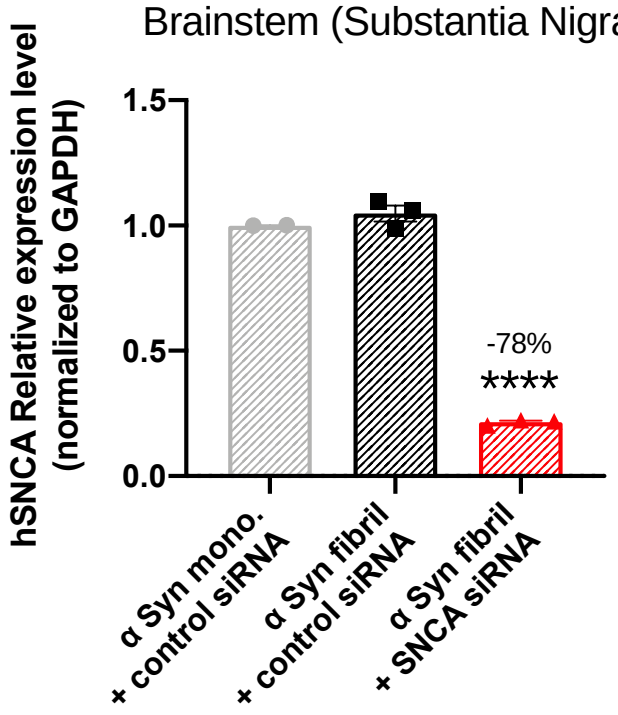
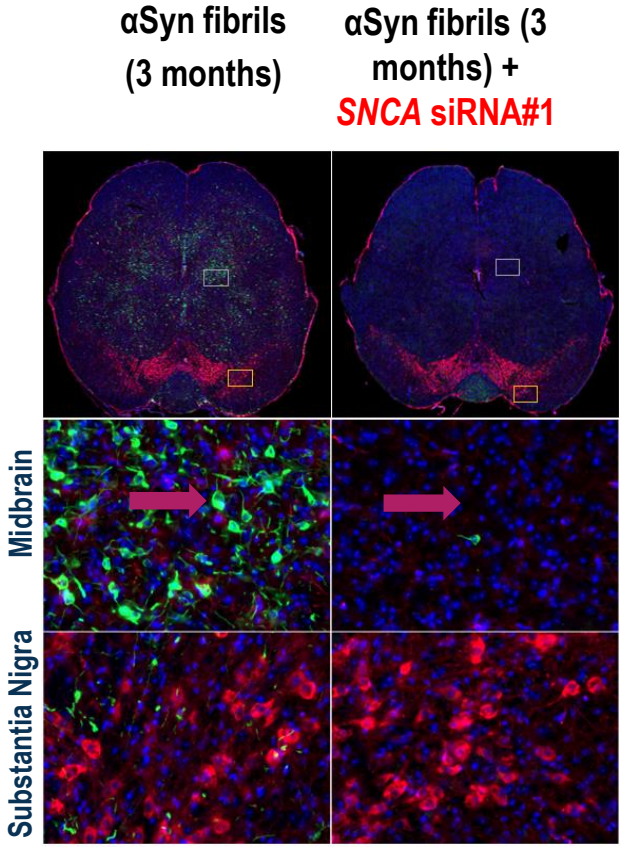
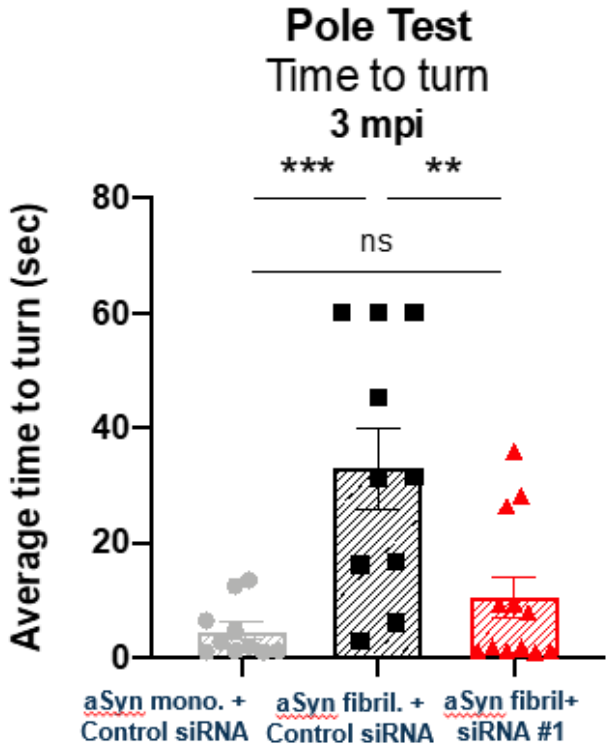
RNAi Therapeutic to SNCA Improves Pathological αSyn Aggregates and Improves Slowness of Movement in Rodent Model

- Transgenic mice overexpressing A53T α-synuclein with fibril seeding in striatum. Mice show early motor impairments, α-synuclein aggregates and NfL elevations. At 3 months, mice show neuroinflammation, neurodegeneration, motor deficits.







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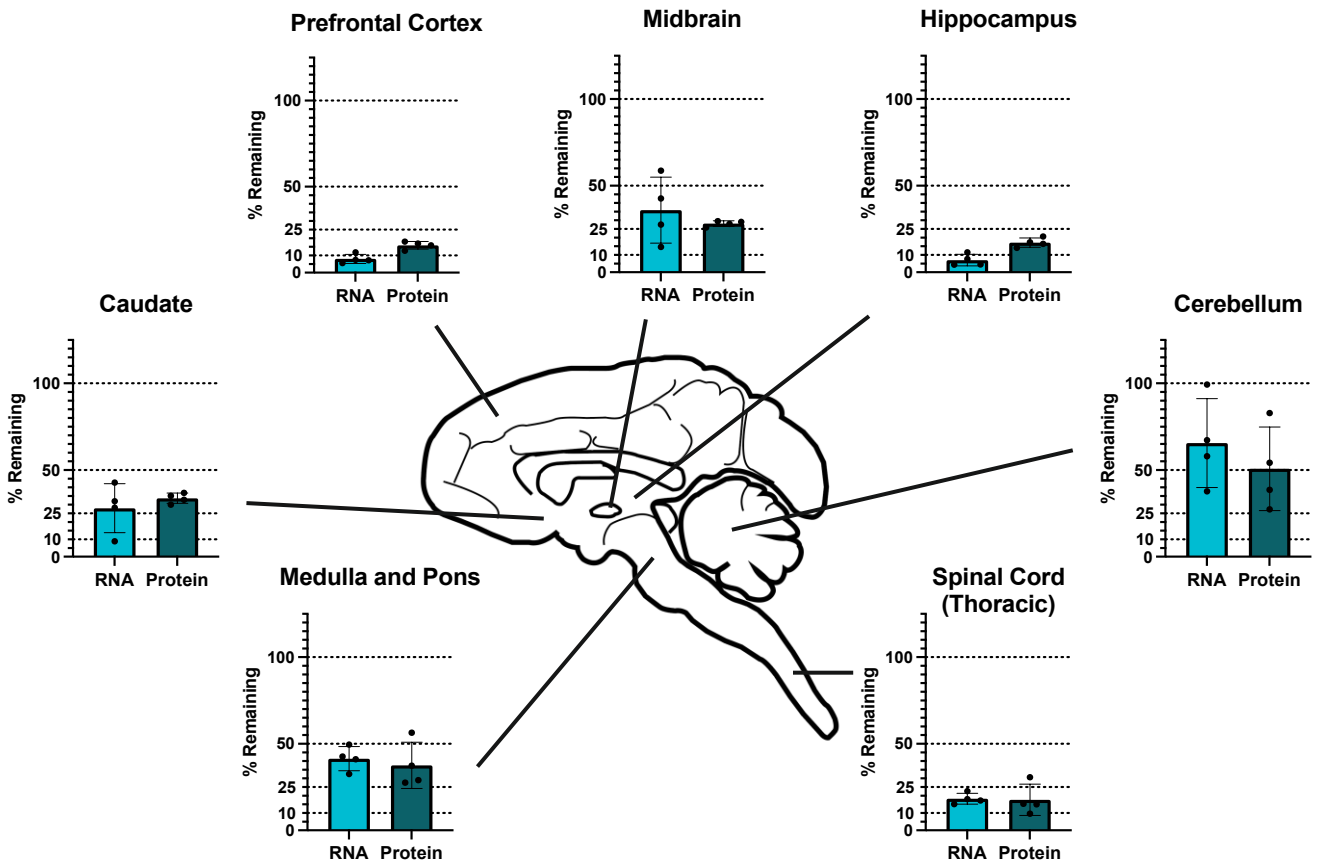
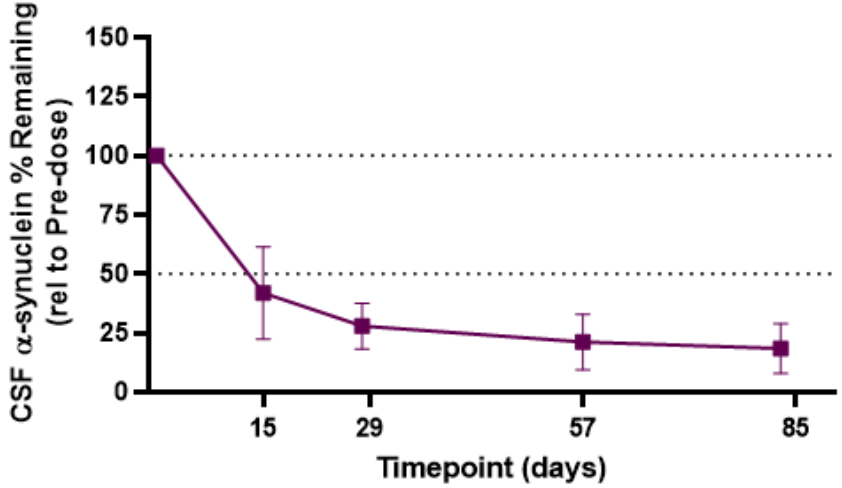
Intrathecal Administration of RNAi Therapeutic Targeting SNCA in NHP



α-synuclein Protein in CSF



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Characterizing HTT Target Engagement in NHP

HTT Protein Measured from Terminal (3M) Tissue

Evaluations:

- Weekly clinical observations
- Monthly neuro evaluations
- No treatment-associated adverse findings in NHPs treated with HTT siRNA at any dose level
- IND-enabling GLP tox studies ongoing

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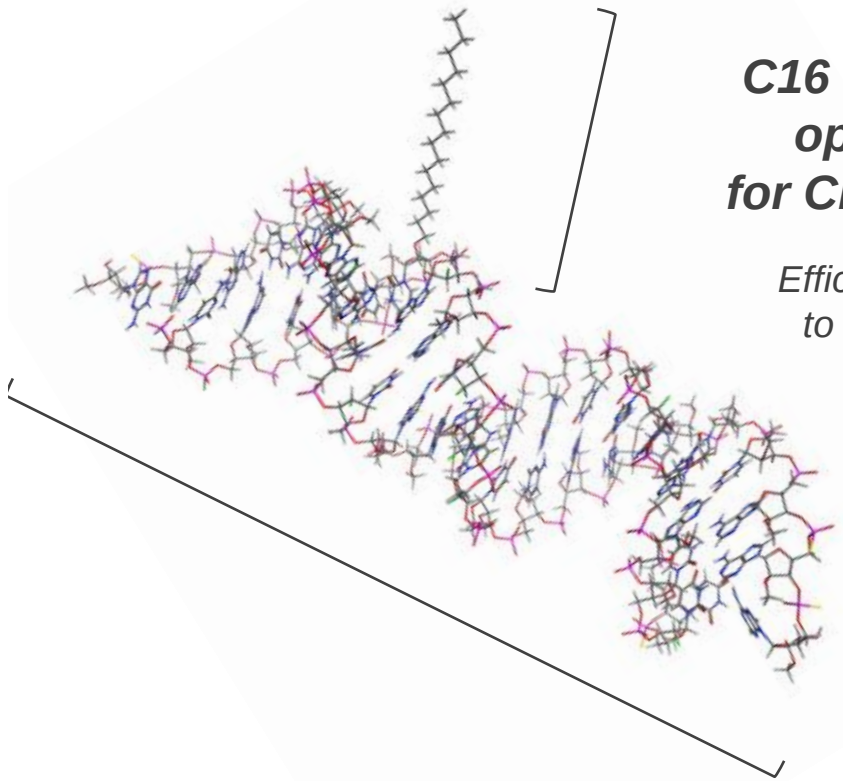
Summary

ARTICLES
https://doi.org/10.1038/s41587-022-01334-x
nature biotechnology
Check for updates

Expanding RNAi therapeutics to extrahepatic tissues with lipophilic conjugates

Kirk M. Brown[1,2], Jayaprakash K. Nair[1,2], Maja M. Janas[1,2], Yesseinia I. Anglero-Rodriguez[1], Lan T. H. Dang[1], Haiyan Peng[1], Christopher S. Theile[1], Elena Castellanos-Rizaldos[1], Christopher Brown[1], Donald Foster[1], Jeffrey Kurz[1], Jeffrey Allen[1], Rajanikanth Maganti[1], Jing Li[1], Shigeo Matsuda[1], Matthew Stricos[1], Tyler Chickering[1], Michelle Jung[1], Kelly Wassarman[1], Jeff Rollins[1], Lauren Woods[1], Alex Kelin[1], Dale C. Guenther[1], Melissa W. Mobley[1], John Petrulis[1], Robin McDougall[1], Timothy Racie[1], Jessica Bombardier[1], Diana Cha[1], Saket Agarwal[1], Lei Johnson[1], Yongfeng Jiang[1], Scott Lentini[1], Jason Gilbert[1], Tuyen Nguyen[1], Samantha Chigas[1], Sarah LeBlanc[1], Urjana Poreci[1], Anne Kasper[1], Arlin B. Rogers[1], Saeho Chong[1], Wendell Davis[1], Jessica E. Sutherland[1], Adam Castoreno[1], Stuart Milstein[1], Mark K. Schlegel[1], Ivan Zlatev[1], Klaus Charisse[1], Mark Keating[1], Muthiah Manoharan[1], Kevin Fitzgerald[1], Jing-Tao Wu[1], Martin A. Maier[1]✉ and Vasant Jadhav[1]✉

Therapeutics based on short interfering RNAs (siRNAs) delivered to hepatocytes have been approved, but new delivery solutions are needed to target additional organs. Here we show that conjugation of 2′-*O*-hexadecyl (C16) to siRNAs enables safe, potent and durable silencing in the central nervous system (CNS), eye and lung in rodents and non-human primates with broad cell type specificity. We show that intrathecally or intracerebroventricularly delivered C16-siRNAs were active across CNS regions and cell types, with sustained RNA interference (RNAi) activity for at least 3 months. Similarly, intravitreal administration to the eye or intranasal administration to the lung resulted in a potent and durable knockdown. The preclinical efficacy of an siRNA targeting the amyloid precursor protein was evaluated through intracerebroventricular dosing in a mouse model of Alzheimer's disease, resulting in amelioration of physiological and behavioral deficits. Altogether, C16 conjugation of siRNAs has the potential for safe therapeutic silencing of target genes outside the liver with infrequent dosing.



C16 conjugate optimized for CNS delivery

Efficient delivery to target cells

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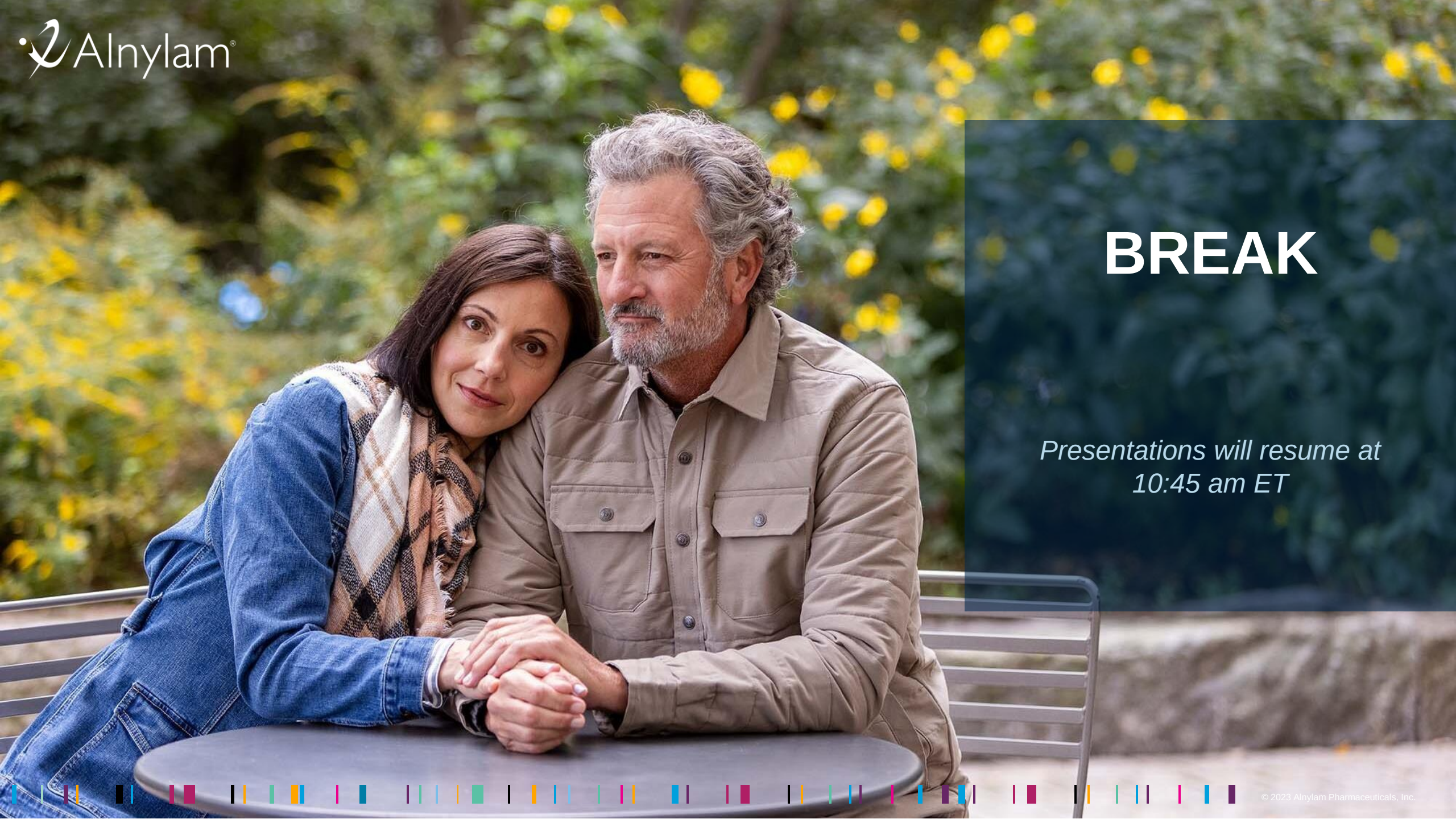
Q&A

Moderator:

- Kevin Fitzgerald, Ph.D. – *Chief Scientific Officer & EVP, Head of Research & Early Development*

Panelists:

- Akshay Vaishnaw, M.D., Ph.D. – *Chief Innovation Officer*
- Vasant Jadhav, Ph.D. – *Chief Technology Officer, SVP*
- Karyn Schmidt, Ph.D. – *Principal Scientist, Research*
- Paul Nioi, Ph.D. – *SVP, Research*
- Anna Borodovsky, Ph.D. – *VP, Research*
- Kirk Brown, Ph.D. – *VP, CNS Research*



BREAK

Presentations will resume at 10:45 am ET

Institut de recherche
Centre universitaire de santé McGill
Research Institute
McGill University Health Centre

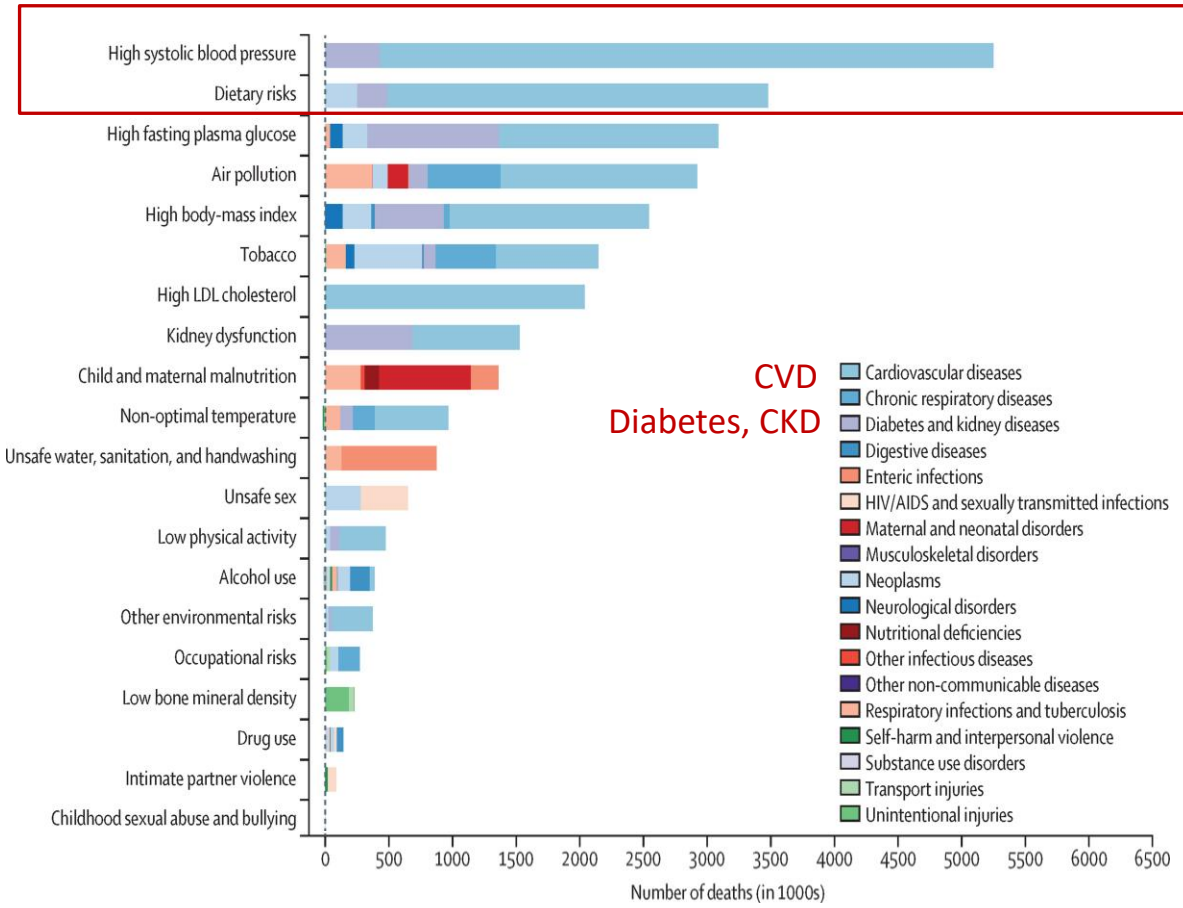
Hypertension treatment: needs and gaps

Rhian Touyz MBBCh, PhD
Research Institute of McGill University Health Centre,
McGill University, Montreal

Disclosure: Nothing to declare

Global attributable deaths and risk factors

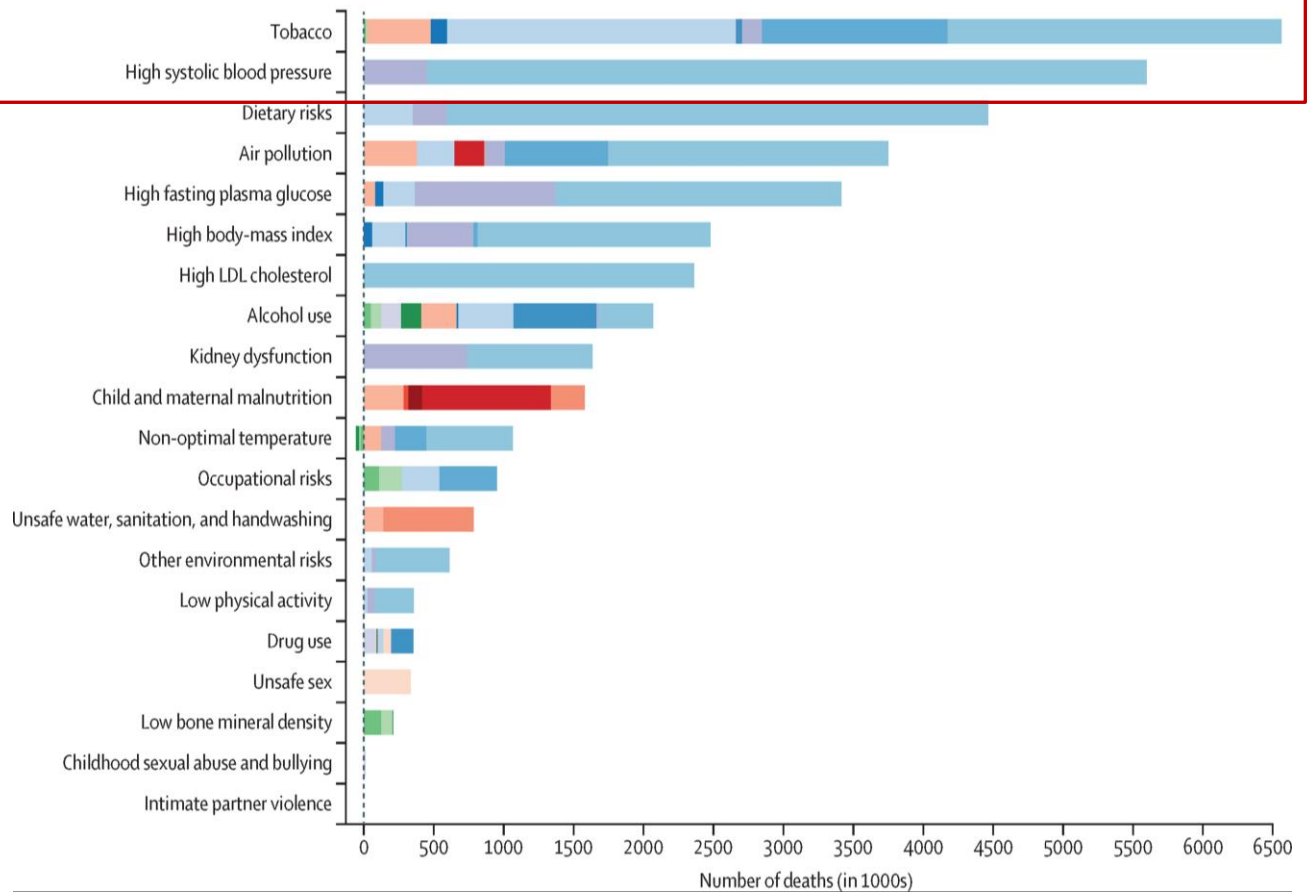
Females



CVD

Diabetes, CKD

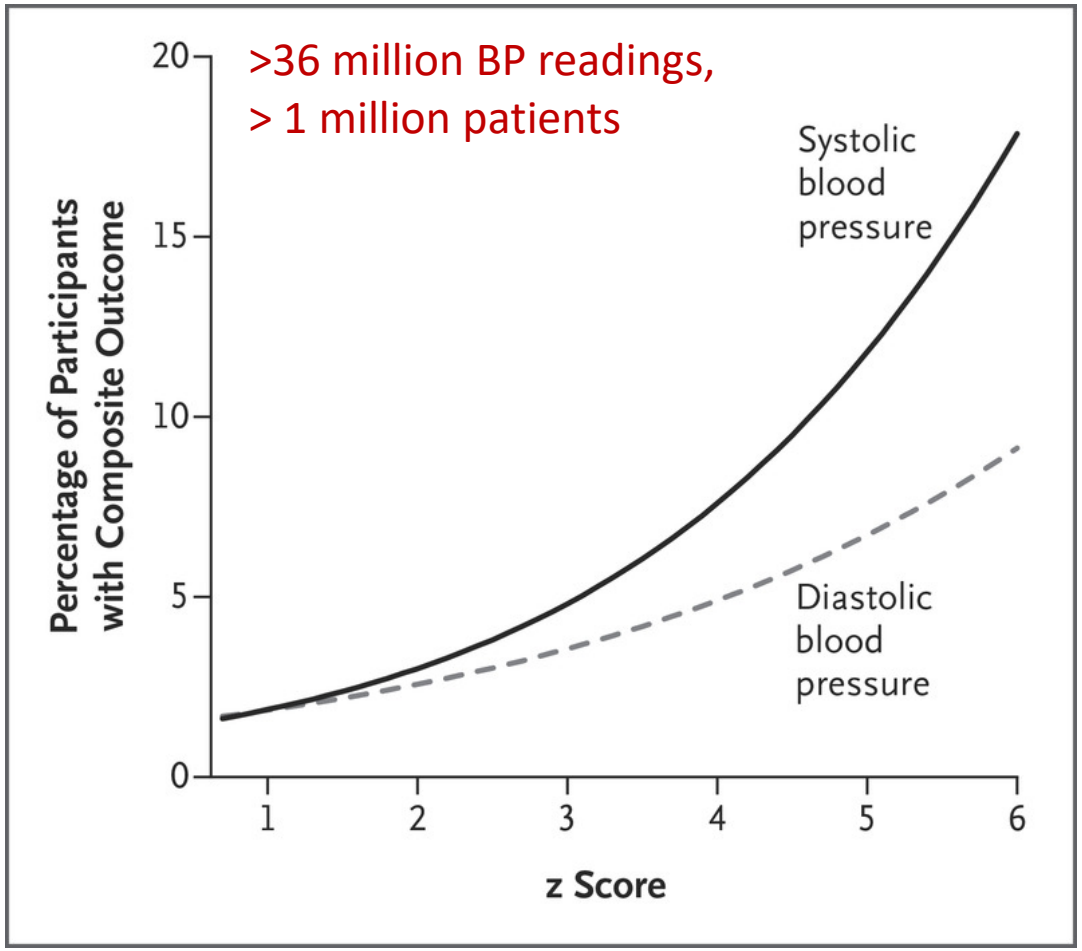
Males



Lancet 2013, Lancet 2016, NEJM 2016, WHO 2016, Lancet 2018; Lancet 2022

SBP and DBP are independently linked to cardiovascular risk

Regardless of definition of hypertension (130/80 mmHg; 140/90 mmHg)

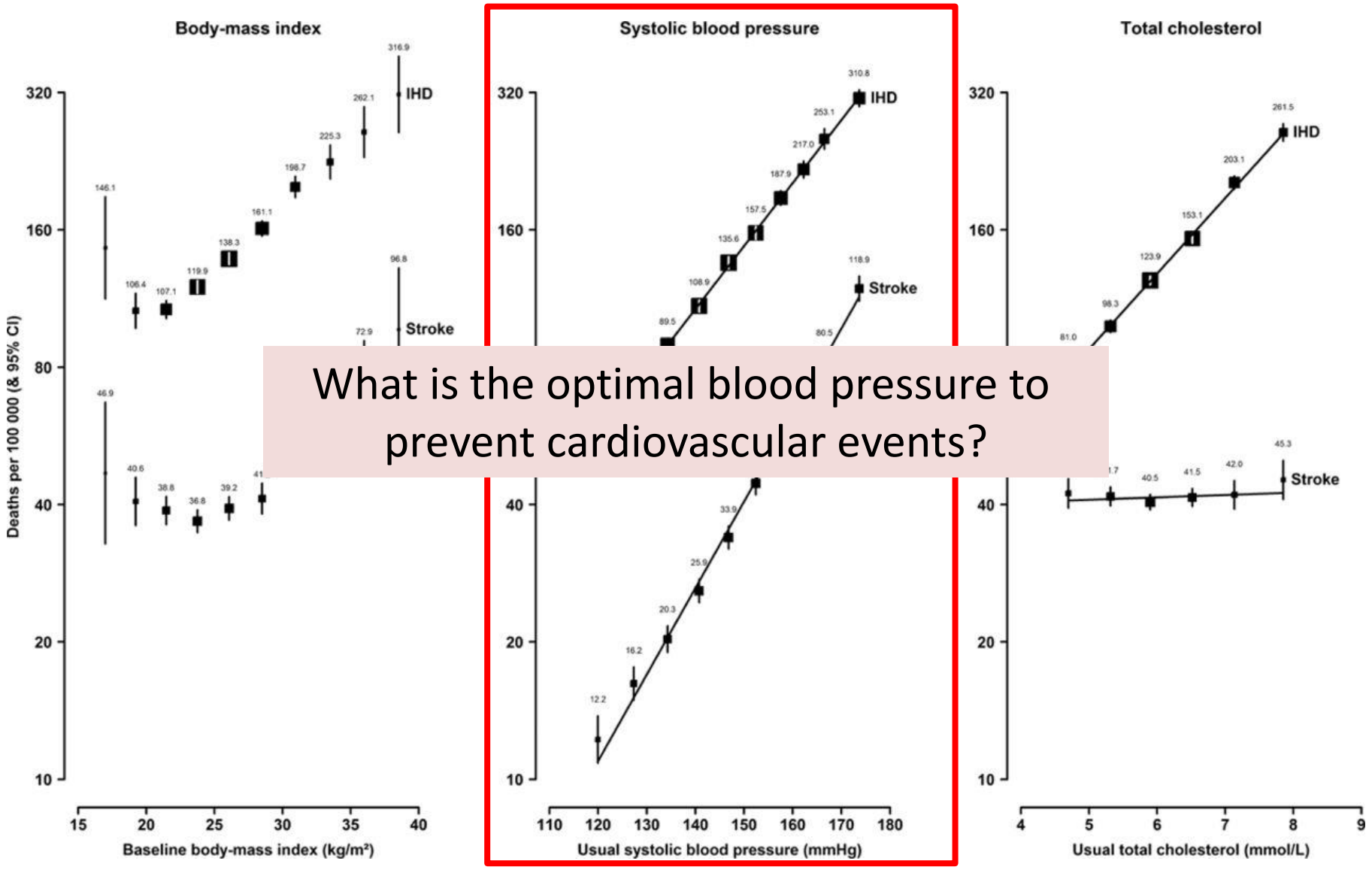


Multivariable modeling of adverse cardiovascular outcomes.

Relationship between SBP and DBP z scores and risk of outcomes, above 75th percentile for SBP or DBP (>133 or 78 mmHg).

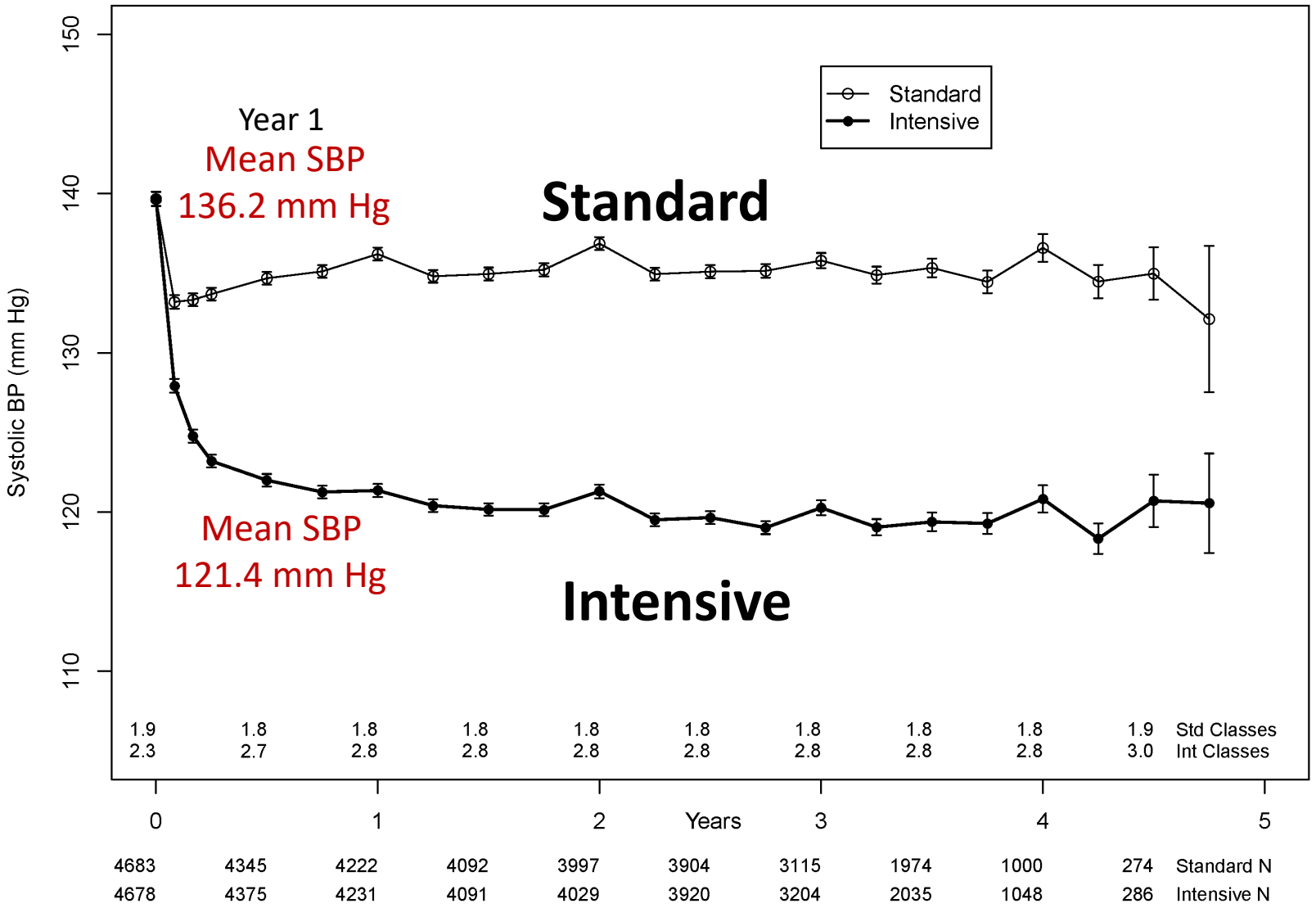
Flint. New Engl J Med 2019

IHD, Stroke and BP
The higher the BP the greater the risk of an event



What is the optimal blood pressure to prevent cardiovascular events?

Landmark trial



SPRINT
Systolic Blood Pressure Intervention Trial

Average SBP

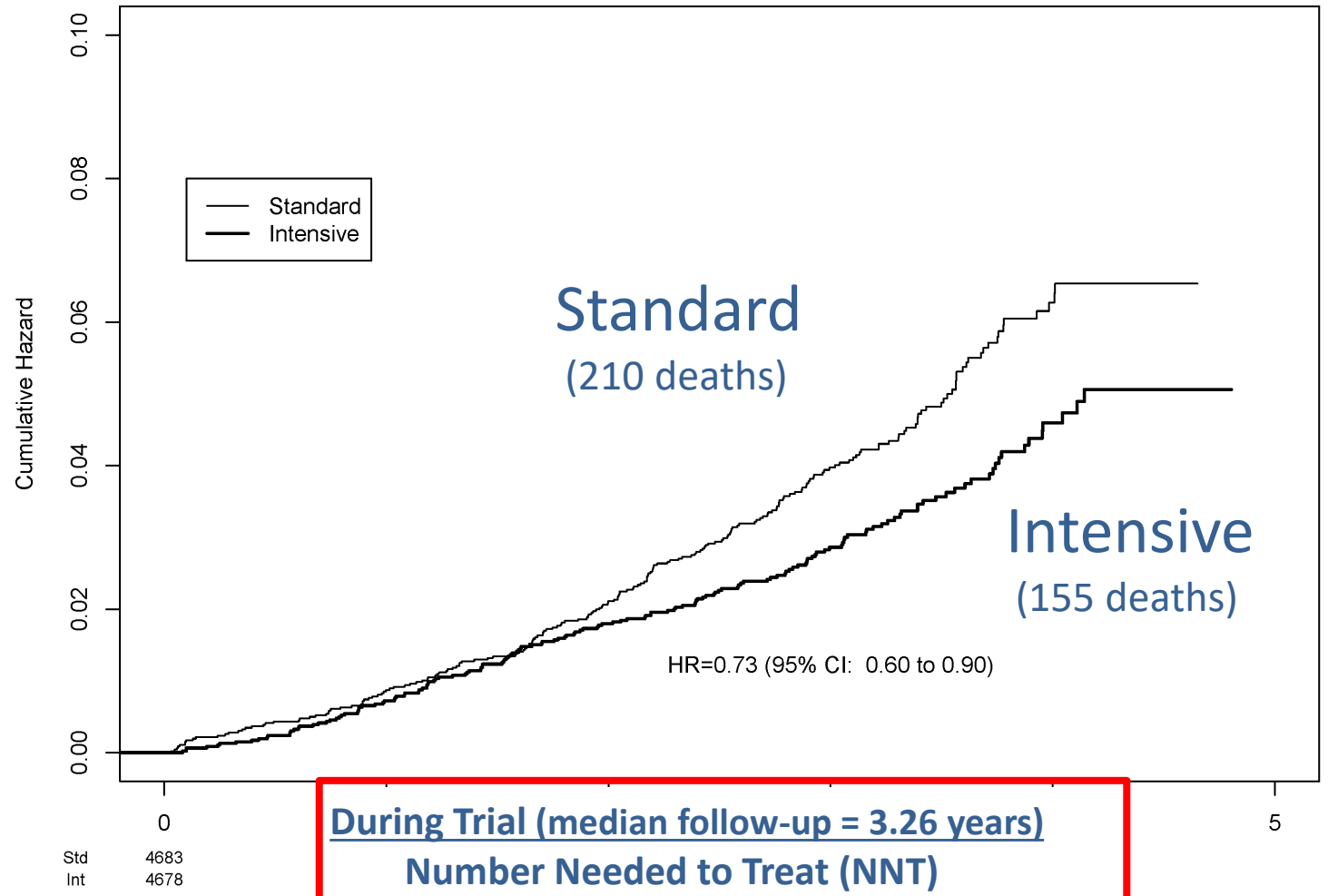
Standard: 134.6 mm Hg

Delta: 13.5 mm Hg

Intensive: 121.5 mm Hg

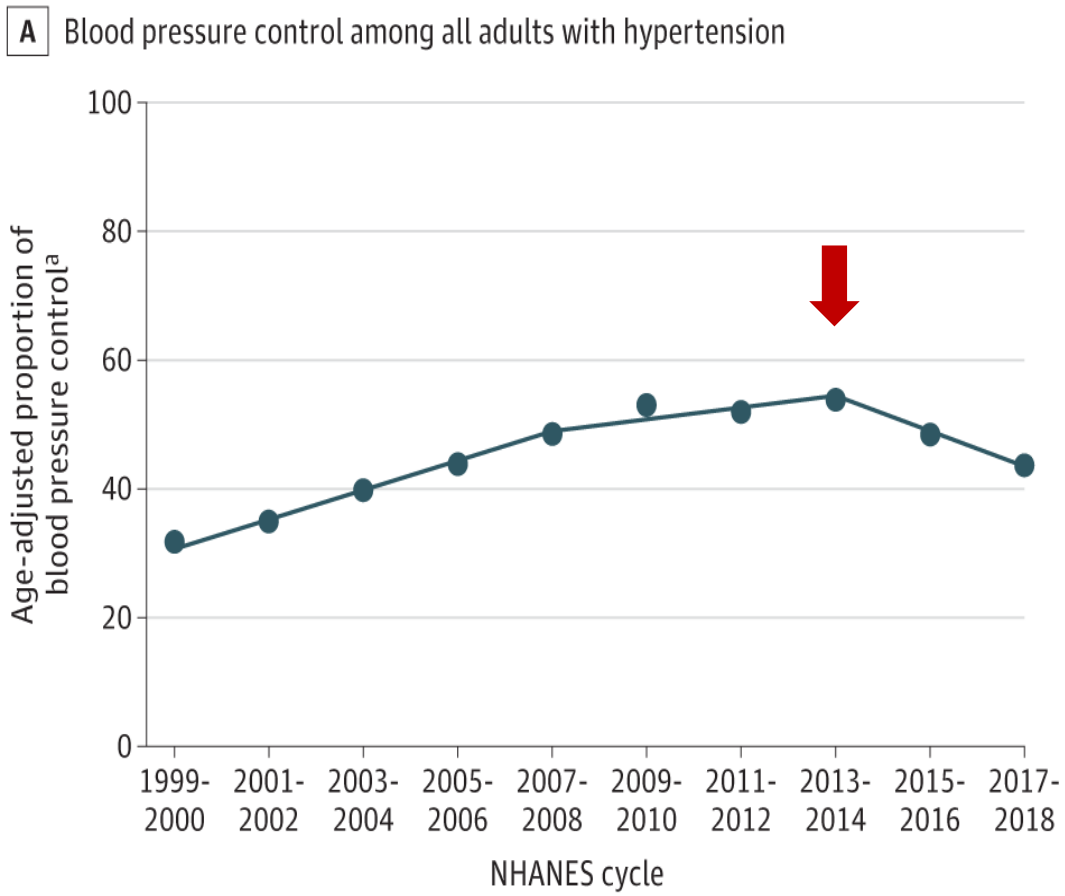
The SPRINT Research Group. N Engl J Med. 2015;373

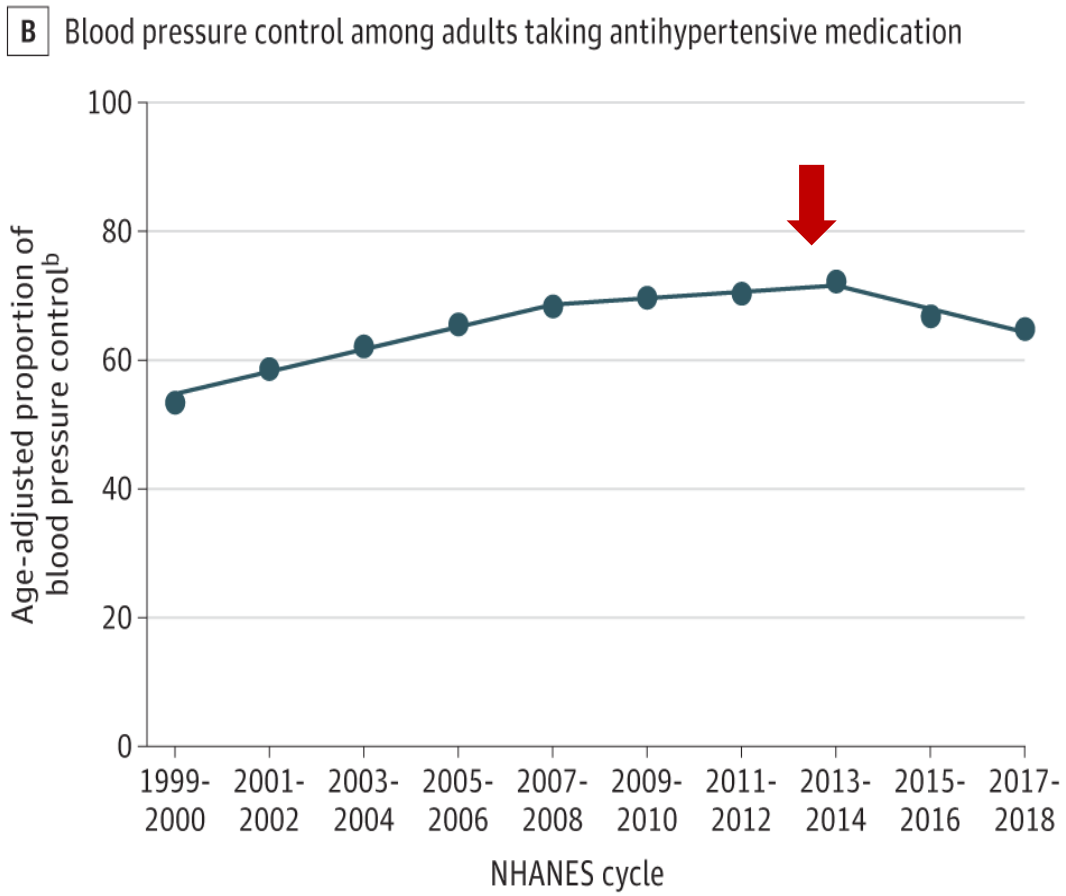
All-cause Mortality: 27% reduction in death



During Trial (median follow-up = 3.26 years)
Number Needed to Treat (NNT)
to Prevent a death = 90

Worsening trends in BP Control in US Adults With Hypertension





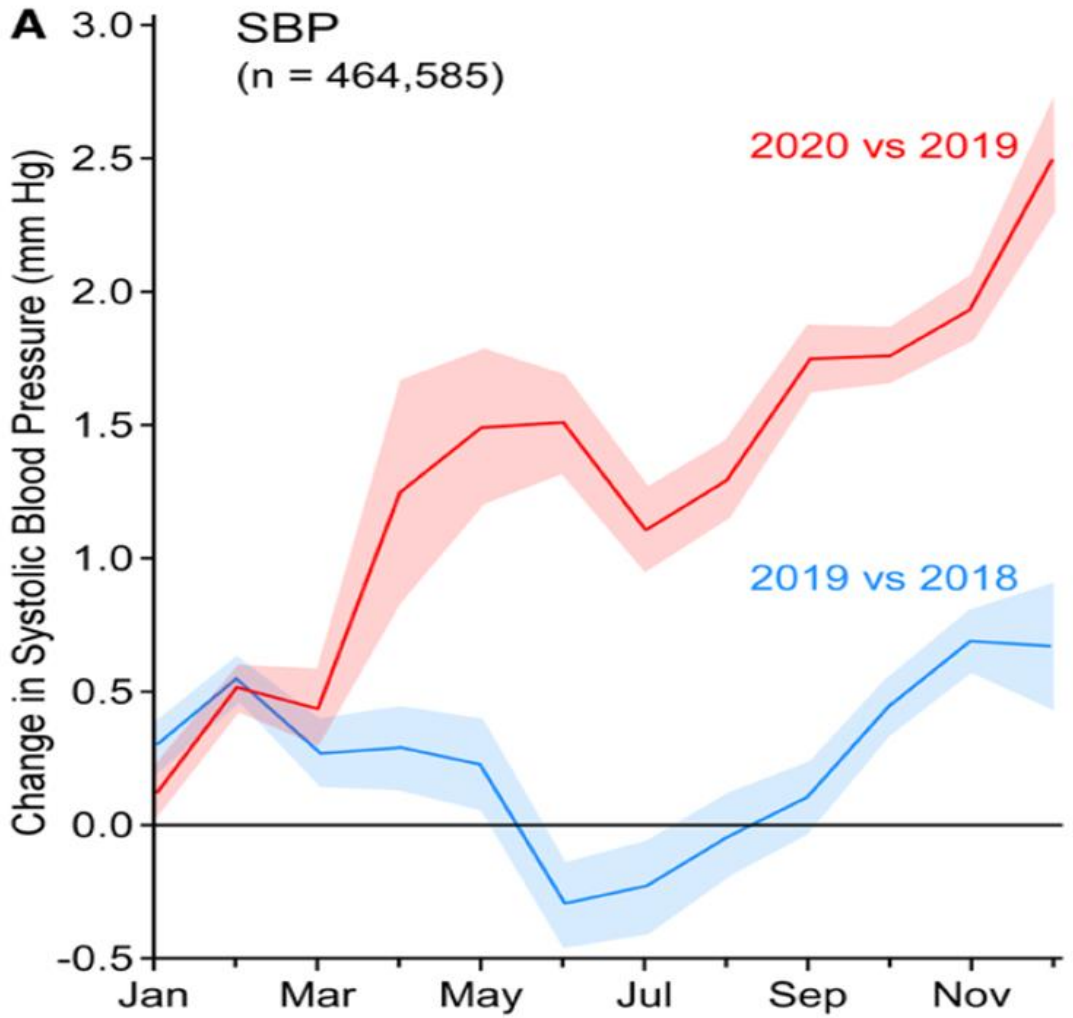
Muntner P. JAMA. 2020;324(12):1190-1200; Hypertension 2022;79:1971.

Additional challenges: COVID-19 Negatively Impacted BP Control

Rise in BP observed in U.S.

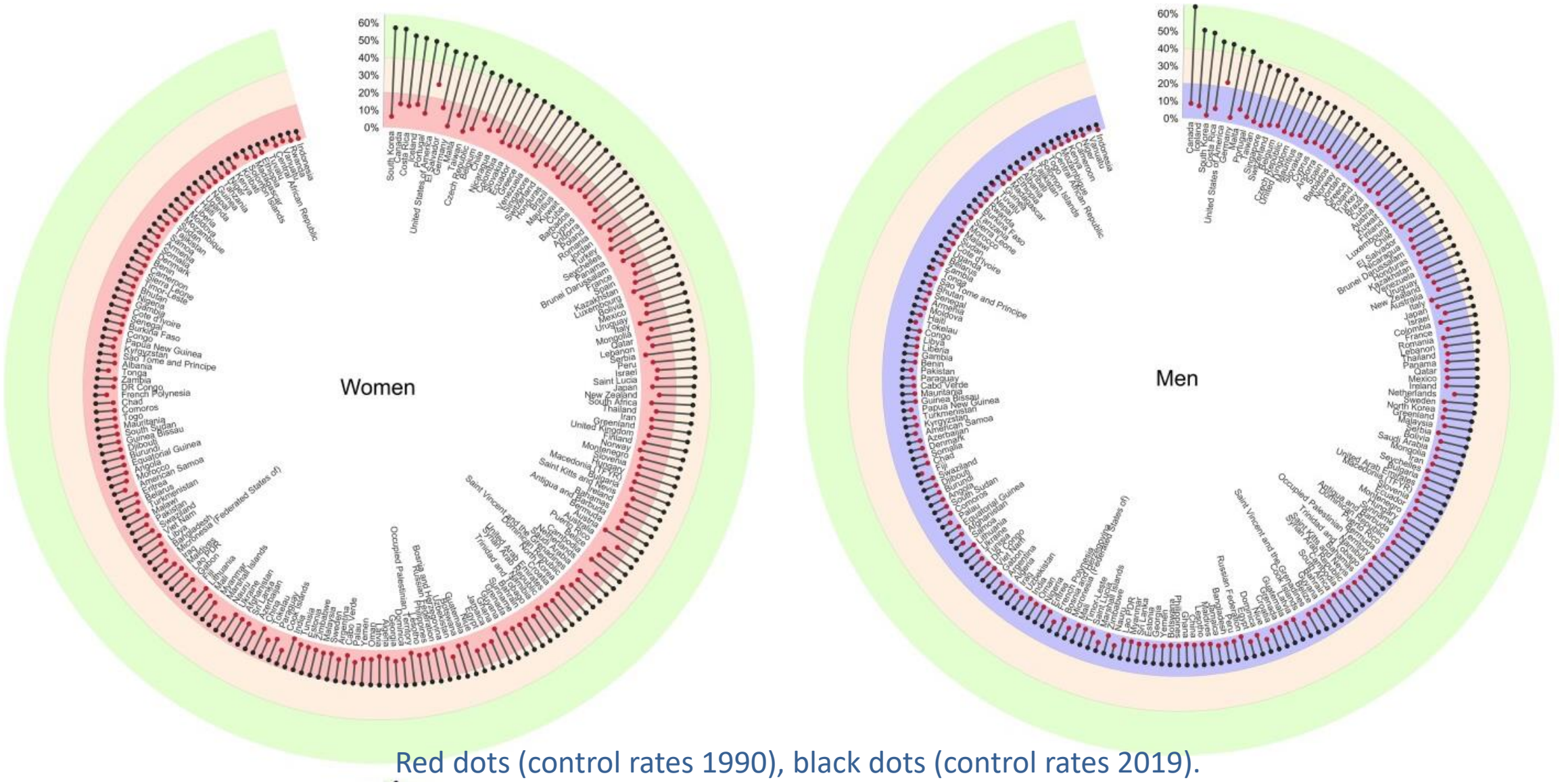
Blood pressure levels have **increased** and HTN control rates have declined

- ~5x greater rate of annual BP increase[1]
- 12% decline in HTN control rates[2]



[1] Laffin LJ, et al. *Circulation*. 2022;145(3):235-237.
[2] Chamberlain AM, et al. AHA 2021

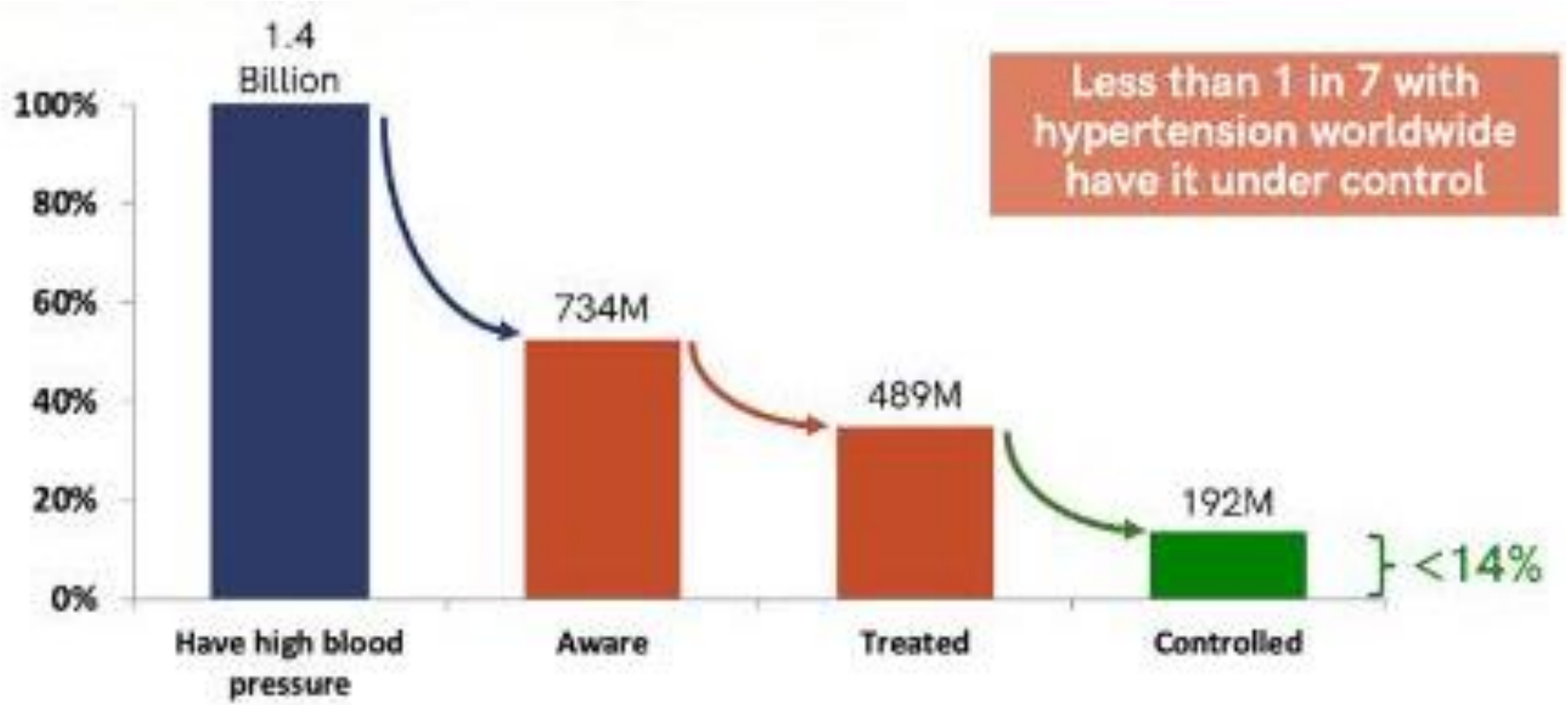
Global blood pressure control rates



Red dots (control rates 1990), black dots (control rates 2019).

Schutte A. Cardiovasc Res 2023;119:381

Most people with hypertension do not have it under control



Hypertension in 2009 and in 2023

- Treatment of HT is one of medicine's major successes
- Advances in therapy provide capacity to lower BP in almost every patient.

However…..

- Uncontrolled disease despite improved therapy
- The Hypertension Paradox

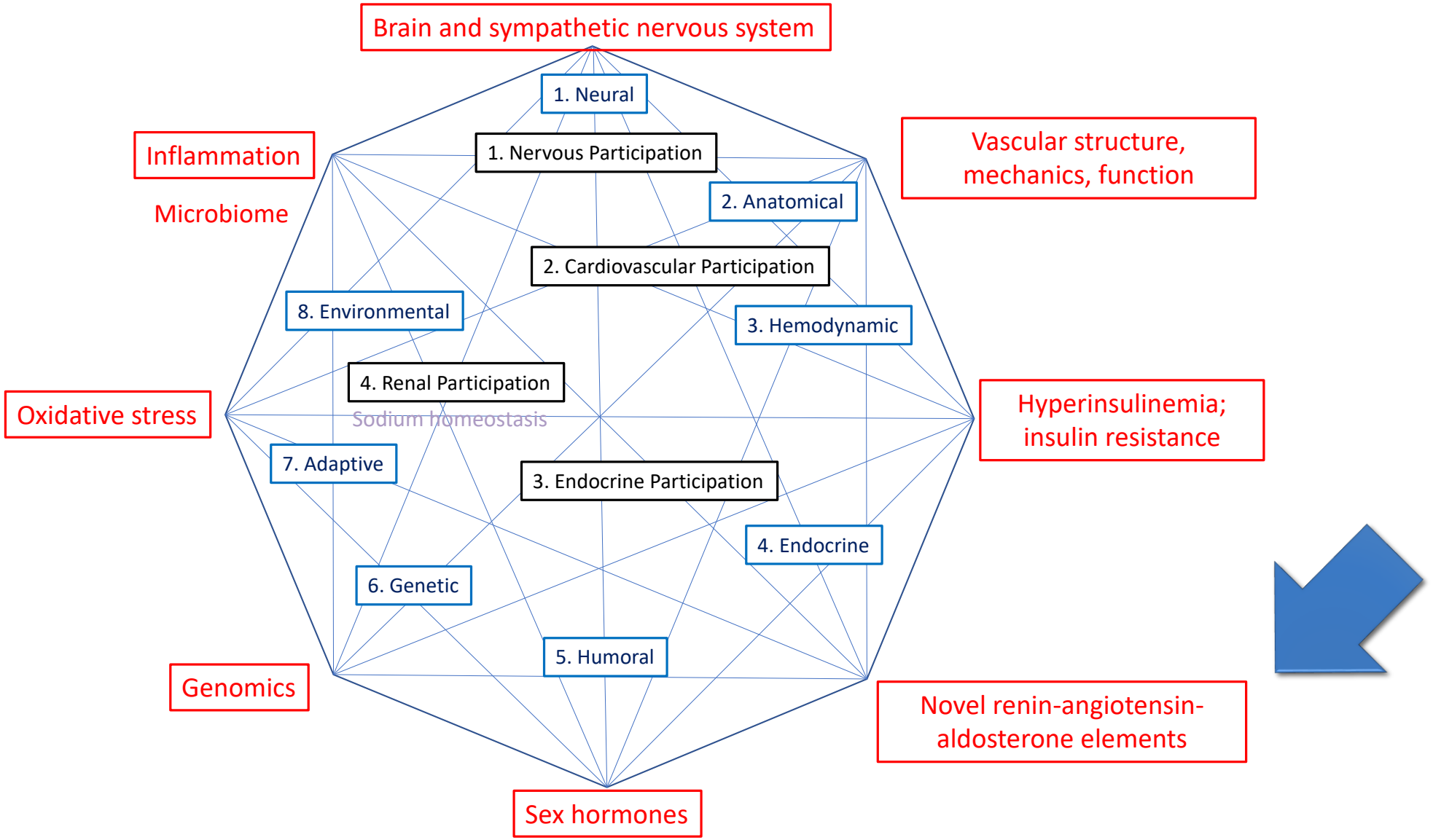
- CVD, stroke, vascular dementia, CKD

Chobanian New Engl J Med 2009;361

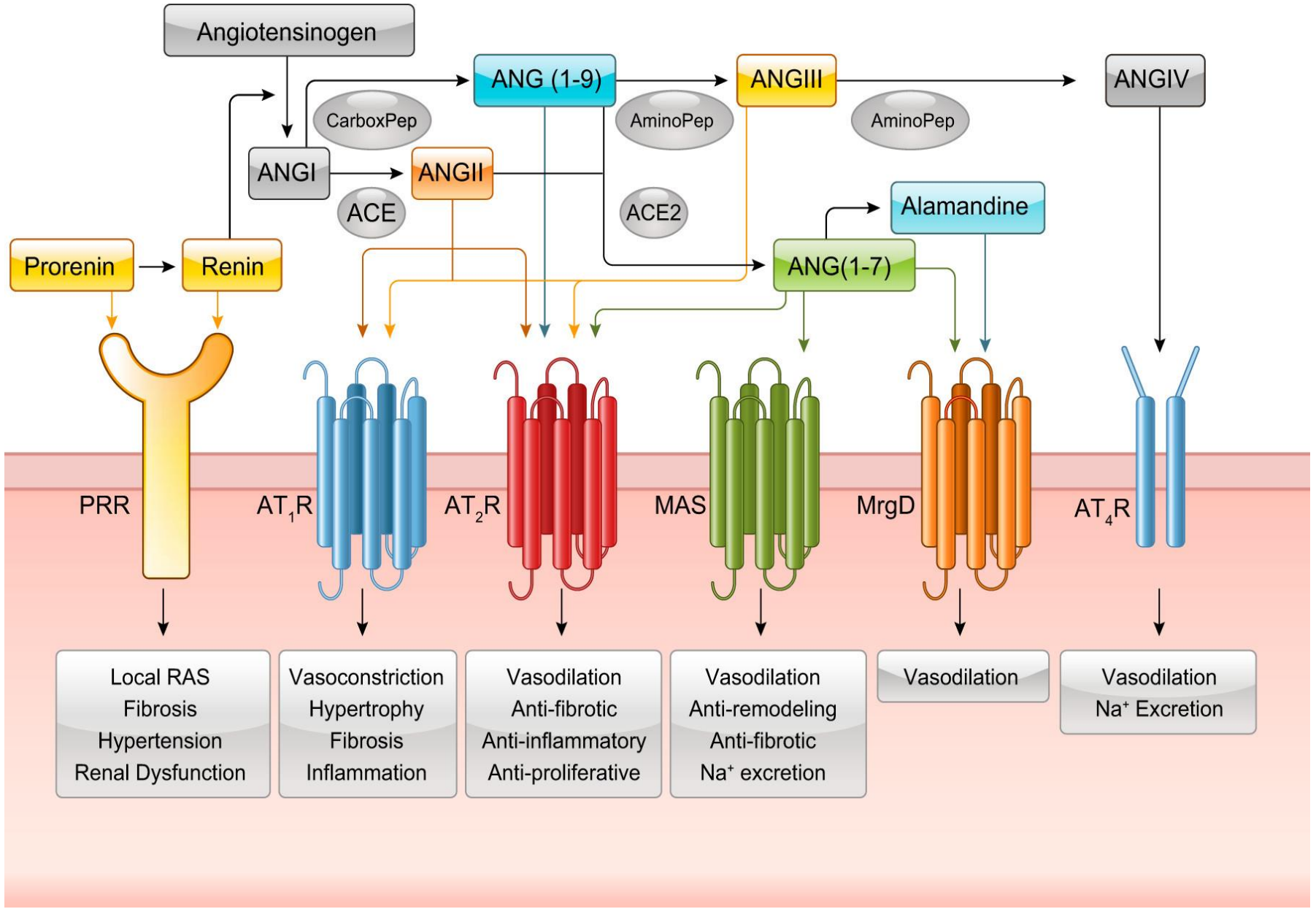
Reasons for the Hypertension Paradox

- Hypertension is a multi-factorial disease.
- Complex environmental factors.
- Adherence and compliance
- Life-long treatment
- Inadequate therapies.
- **The pathogenesis remains unclear**

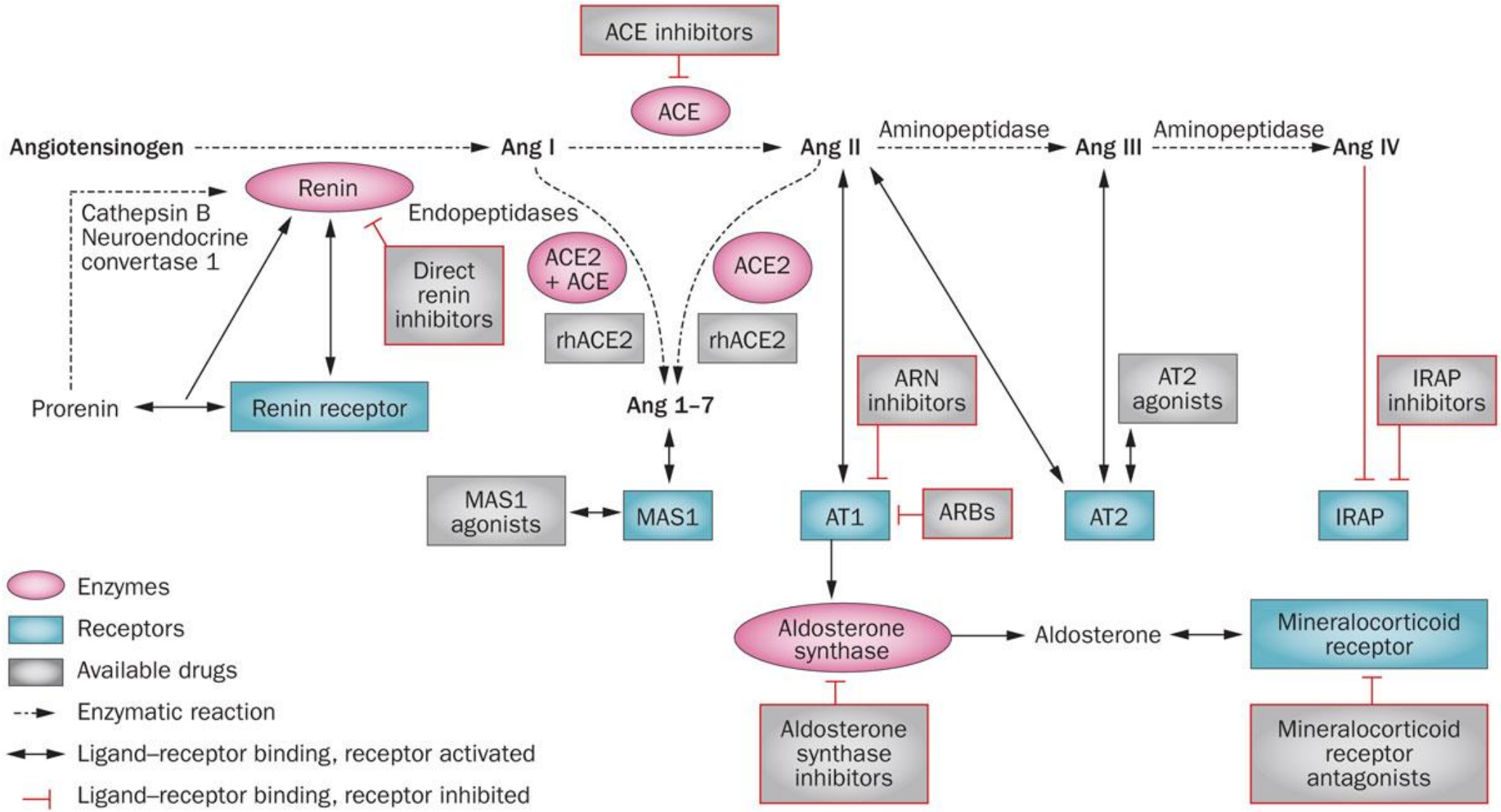
A new look at the mosaic theory of hypertension



The RAS


Angiotensinogen
ANG (1-9)
ANGIII
ANGIV
CarboxPep
AminoPep
AminoPep
ANGI
ANGII
ACE
ACE2
Alamandine
Prorenin
Renin
ANG(1-7)
PRR
AT1R
AT2R
MAS
MrgD
AT4R
Local RAS
Fibrosis
Hypertension
Renal Dysfunction
Vasoconstriction
Hypertrophy
Fibrosis
Inflammation
Vasodilation
Anti-fibrotic
Anti-inflammatory
Anti-proliferative
Vasodilation
Anti-remodeling
Anti-fibrotic
Na+ excretion
Vasodilation
Vasodilation
Na+ Excretion

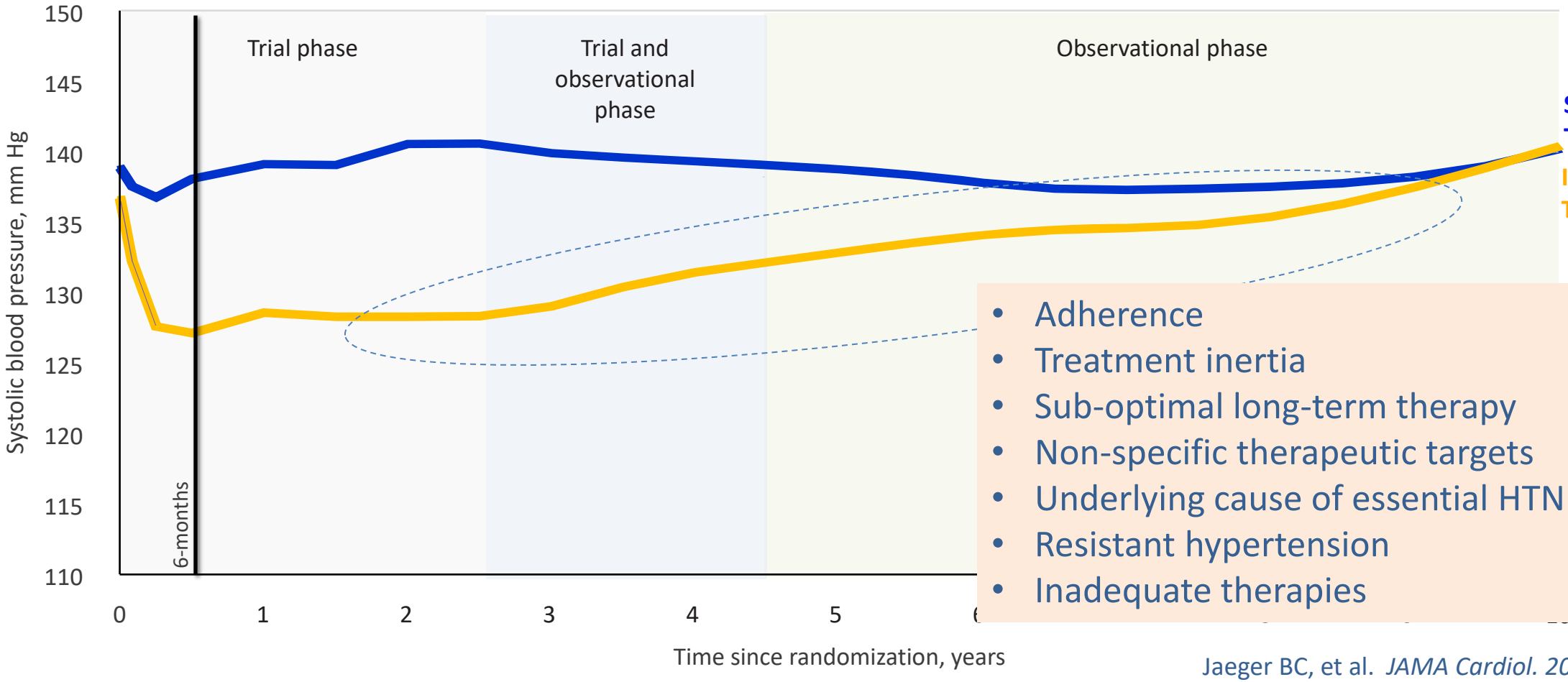
Main classes of pharmacological activators and inhibitors of the RAAS



Nature Reviews | Endocrinology

Long-term SPRINT trial shows loss of medication effect over time

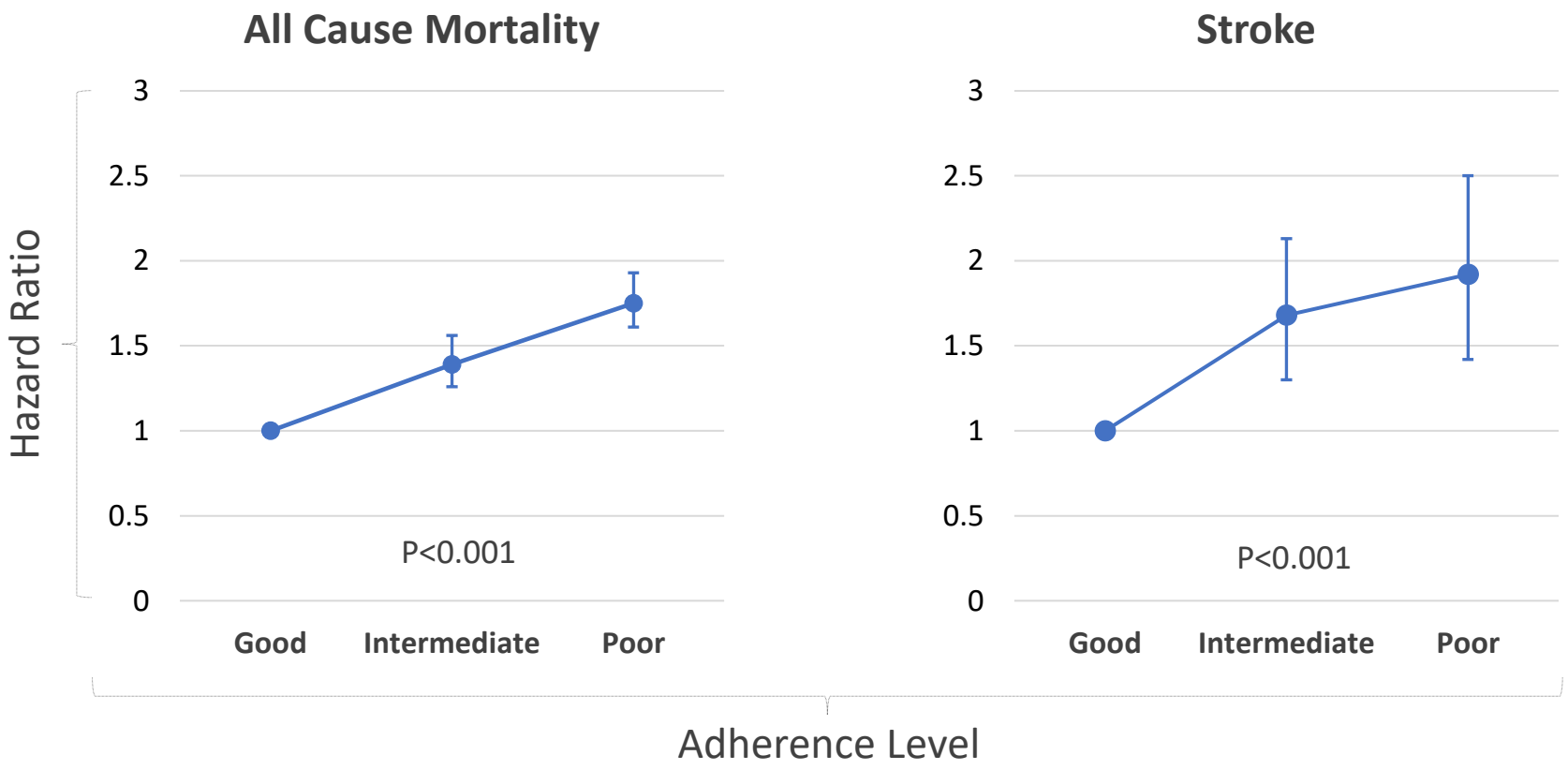
BP increases as patients unable to persist with medication intensification



- Adherence
- Treatment inertia
- Sub-optimal long-term therapy
- Non-specific therapeutic targets
- Underlying cause of essential HTN is unclear
- Resistant hypertension
- Inadequate therapies

Jaeger BC, et al. *JAMA Cardiol. 2022;7:1138-1146*

“Poor” Antihypertensive Drug Adherence is Associated with Increased Mortality Risk



error bars: 95% CI

Cohort (n):	**12,316**	**10,568**	**10,844**	**Cohort (n):**	**12,316**	**10,568**	**10,844**
Cases (n):	742	897	880	**Cases (n):**	99	145	135

Adapted from Kim S, et al. *Hypertension*. 2016;67:506-12

Barriers to blood pressure control

Patient

- Limited access to treatment
- Lack of education about hypertension
- Poor adherence
- Failure to adhere to lifestyle modification
- Hypertension is a chronic condition and needs long-term treatment

Health Care Provider

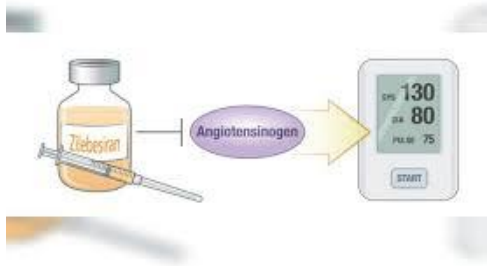
- Reluctance to treat
- Therapeutic inertia
- Lack of adherence to current guidelines

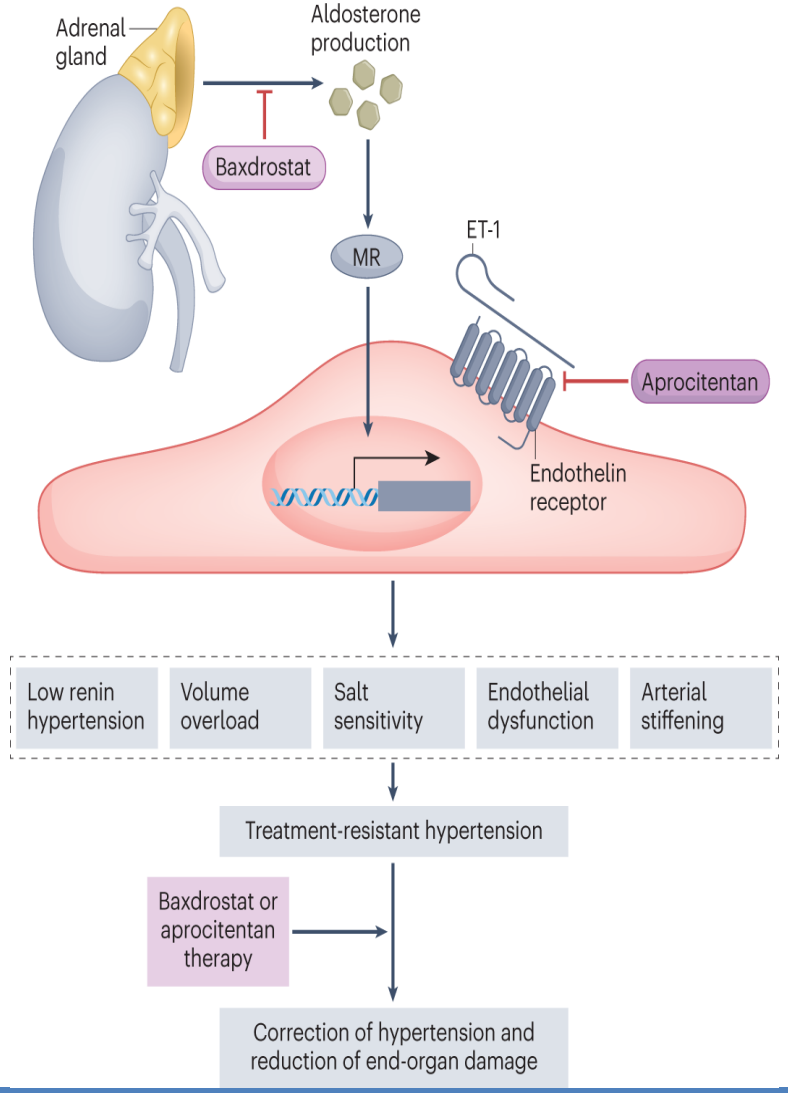
Health systems

- Failure to delegate responsibility to non-health care provider
- Inappropriate/inadequate follow up
- Challenges related to supply, access, costs of drugs
- Complex medication combinations (usually >3), on a daily basis

Therapeutic gaps:
New era in hypertension trials

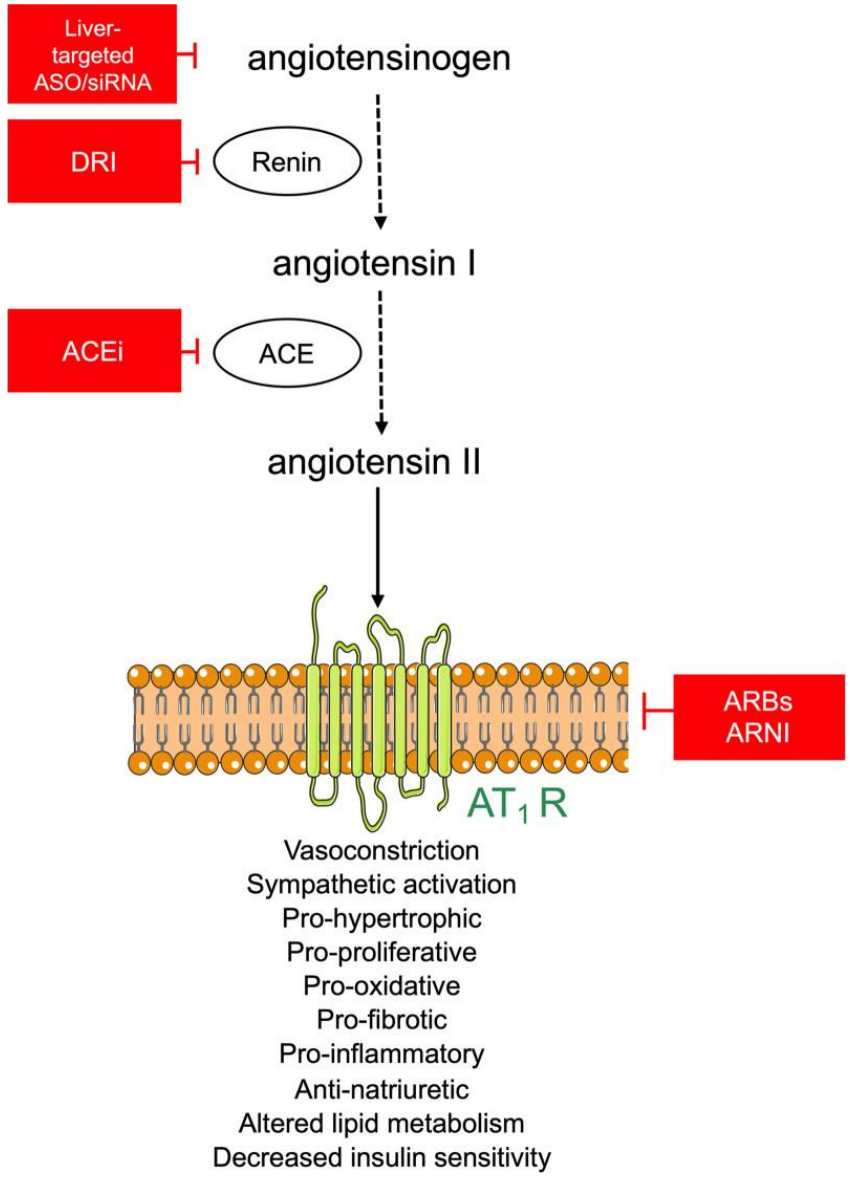
- Aldosterone synthase inhibitors (Baxdrostat)
- Endothelin receptor blockers (Aprocitentan)
- SGLT2 inhibitors and
- Non-steroidal MRA
- Renal denervation
- Silencing RNA-Agt (Zilbesiran)





Touyz. Nat Rev Neph 2023;19:216

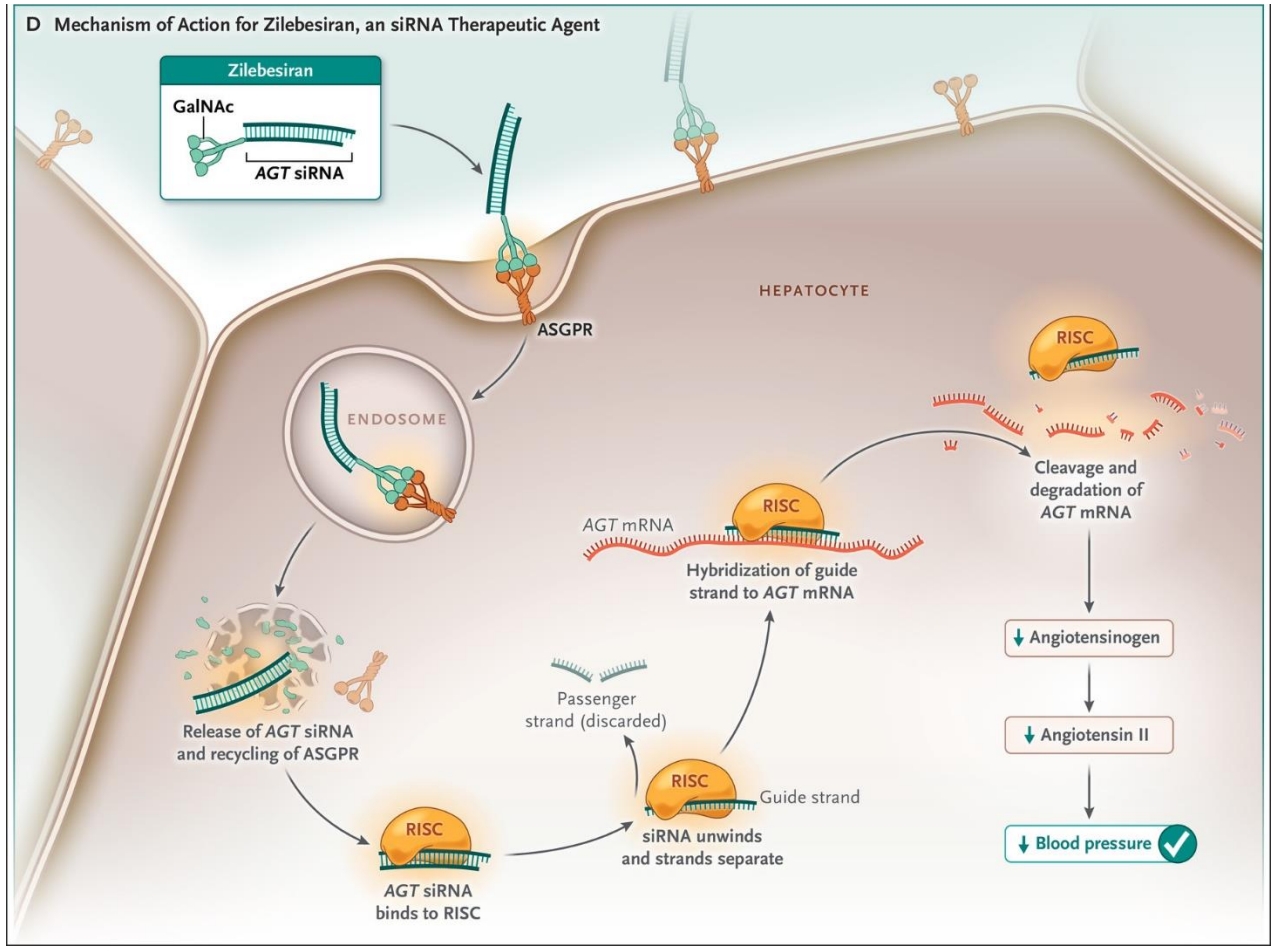
Angiotensinogen- a new therapeutic target in the RAAS



Crus-Lopez. Hypertension. 2022; 79(10): 2115–2126.

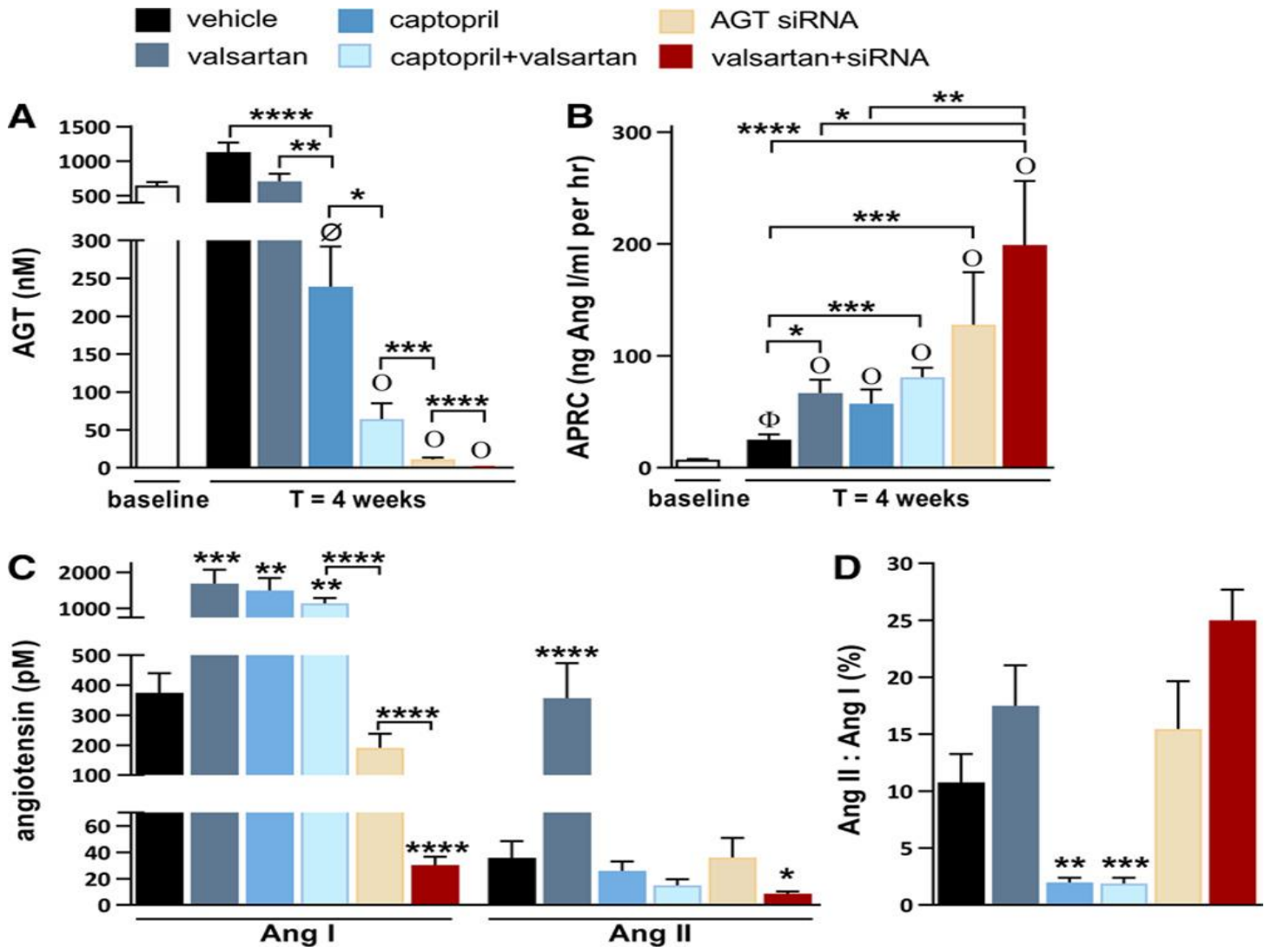
RESEARCH SUMMARY

Zilebesiran, an RNA Interference Therapeutic Agent for Hypertension



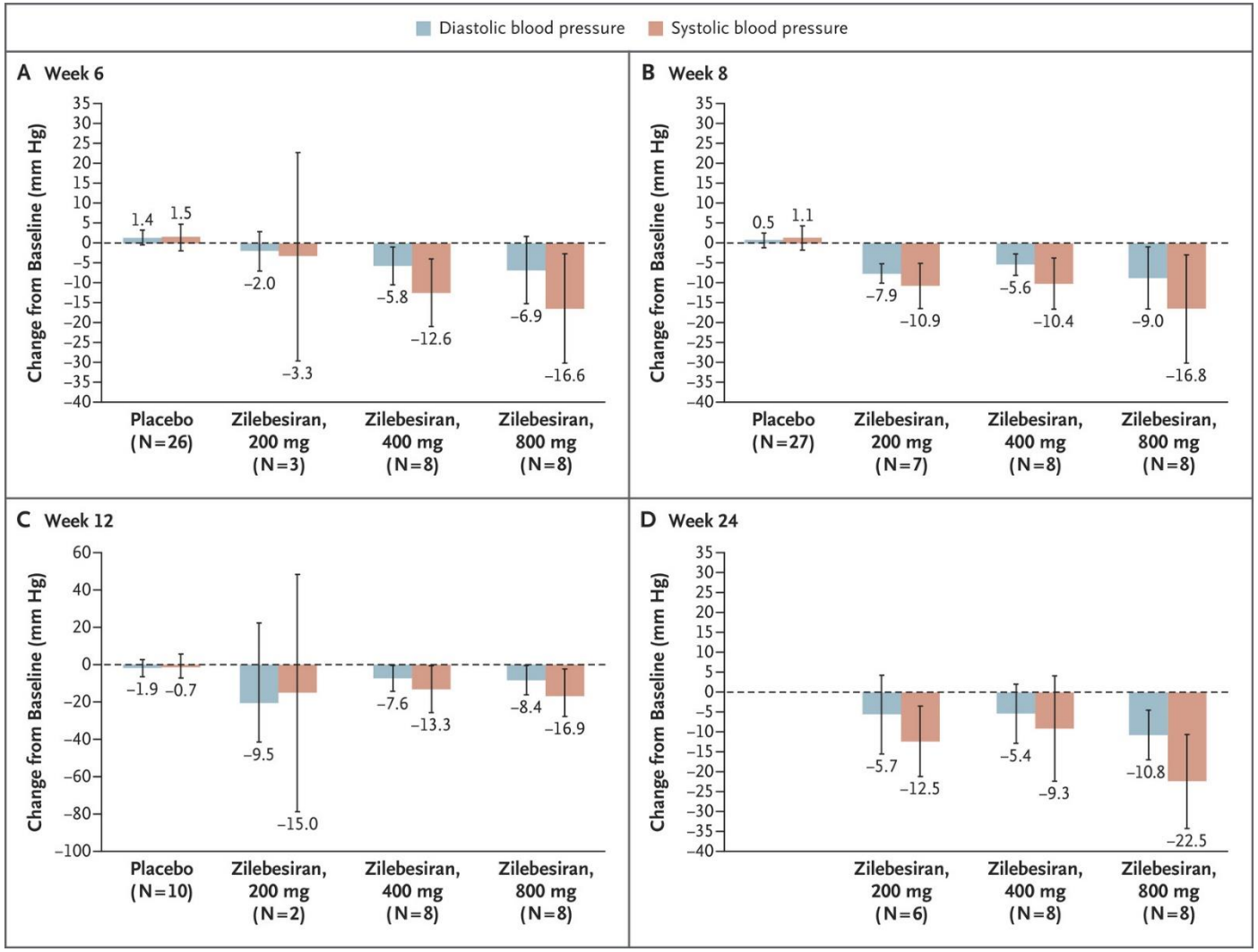
Desai AS. New Engl J Med 2023;389:228-238
Touyz RM. New Engl J Med 2023;389

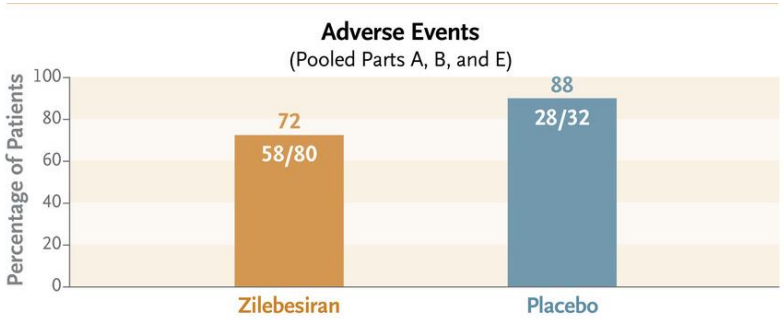
Effects of RAS inhibitors on renin-angiotensin system parameters in plasma
Renin escape phenomenon



active plasma renin concentration (APRC)

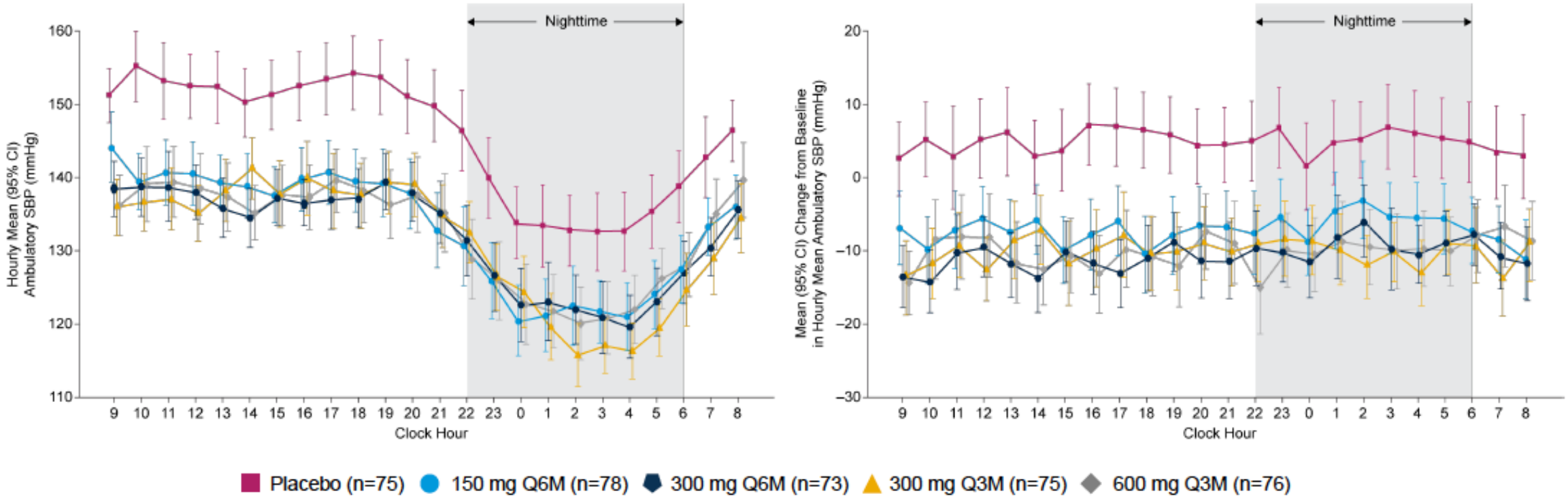
Decreases in BP and event rate after Single Doses of Zilebesiran





Consistent 24-Hour SBP Control Observed Through Month 3

Hourly Mean SBP and Change from Baseline in Hourly Mean SBP Assessed by Ambulatory BPM over 24 Hours

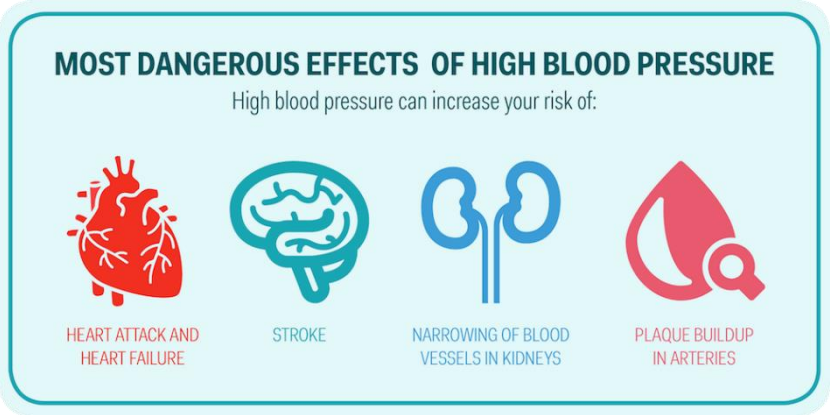


- SBP data to Month 6 were consistent with SBP data to Month 3
- DBP data to Month 3 and Month 6 were consistent with SBP data

13 Daytime is from 6:00 a.m. to 9:59 p.m. Nighttime is from 10:00 p.m. to 5:59 a.m. BPM, blood pressure monitoring; CI, confidence interval; Q3M, every 3 months; Q6M, every 6 months; SBP, systolic blood pressure.

Take home message: needs, challenges and gaps

- Hypertension is the world's number 1 killer



- Prevalence is increasing, especially in women
- CVD events increase at high normal BP levels
- Targeting 120/80 mmHg reduces mortality by almost 30%
- Control rates are declining globally
- Emphasis on increased adherence and more user-friendly approaches for lifetime therapy
- Need to define new mechanisms and therapeutic targets
- Promising new therapies

Zilebesiran: Reimagining the Treatment of Hypertension

Simon Fox, Ph.D.

Vice President, Zilebesiran Program Lead

A Significant Unmet Need in Hypertension

- **~219MM** adults with primary hypertension[1]
- Hypertension is the **leading cause of morbidity and mortality**[2,3]
- Up to **80%** have uncontrolled disease[4,5]
- **Variability in BP, lack of nighttime dipping, poor medication adherence** further exacerbate CV risk[7]

American Heart Association Scientific Sessions 2023

"Up to 80% of patients with hypertension remain uncontrolled, which carries a substantial risk of morbidity and mortality, resulting in lowered quality of life and substantial significant health care and societal costs," George Bakris, MD.

[1] Extrapolated for 7 major markets (7MM) based on proportion of US hypertension population with prior history of CVD or Framingham Risk Score of >10%, excluding patients with history of stroke and women of child-bearing potential; [2] Zhou B et al. Nat Rev Cardiol 2021;18:785–802; [3] Danaei G et al. PLoS Med 2009;6:e1000058; [4] Available from: www.who.int/news-room/fact-sheets/detail/hypertension (Accessed September 14, 2023); [5] Centers for Disease Control and Prevention. Estimated hypertension prevalence, treatment, and control among U.S. adults. 2022. Available from: https://millionhearts.hhs.gov/data-reports/hypertension-prevalence.html (Accessed September 14, 2023); [6] Ettehad D et al. Lancet 2006; 387: 957-67; [7] Desai AS et al. N Engl J Med 2023;389:228–38

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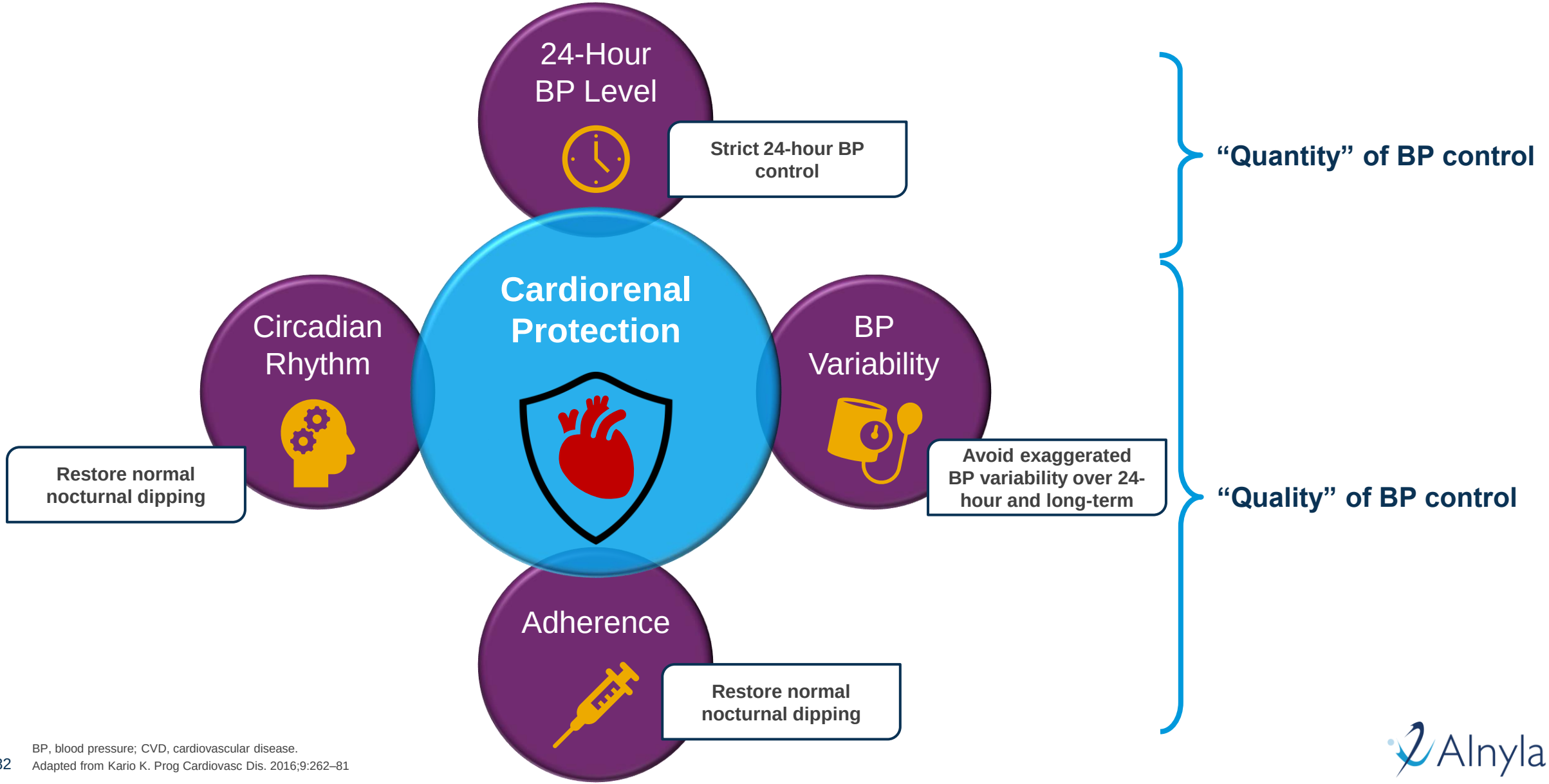
Targeting “Tonic” BP Control to Reduce Cardiovascular and Renal Risks

Achieving Quartet Could Further Reduce Risk of Organ Damage and Risk of CVD Events



BP, blood pressure; CVD, cardiovascular disease.
Adapted from Kario K. Prog Cardiovasc Dis. 2016;9:262–81

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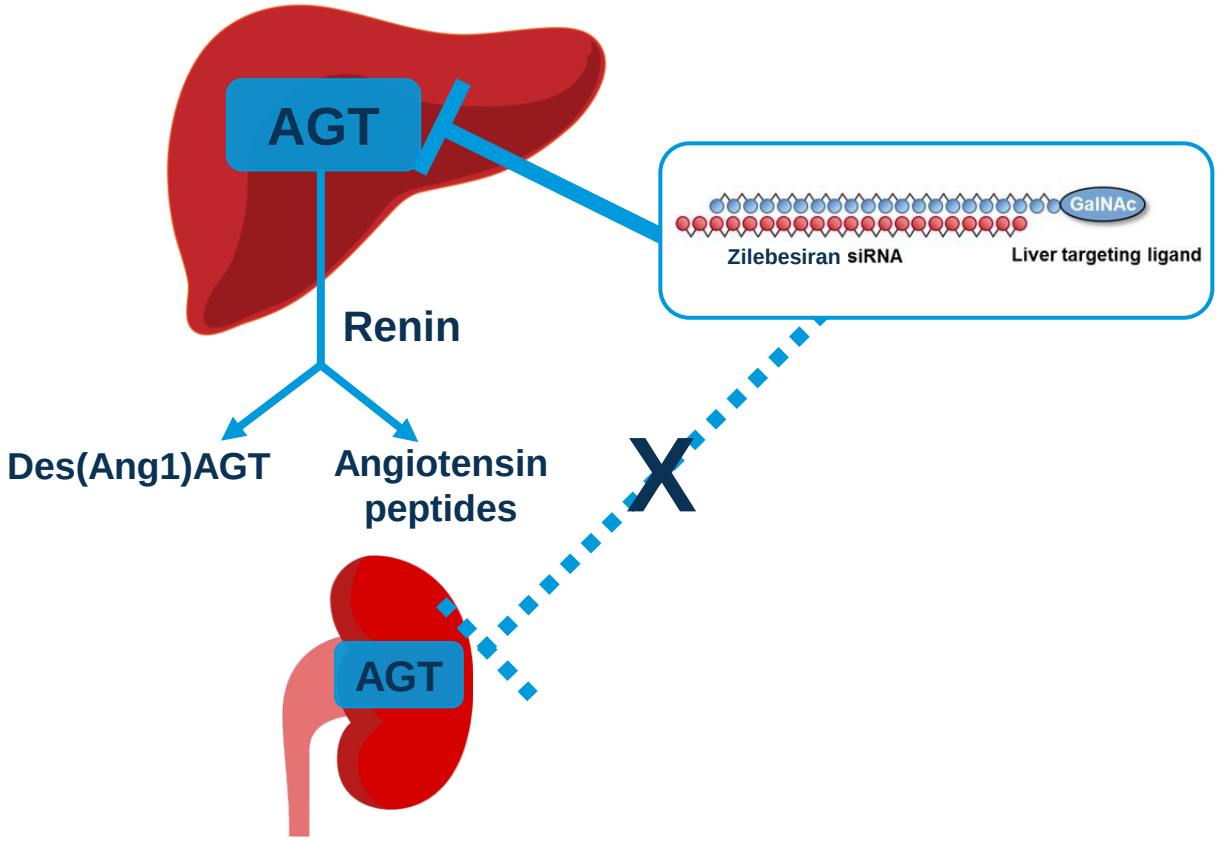
Zilebesiran: Innovative Approach for Treatment of Hypertension

Zilebesiran

- Subcutaneous RNA interference therapeutic that targets **hepatic AGT synthesis**
- Sustained dose-dependent reductions of **serum AGT and blood pressure through 24 weeks**[1]
- Potential for **quarterly or biannual dosing**

Liver-Specific AGT Knockdown



[1] Desai AS et al. N Engl J Med 2023;389:228–38

AGT, angiotensinogen; BP, blood pressure; GalNAc, N-Acetylgalactosamine; q3M; every 3 months; RAAS, renin angiotensin aldosterone system; siRNA, small interfering ribonucleic acid.

The safety and efficacy of zilebesiran in patients with hypertension have not been established or reviewed by any regulatory agency

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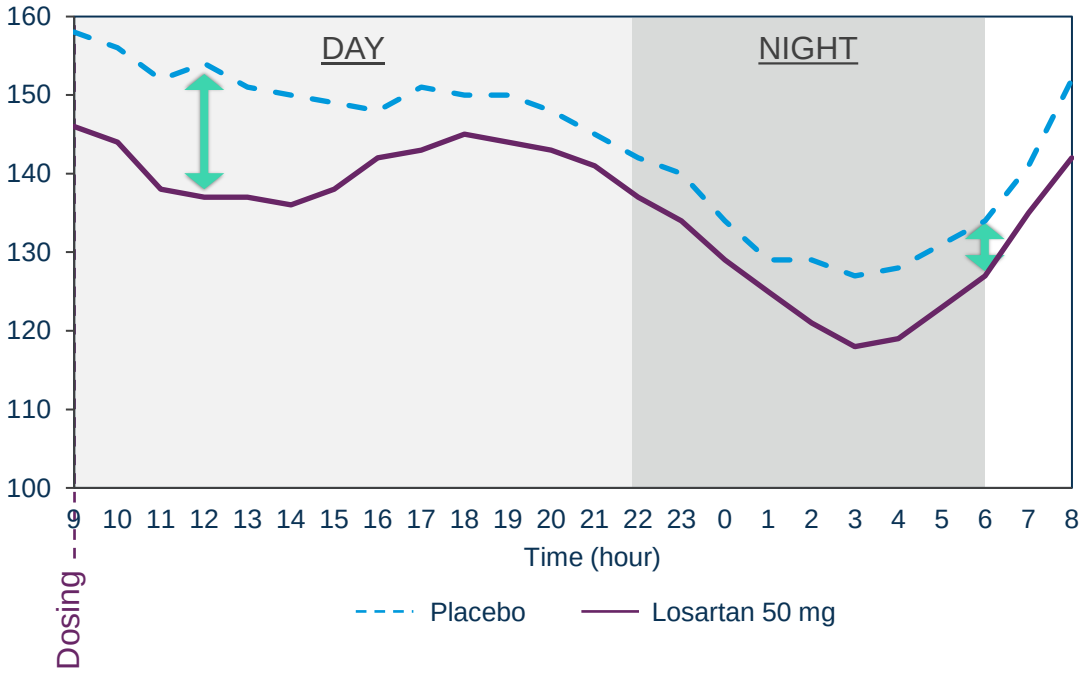
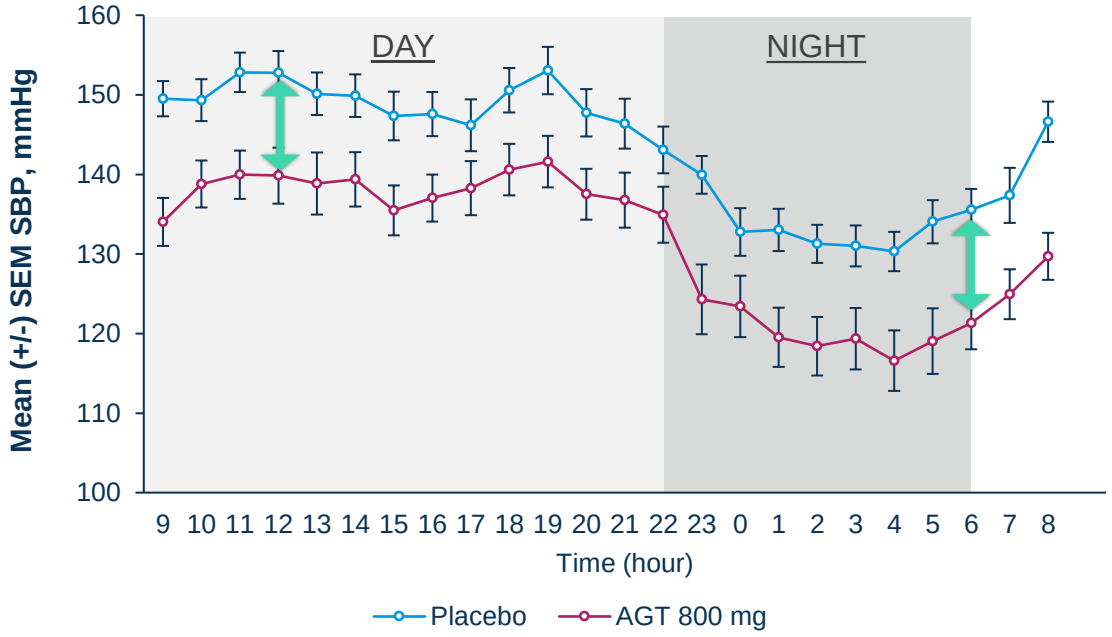
Early Evidence of Tonic Blood Pressure Control Seen in Phase 1[1]

Zilebesiran Achieves Consistent and Durable 24-Hour Tonic Blood Pressure Control After One Dose

Losartan: 24-Hour SBP at Week 4[2]



Zilebesiran: 24-Hour SBP at Week 6



Presented for illustrative purposes only. Not intended to be interpreted as comparison of two studies

[1] Desai AS et al. N Engl J Med 2023;389:228–38; [2] Adapted from Fogari et al. (1999) Current Therapeutic Research 60(4):195-206

AGT: angiotensinogen; BP: blood pressure; SBP: systolic blood pressure.

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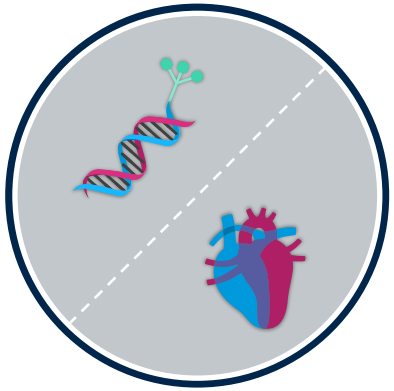
Leveraging Partner Expertise to Maximize Potential in Hypertension



Partnership to realize full potential of zilebesiran as innovative treatment for hypertension

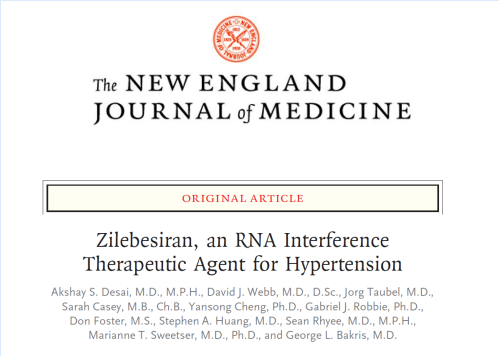
- Enables robust development plan with outcomes data at launch, optimizing commercial potential
- Significant economics enables Alnylam investment across broad pipeline
- Builds go-to-market expertise and commercial capabilities

Zilebesiran Development Plan

Exploring Benefits of Tonic BP Control to Reduce CV Risk, Delivering CV Outcomes at Launch

Phase 1 ✓

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



Phase 2

KARDIA-1 ✓

Zilebesiran monotherapy in patients with mild-to-moderate hypertension

Results presented at AHA Nov 2023

KARDIA-2

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

Topline results expected early 2024

KARDIA-3

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

Initiation expected early 2024

Phase 3

Cardiovascular Outcomes Trial (CVOT)

Study in patients with uncontrolled hypertension at high CV risk, evaluating MACE-type endpoint

Launch

Launch with label to reduce cardiovascular morbidity and mortality

Expected ~2030

MACE, major adverse cardiovascular event; RNAi, RNA interference

[1] Desai AS, et al. N Engl J Med. 2023;389:228-238

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KARDIA-1 Randomized, Double-Blind, Dose-Ranging Study of Zilebesiran in Patients with Mild-to-Moderate Hypertension[1]

Patient Population

(N=394)

Key Inclusion Criteria

- Adults 18-75 years of age
- Daytime mean SBP ≥ 135 mmHg and ≤160 mmHg by ambulatory BPM, after washout of previous antihypertensive medication for 2-4 weeks[a]

ClinicalTrials.gov; NCT04936035

1:1:1:1:1 RANDOMIZATION

- Placebo q3M SC
- OR
- Zilebesiran 150 mg q6M SC
- OR
- Zilebesiran 300 mg q6M SC
- OR
- Zilebesiran 300 mg q3M SC
- OR
- Zilebesiran 600 mg q6M SC

Outcomes and Endpoints

Primary Endpoint

- Change at Month 3 in 24-hour mean ambulatory SBP[b]

Key Secondary Endpoints

- Change at Month 3 in office SBP[b]
- Change at Month 6 in 24-hour mean ambulatory SBP
- Change at Month 6 in office SBP
- Proportion of patients with 24-hour mean ambulatory SBP <130 mmHg and/or reduction ≥20 mmHg at Month 6

Safety Endpoint

- Frequency of AEs

[1] Bakris et al. AHA Scientific Sessions 2023; [a] Patients previously taking medication for hypertension must have been without antihypertensives for ≥2 weeks before randomization. Four weeks of washout was required for long-acting antihypertensive medications, such as long-acting diuretics (e.g., chlorthalidone) or CCBs (e.g., amlodipine); [b] For analyses of Month 3 endpoints, zilebesiran 300 mg Q3M and Q6M data were pooled together; AE, adverse event; BP, blood pressure; BPM, blood pressure monitoring; CCB, calcium channel blocker; Q3M, every 3 months; Q6M, every 6 months; SBP, systolic blood pressure; SC, subcutaneous.

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Demographics

Demographics Well-Balanced Across Dosing Arms; Representative Patient Population[1]

	Total (N = 377)
Age, years (min, max)	56.8 (22, 75)
Sex, male, n (%)	210 (55.7)
BMI, ≥30 kg/m^2, n (%)	214 (56.8)
Baseline BP, mmHg (SD)	
24-hr mean SBP	141.8 (8.4)
24-hr mean DBP	81.8 (8.3)
Office SBP	141.8 (11.5)
Office DBP	87.0 (9.4)

2020 Census Data	KARDIA-1 Enrollment
Black & African American adults (14%)	25%
White adults (68%)	69%
Asian adults (5%)	6%

- Majority of patients (92.6%) completed 6-month double-blind period
  - Note: 16 Ukraine patients excluded from analysis

*Ethnicity – Hispanic adults Includes patients of Caucasian or African American race

[1] Bakris et al. AHA Scientific Sessions 2023

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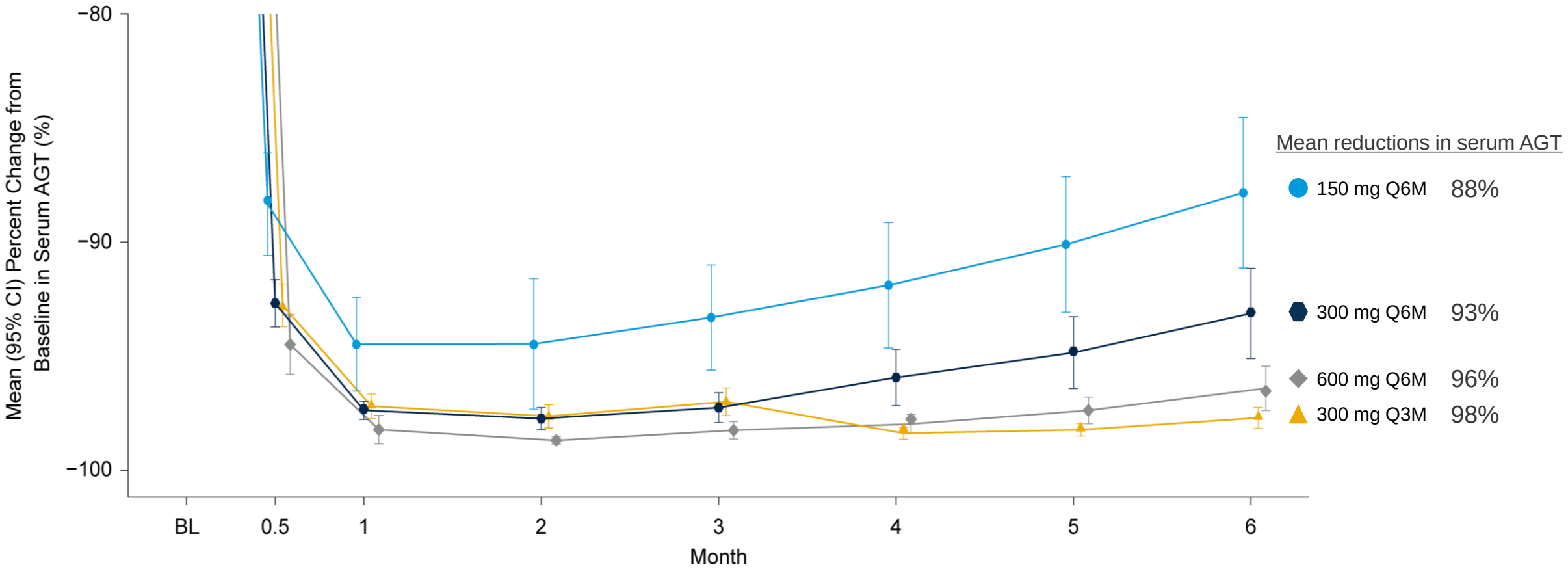
Pharmacodynamic Effect of Zilebesiran on AGT Through Month 6

Zilebesiran 300mg & 600mg Achieved Potent, Dose Dependent Reductions in AGT Through Month 6[1]

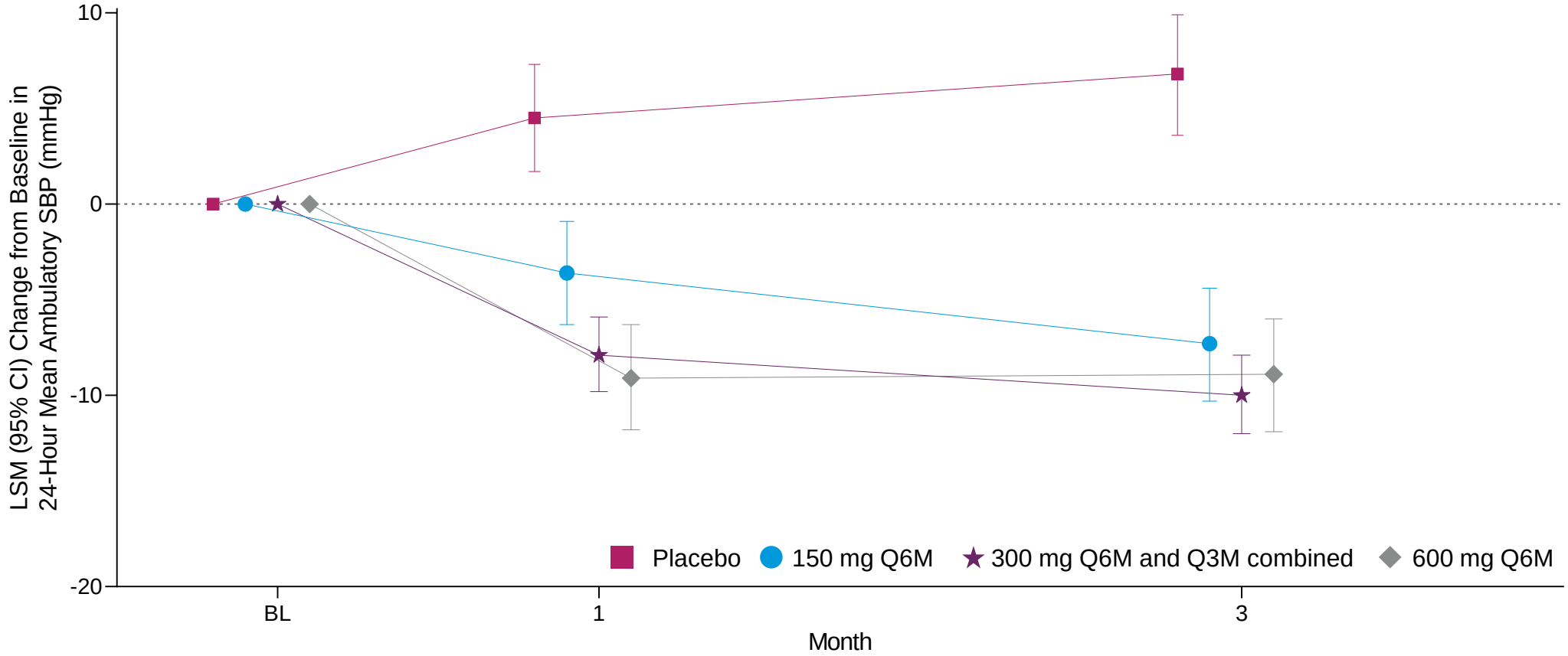


Data points are staggered for visualization. AGT, angiotensinogen; BL, baseline; CI, confidence interval; Q3M, every 3 months; Q6M, every 6 months; SBP, systolic blood pressure.

[1] Bakris et al. AHA Scientific Sessions 2023

24-Hour Mean Ambulatory SBP at Month 3

Zilebesiran Achieved 24-Hour Mean SBP Reduction of up to 16.7 mmHg (Placebo Adjusted)[1]

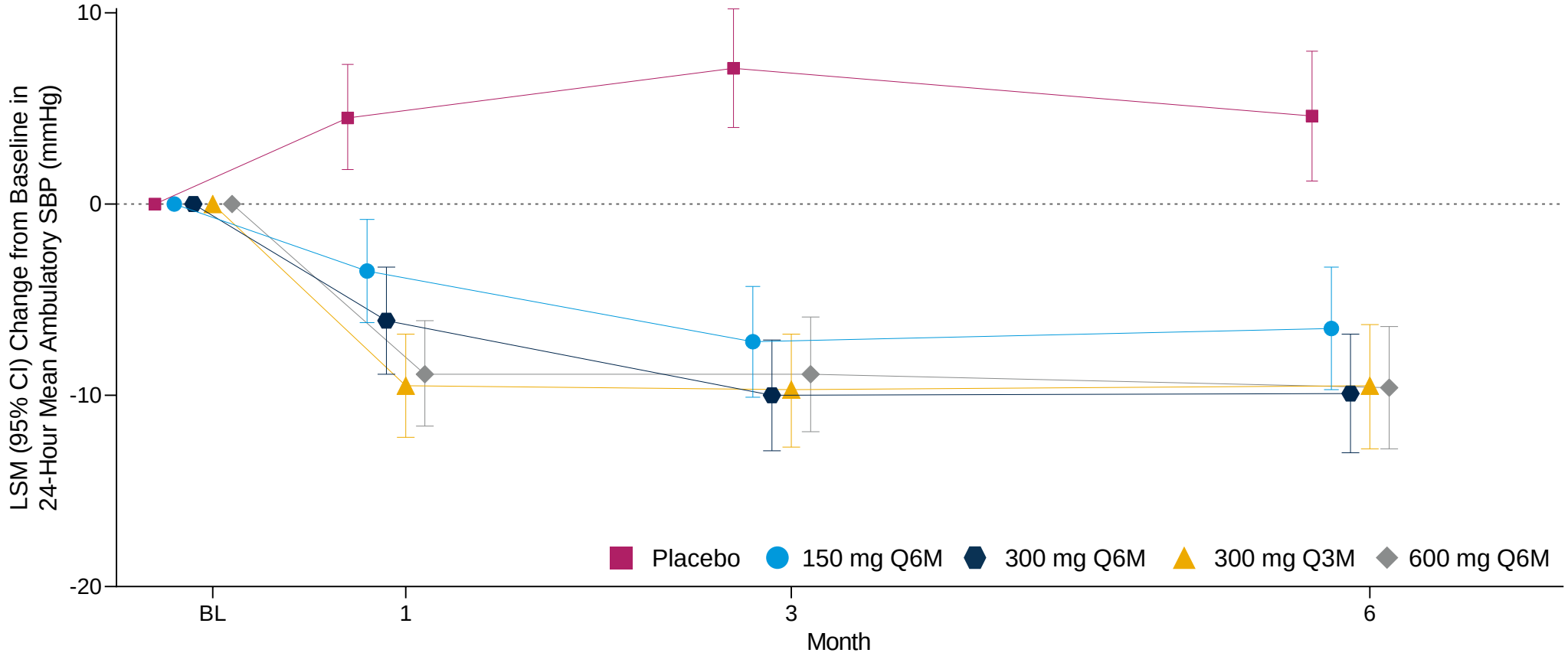


Month 3 (Primary Endpoint)	150 mg Q6M	300 mg Q3M and Q6M	600 mg Q6M
LSMD vs placebo, mmHg (95% CI)[a]	**−14.1** (−19.2, −9.0), p<0.0001	**−16.7** (−21.2, −12.3), p<0.0001	**−15.7** (−20.8, −10.6), p<0.0001

[1] Bakris et al. AHA Scientific Sessions 2023; [a] Adjusted 95% CIs and p values for the Month 3 primary analysis are based on Dunnett's test. BL, baseline; CI, confidence interval; LSM, least-squares mean; LSMD, LSM difference; Q3M, every 3 months; Q6M, every 6 months; SBP, systolic blood pressure; 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.

24-Hour Mean Ambulatory SBP at Month 6

Zilebesiran Achieved 24-Hour Mean SBP Reduction of up to 14.5 mmHg (Placebo Adjusted)[1]

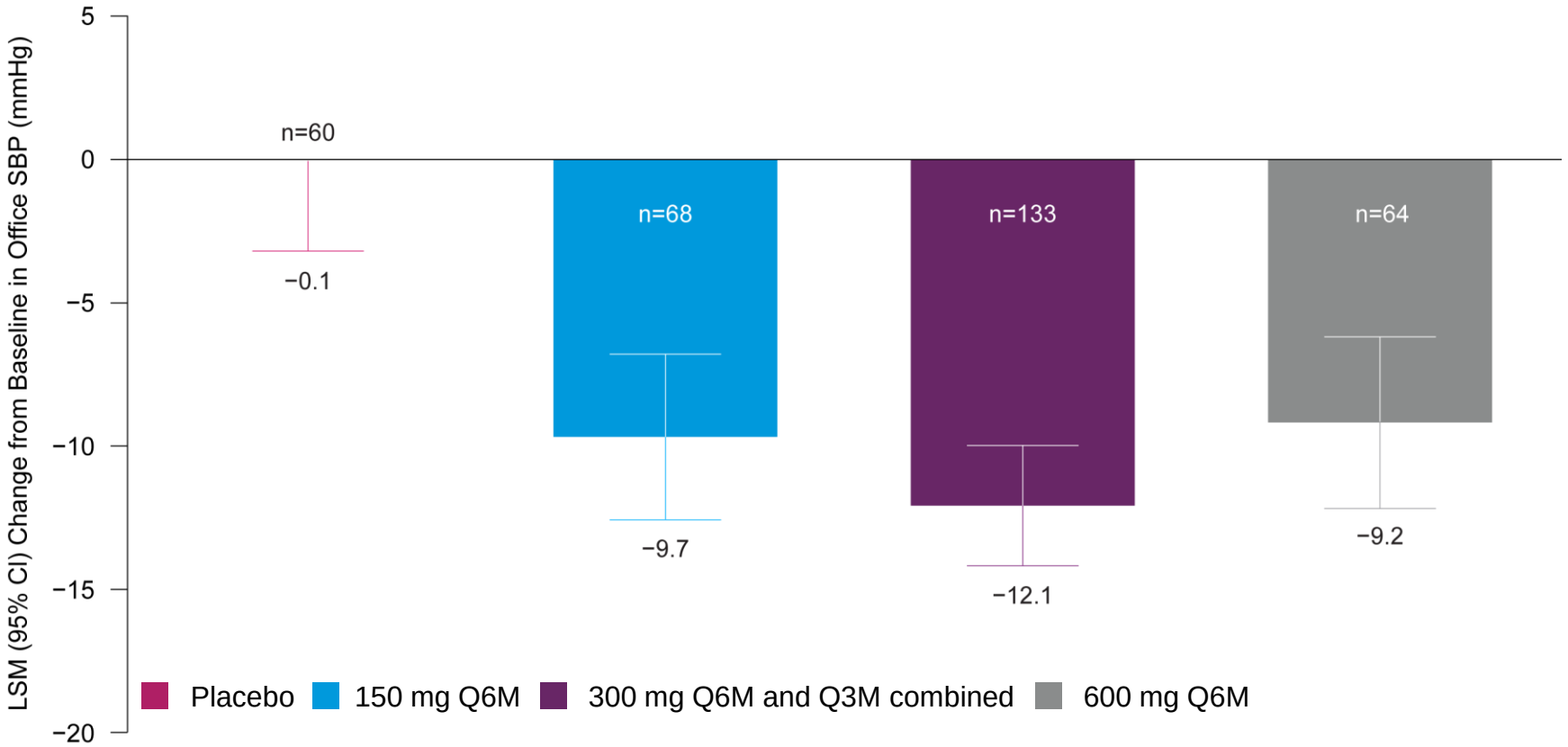


Month 6 (Key Secondary Endpoint)	150 mg Q6M	300 mg Q6M	300 mg Q3M	600 mg Q6M
LSMD vs placebo, mmHg (95% CI)	**−11.1** (−15.8, −6.4), p<0.0001	**−14.5** (−19.1, −9.9), p<0.0001	**−14.1** (−18.9, −9.4), p<0.0001	**−14.2** (−18.9, −9.5), p<0.0001

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; [1] Bakris et al. AHA Scientific Sessions 2023; [a] Adjusted 95% CIs and p values for the Month 3 primary analysis are based on Dunnett's test; BL, baseline; CI, confidence interval; LSM, least-squares mean; LSMD, LSM difference; Q3M, every 3 months; Q6M, every 6 months; SBP, systolic blood pressure.

Change from Baseline in Office SBP at Month 3

Zilebesiran Achieved Office SBP Reductions of up to 12.0 mmHg at Month 3 (Placebo Adjusted)[1]

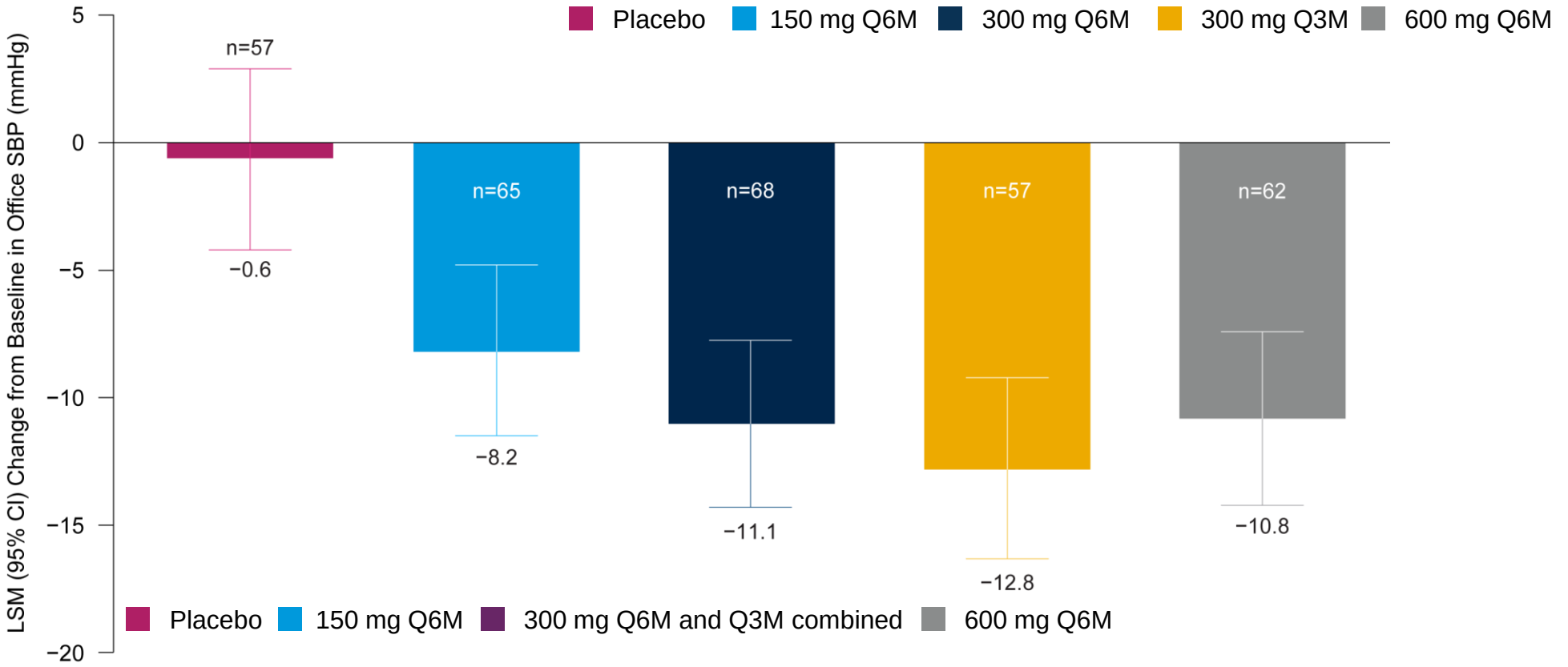


Month 3 (Key Secondary Endpoint)	150 mg Q6M	300 mg Q3M and Q6M	600 mg Q6M
LSMD vs placebo, mmHg (95% CI)	**−9.6** (−13.8, −5.3), P<0.0001	**−12.0** (−15.7, −8.3), P<0.0001	**−9.1** (−13.4, −4.8), P<0.0001

Blood pressure assessments were censored if taken while patients were receiving or within 2 weeks after stopping any rescue medication.
CI, confidence interval; LSM, least-squares mean; LSMD, LSM difference; Q3M, every 3 months; Q6M, every 6 months; SBP, systolic blood pressure.
[1] Bakris et al. AHA Scientific Sessions 2023

Change from Baseline in Office SBP at Month 6

Zilebesiran Achieved Office SBP Reductions of up to 12.1 mmHg at Month 6 (Placebo Adjusted)[1]



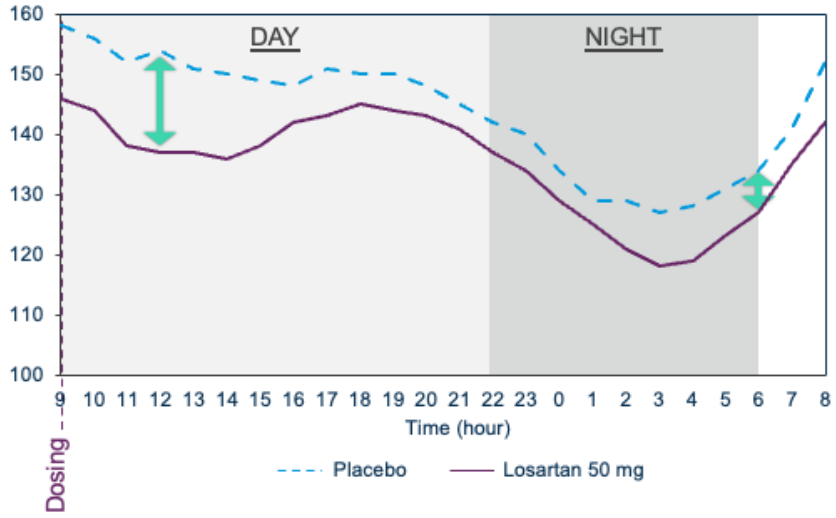
Month 6 (Key Secondary Endpoint)	150 mg Q6M	300 mg Q6M	300 mg Q3M	600 mg Q6M
LSMD vs placebo, mmHg (95% CI)	**−7.5** (−12.4, −2.7), p=0.0025	**−10.5** (−15.3, −5.7), P<0.0001	**−12.1** (−17.2, −7.1), P<0.0001	**−10.2** (−15.1, −5.3), p<0.0001

Blood pressure assessments were censored if taken while patients were receiving or within 2 weeks after stopping any rescue medication.
CI, confidence interval; LSM, least-squares mean; LSMD, LSM difference; Q3M, every 3 months; Q6M, every 6 months; SBP, systolic blood pressure.
[1] Bakris et al. AHA Scientific Sessions 2023

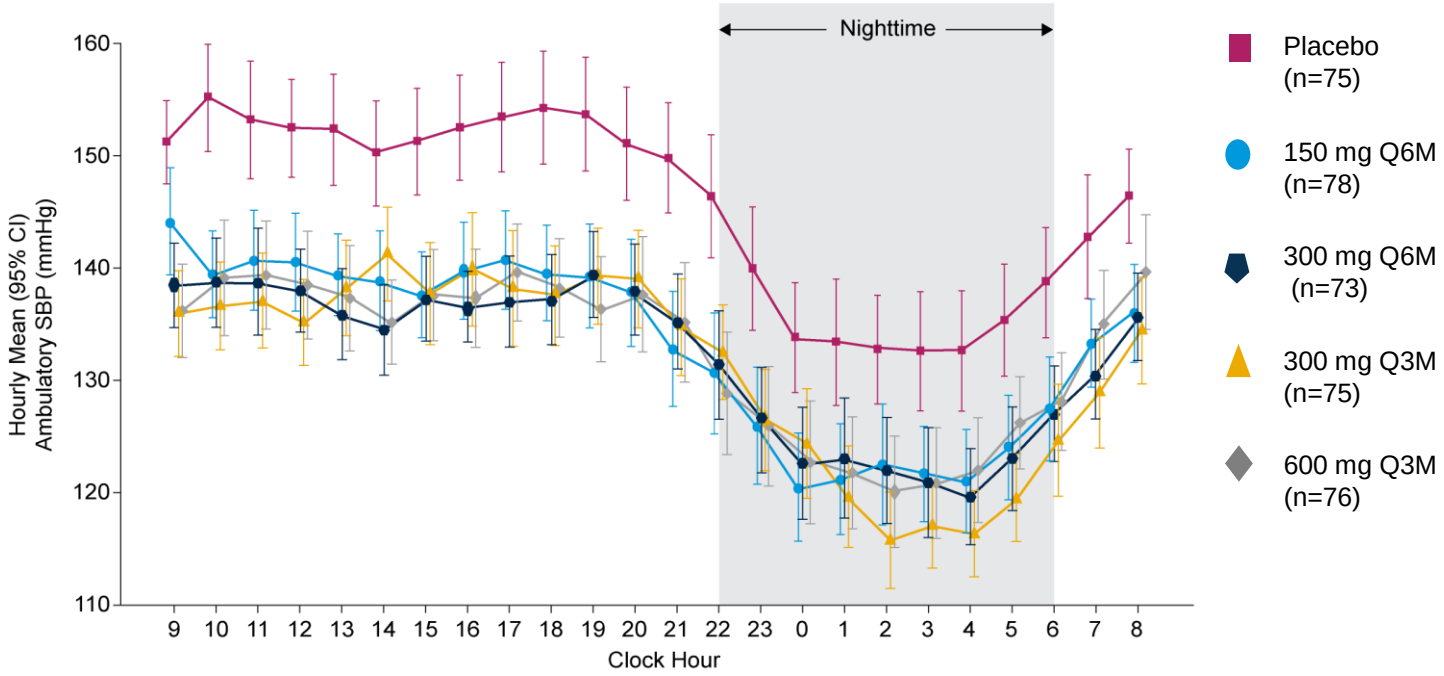
Zilebesiran Achieved Tonic BP Control at Month 3 After Single Dose[1]

KARDIA-1 Replicates Phase 1 Results in Larger Study Across Multiple Doses

Losartan: Hourly Mean Ambulatory SBP[2]



Zilebesiran Hourly Mean Ambulatory SBP



Magnitude and consistency of blood pressure control decreases at nighttime and out to end of dosing interval

24-hour tonic BP control also consistent & sustained at month 6

Presented for illustrative purposes only. Not intended to be interpreted as comparison of two studies

1. Bakris et al. AHA Scientific Sessions 2023. 2. Adapted from Fogari et al. (1999) Current Therapeutic Research 60(4):195-206

SBP: systolic blood pressure

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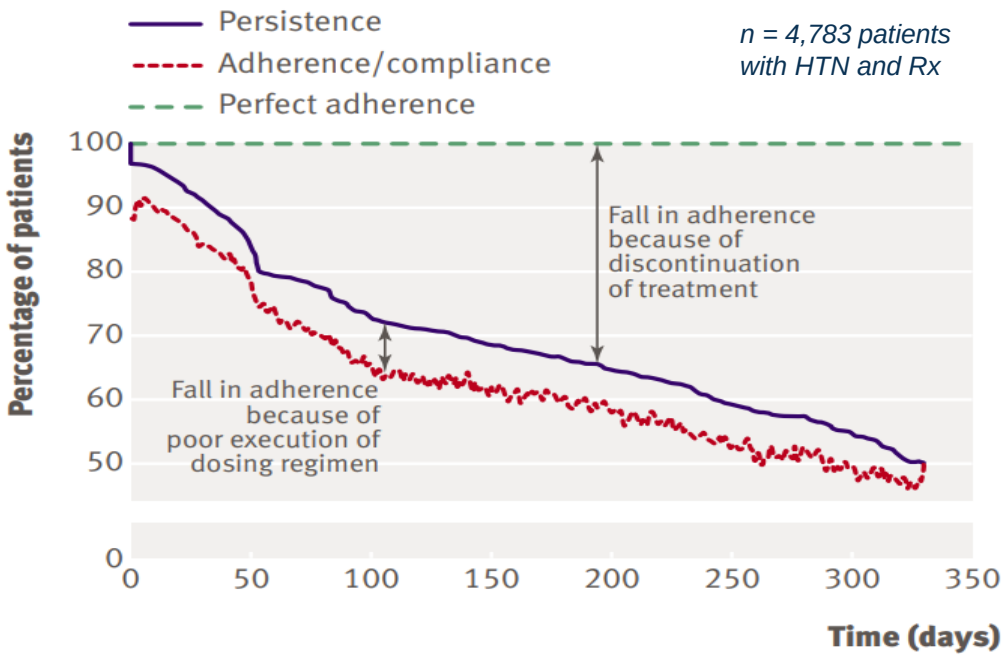
Adherence and Nighttime Blood Pressure[2] Contribute to CV Risk

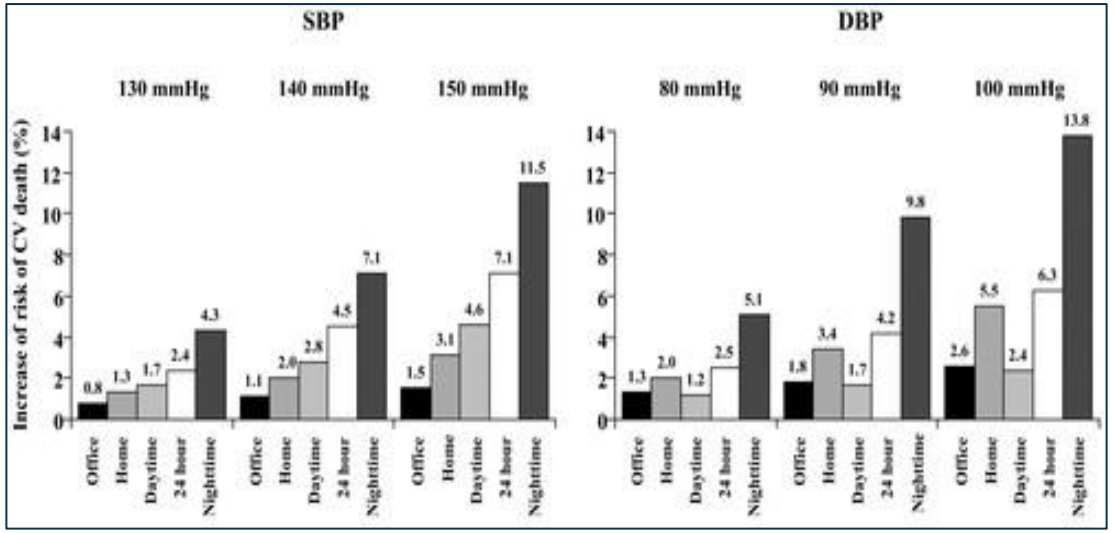
Poor adherence remains a significant issue



Within 6 months almost 35% of patients stop antihypertensive treatment[2]

Low adherence is associated with an increased CV risk[3]

Nighttime BP Strongest predictor of CV Mortality



10 mmHg increases in SBP during nighttime significantly increases risk of CV death[3]

1 Vrijens B. et al BMJ 2008. 336(7653):1114-7; 2. Mazzaglia G et al. Circulation. 2009;120(16):1598-1605; 3. Sega R, et al. Circulation. 2005
SBP: systolic blood pressure

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Zilebesiran Had Encouraging Safety Profile[1]

- No drug-related AEs were classified as serious or severe
- One death due to cardiopulmonary arrest occurred in patient receiving 300 mg q3M zilebesiran
  - Not classified as drug-related
- Drug-related AEs leading to discontinuation of zilebesiran were orthostatic hypotension (n=2), BP elevation (n=1), and ISR (n=1)
- Most ISR and hyperkalemia AEs were mild, transient, and did not require therapeutic intervention
- Hypotension AEs were mild or moderate in severity and transient; most did not require therapeutic intervention
- No clinically relevant changes in renal or hepatic function were observed

[1] Bakris et al. AHA Scientific Sessions 2023

Ongoing Phase 2 Clinical Development Plan

KARDIA-2

Combination Phase 2 Study (N = 672)

- Evaluate efficacy and safety of zilebesiran as combination therapy
- Background treatment standardized with ARB, calcium channel blocker or diuretic
- Enrollment completed June 2023; topline results expected **early 2024**

KARDIA-3

Combination Phase 2 Study in high CV risk (N = up to 390)

- Evaluate efficacy and safety of zilebesiran as combination therapy in high CV risk patients with uncontrolled hypertension (2+ background antihypertensive treatment; usual care)
- Expect study initiation **early 2024**

ARB, angiotensin receptor blocker.

KARDIA-3 Phase 2 Combination Study in High CV Risk

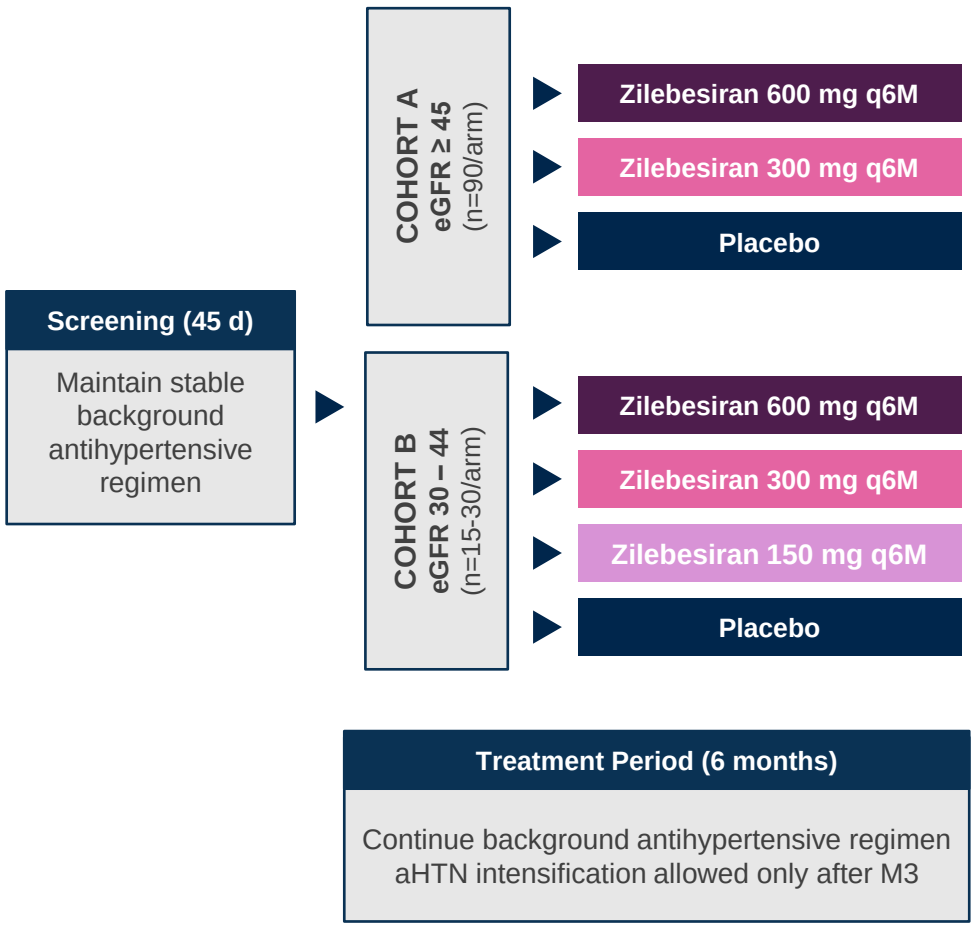
Randomized, Double-Blind Study in High CV Risk Patients with Uncontrolled Hypertension

Study Population

Cohort A: eGFR ≥ 45 (N~270)
Cohort B: eGFR 30 – 44 (N~60-120)

Key Inclusion Criteria

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



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

Initiate
Early 2024

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

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Building ATTR Amyloidosis Market Leadership

John Vest, M.D.
SVP, Clinical Research

Ali Murad, M.D.
Senior Director, Clinical Research

ATTR Amyloidosis

Rare, Progressively Debilitating, and Fatal Disease

Description

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

Hereditary ATTR (hATTR) Amyloidosis

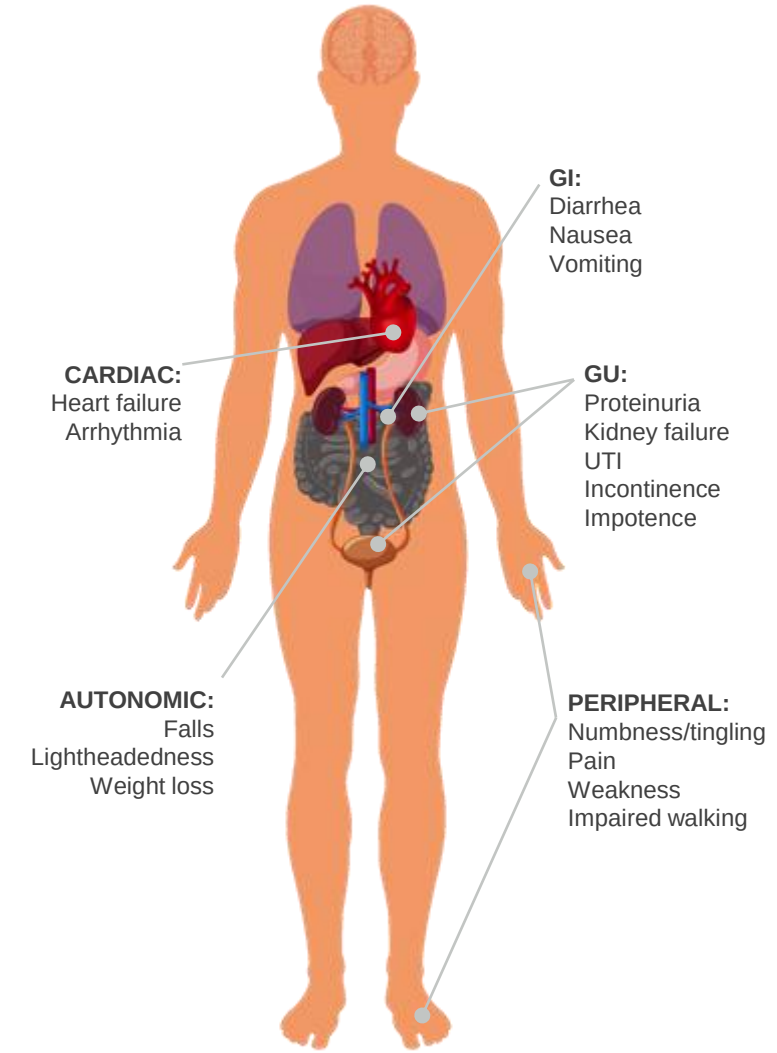
~50,000

patients worldwide[2]

Wild-Type ATTR (wtATTR) Amyloidosis

~200,000 – 300,000

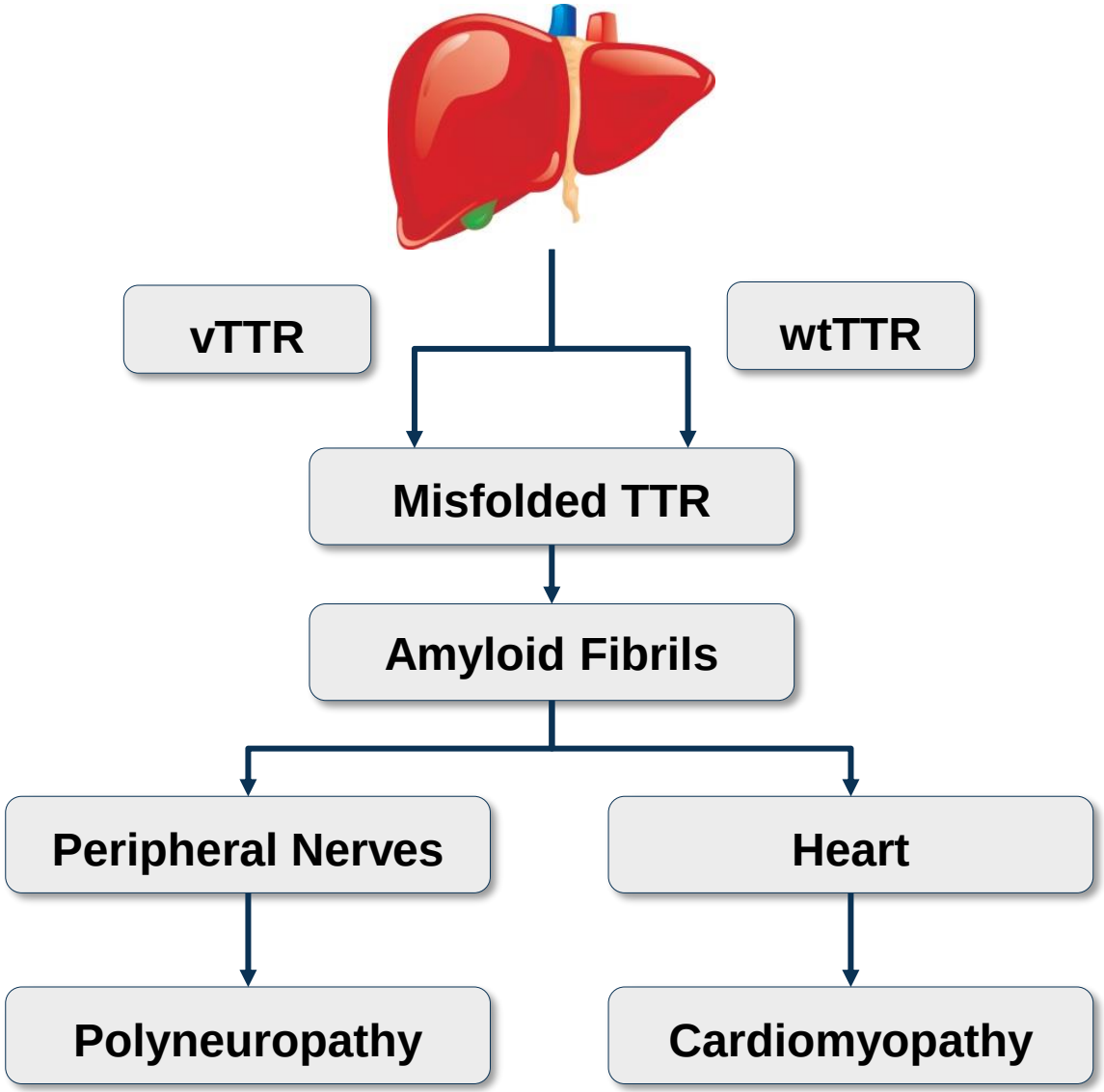
patients worldwide[3]



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

ATTR Amyloidosis

Same Pathophysiology Drives Two Key Manifestations of the Disease



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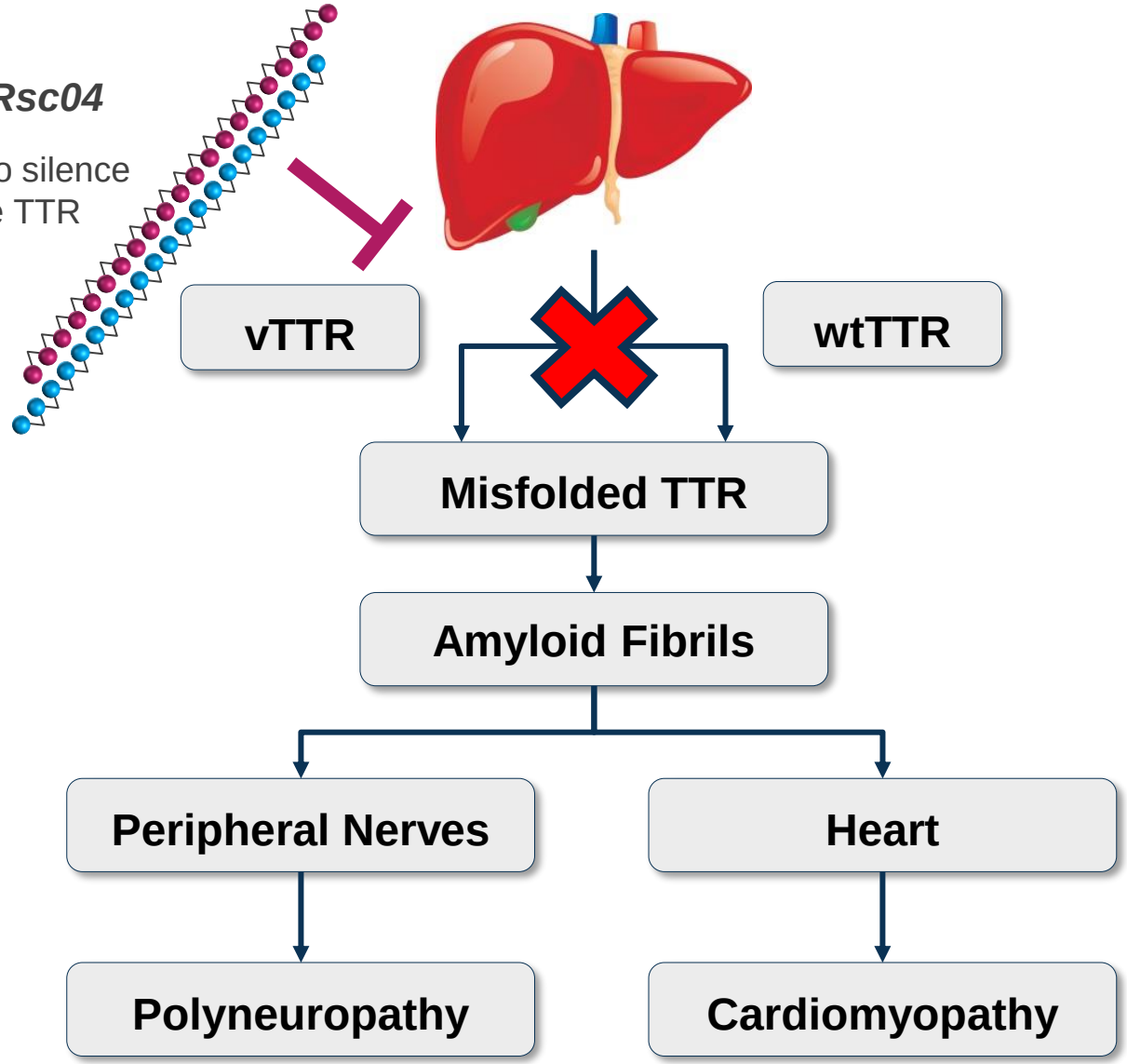
RNAi Therapeutic Hypothesis in ATTR Amyloidosis

Silencing TTR Gene Expression Can Potentially Address Underlying Cause of Disease

PATISIRAN / VUTRISIRAN / ALN-TTRsc04

siRNA sequences selected to silence both variant and wild-type TTR



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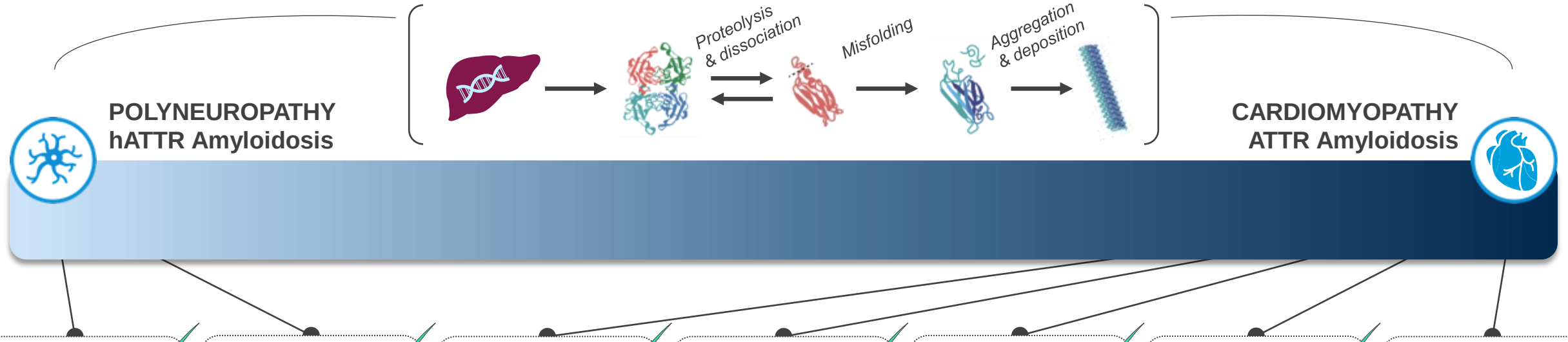
Potential for Broad Impact of RNAi Therapeutics Across Disease Spectrum



ONPATTRO
Primary endpoint
- mNIS+7

All secondary endpoints

APOLLO

AMVUTTRA
Primary endpoint
- mNIS+7

All secondary endpoints

HELIOS·A

ONPATTRO
Post hoc analyses[1]
- Reduction in mortality and hospitalization

Exploratory endpoints
- NT-proBNP, LV thickness, 10-meter walk test

APOLLO

PATISIRAN[3]
IIS[2]
- Clearance of cardiac amyloid, improvement in 6-minute walk test

VUTRISIRAN[4]
Exploratory cardiac endpoints
- NT-proBNP, echo parameters, technetium imaging

HELIOS·A

PATISIRAN[3]
Primary endpoint
- 6-minute walk test

Key secondary endpoint
- KCCQ-OS

Exploratory endpoints
- Cardiac biomarkers, echo parameters, imaging

Favorable trends on mortality & CV events

APOLLO-B

VUTRISIRAN[4]
Primary endpoint
- Mortality & CV events

N = 655

Up to 36 months

Topline results early 2024

HELIOS·B

[1] Solomon S, et al. Circulation 2018 [2] Fontana, et al. J Am Coll Cardiol Cardiovasc Imaging. Oct 28, 2020. Epublished DOI: 10.1016/j.jcmg.2020.07.043t. [3] The FDA issued a Complete Response Letter to the sNDA for patisiran for treatment of the cardiomyopathy of ATTR amyloidosis. Patisiran 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. [4] Vutrisiran has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis

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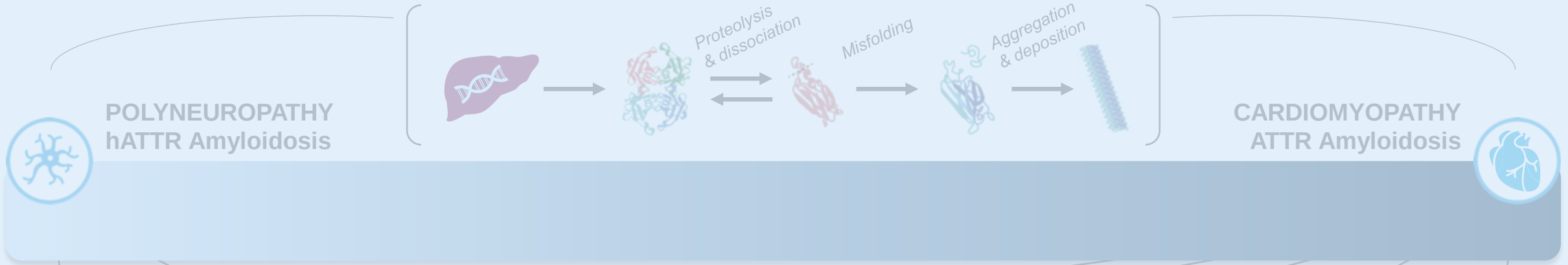
Potential for Broad Impact of RNAi Therapeutics Across Disease Spectrum



ONPATTRO
Primary endpoint
- mNIS+7

All secondary endpoints

APOLLO

AMVUTTRA
Primary endpoint
- mNIS+7

All secondary endpoints

HELIOS·A

ONPATTRO
Post hoc analyses[1]
- Reduction in mortality and hospitalization

Exploratory endpoints
- NT-proBNP, LV thickness, 10-meter walk test

APOLLO

PATISIRAN[3]
IIS[2]
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HELIOS·A

PATISIRAN[3]
Primary endpoint
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Key secondary endpoint
- KCCQ-OS

Exploratory endpoints
- Cardiac biomarkers, echo parameters, imaging

Favorable trends on mortality & CV events

APOLLO-B

VUTRISIRAN[4]
Primary endpoint
- Mortality & CV events

N = 655

Up to 36 months

Topline results early 2024

HELIOS·B

[1] Solomon S, et al. Circulation 2018 [2] Fontana, et al. J Am Coll Cardiol Cardiovasc Imaging. Oct 28, 2020. Epublished DOI: 10.1016/j.jcmg.2020.07.043t. [3] The FDA issued a Complete Response Letter to the sNDA for patisiran for treatment of the cardiomyopathy of ATTR amyloidosis. Patisiran 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. [4] Vutrisiran has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis

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HELIOS-B Poised to Address Remaining Unmet Need in ATTR Amyloidosis with Cardiomyopathy

Stabilizer Landscape

Continued disease progression across multiple endpoints

Delayed impact on mortality

Greater benefit in **NYHA Class I / II** patients

RNAi Therapeutics Offer Differentiated Profile

Rapid knockdown drives potential for early clinical benefit

Halting or reversal of disease progression demonstrated across multiple studies in PN; potential in CM

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Powered to deliver outcomes; overenrolled and enriched for patients most likely to benefit

Potential for **robust data package** with follow-up to 36M and analyses for consistency of effect across key subgroups

>10 **years of experience** in ATTR amyloidosis trials

Promising Foundation for ATTR Amyloidosis Market Leadership

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Data from TTR Stabilizers: Substantial Unmet Need Remains

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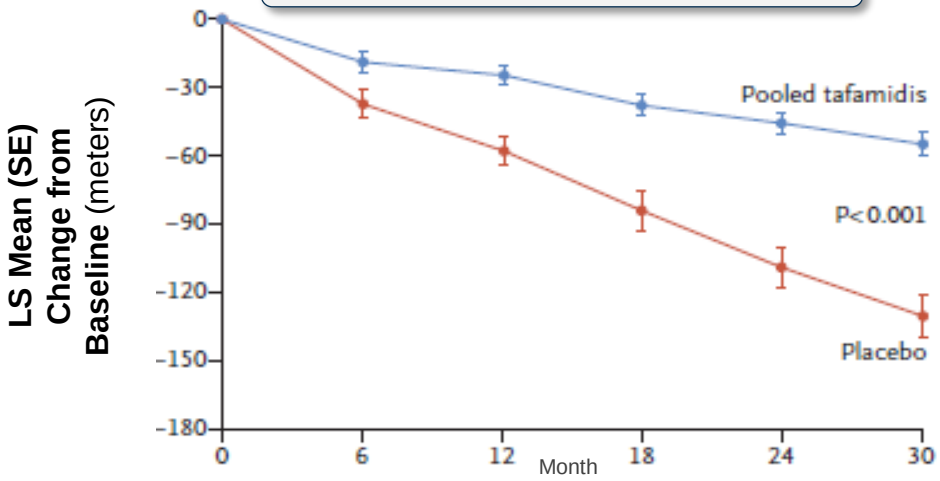
Select Stabilizer Data in ATTR Amyloidosis with Cardiomyopathy

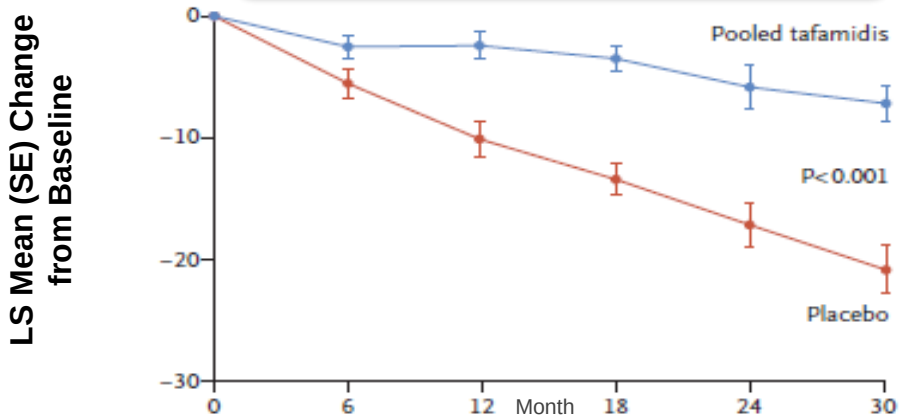
Functional Capacity (6MWT) and Quality of Life (KCCQ)

ATTR-ACT[1,2]

6MWT Change from Baseline[2]

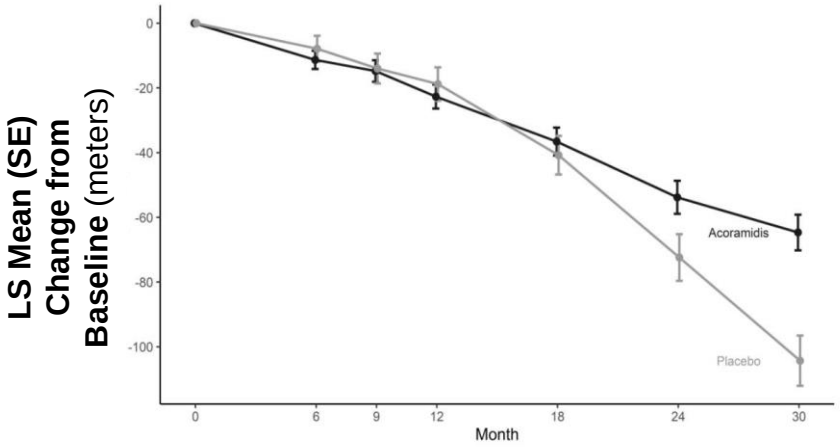


KCCQ-OS Change from Baseline[2]

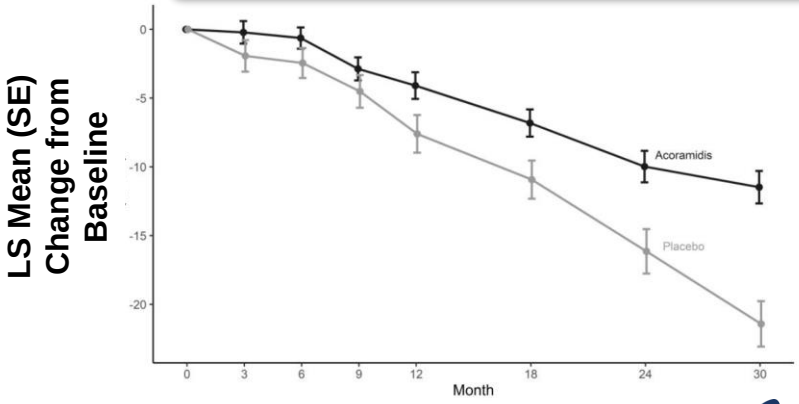


ATTRibute-CM[3]

6MWT Change from Baseline[3]



KCCQ-OS Change from Baseline[3]



[1] Vyndaqel/Vyndamax has been approved by the FDA for the treatment of the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis in adults reduce cardiovascular mortality and cardiovascular-related hospitalization. Vyndaqel has been approved by the EMA for the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy and stage 1 symptomatic transthyretin amyloid polyneuropathy to delay peripheral neurologic impairment [2] Maurer, et al, New England Journal of Medicine 2018. [3] BridgeBio Corporate Deck; https://investor.bridgebio.com/static-files/5adfc161-8a57-40e3-9b26-39d11d5eb709. No head-to-head studies have been conducted with tafamidis and acoramidis. Acoramidis is not approved for the treatment of the cardiomyopathy of ATTR amyloidosis.

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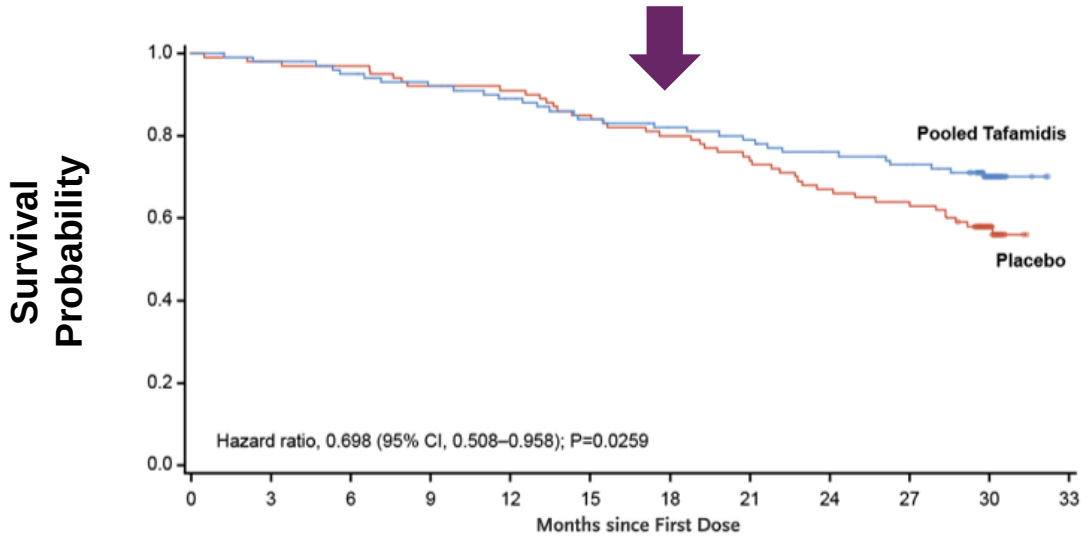
All-Cause Mortality in ATTR-ACT and ATTRibute-CM

All-Cause Mortality Benefits Emerge at 18 Months or Later; Unmet Need Remains

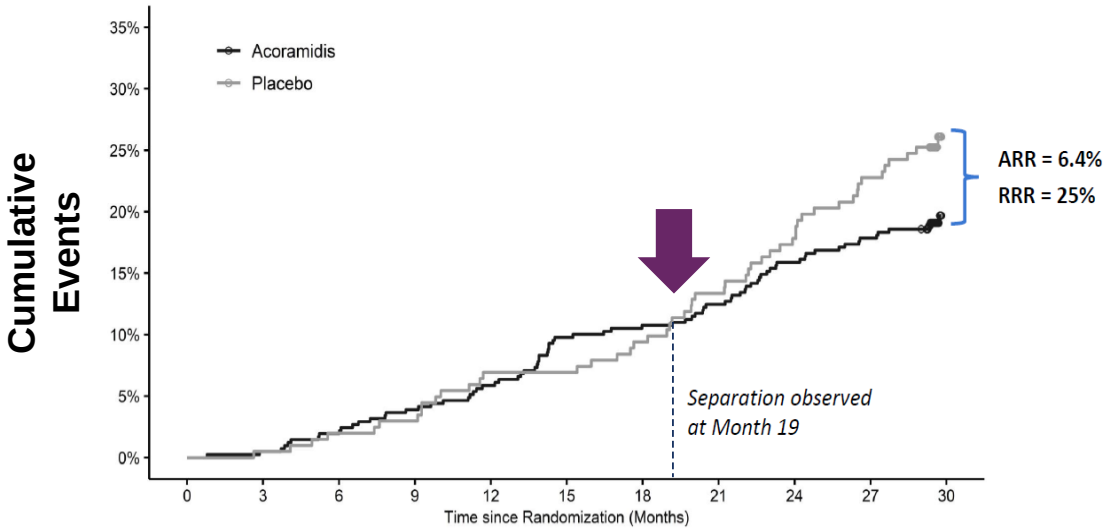
ATTR-ACT[1,2]

All-Cause Mortality



ATTRibute-CM[3]

All-Cause Mortality



Study	Hazard Ratio (95% CI)
ATTR-ACT[1,2]	0.70 (0.51-0.96)
ATTR-ACT (NYHA I/II)[1,2]	0.56 (0.38-0.82)
ATTRIBUTE-CM[4]	0.77 (0.14-1.10)

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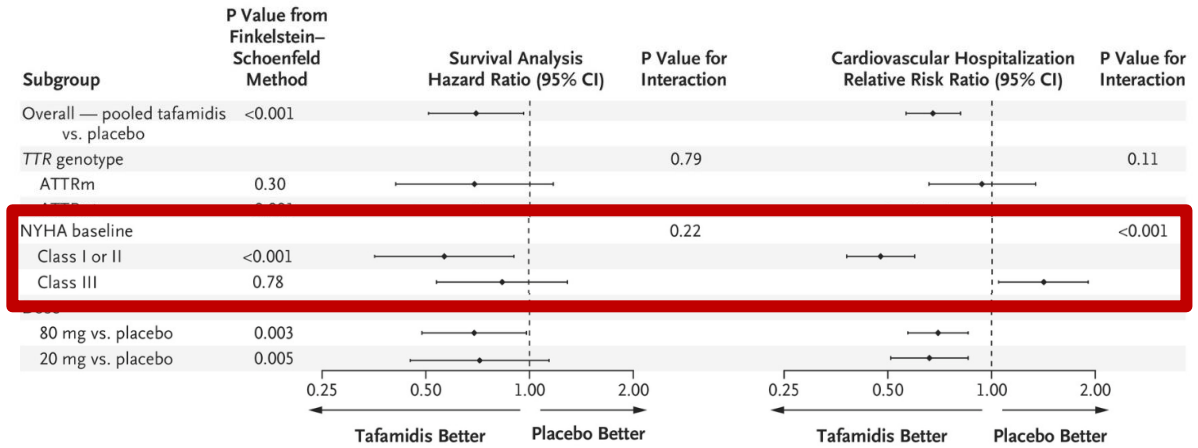
Subgroup Data in ATTR Amyloidosis with Cardiomyopathy with Stabilizers

NYHA Class I/II Patients Experience Largest Treatment Benefit

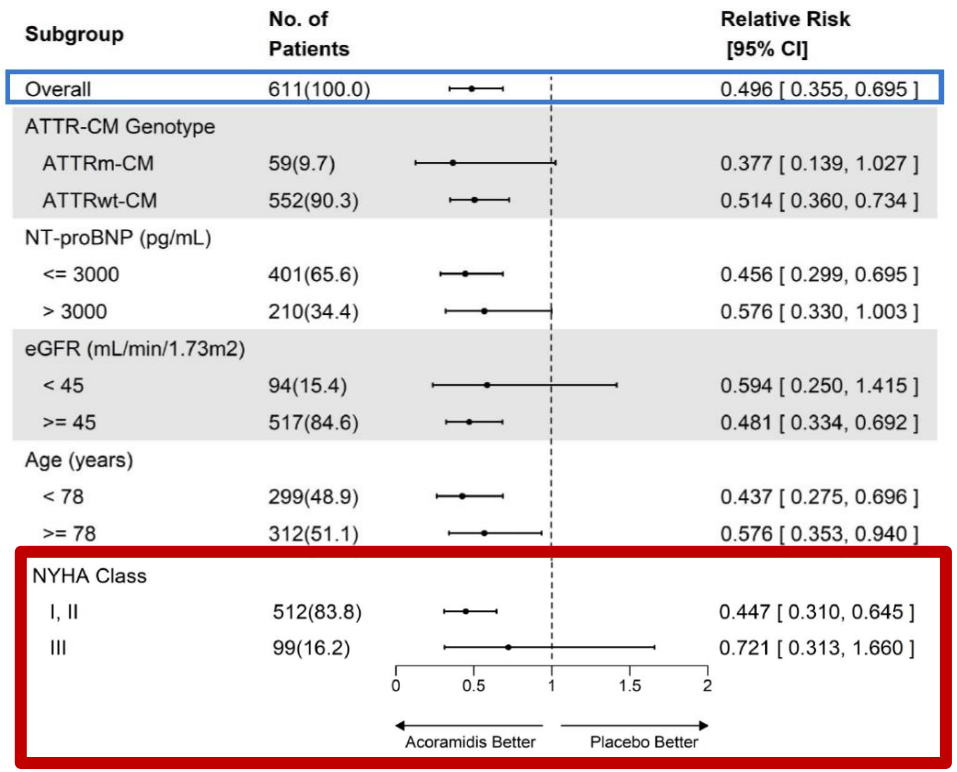
ATTR-ACT[1,2]

Overall and Subgroup Results



ATTRibute-CM[3]

Primary Outcome Overall and by Subgroups



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RNAi Therapeutics: Potential to Halt or Reverse Disease Progression

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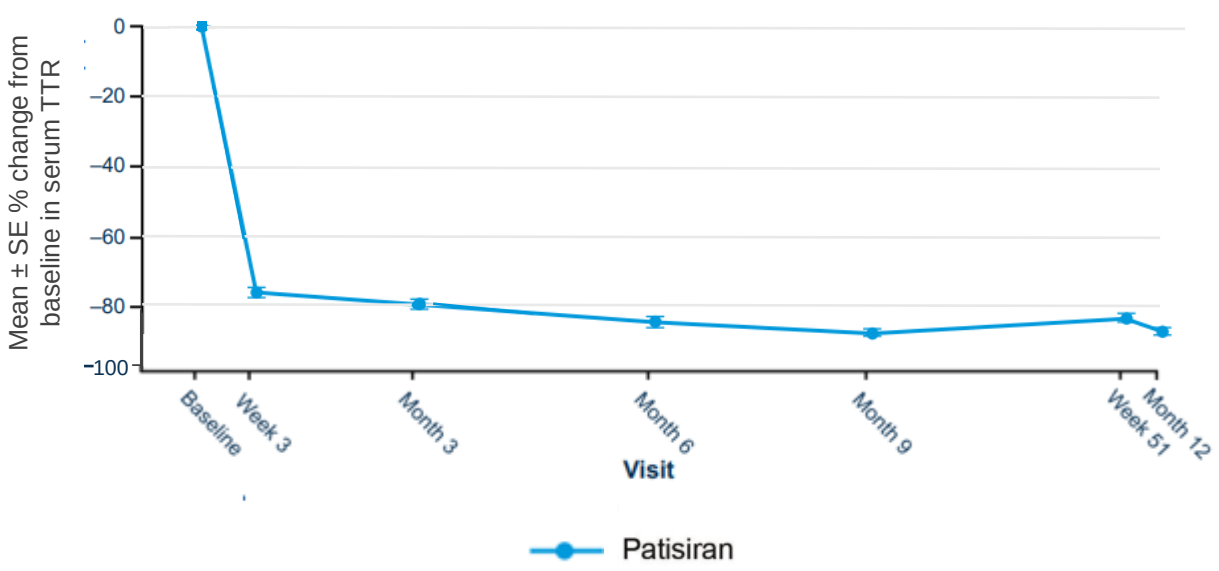
Rapid Knockdown Demonstrated with Patisiran and Vutrisiran

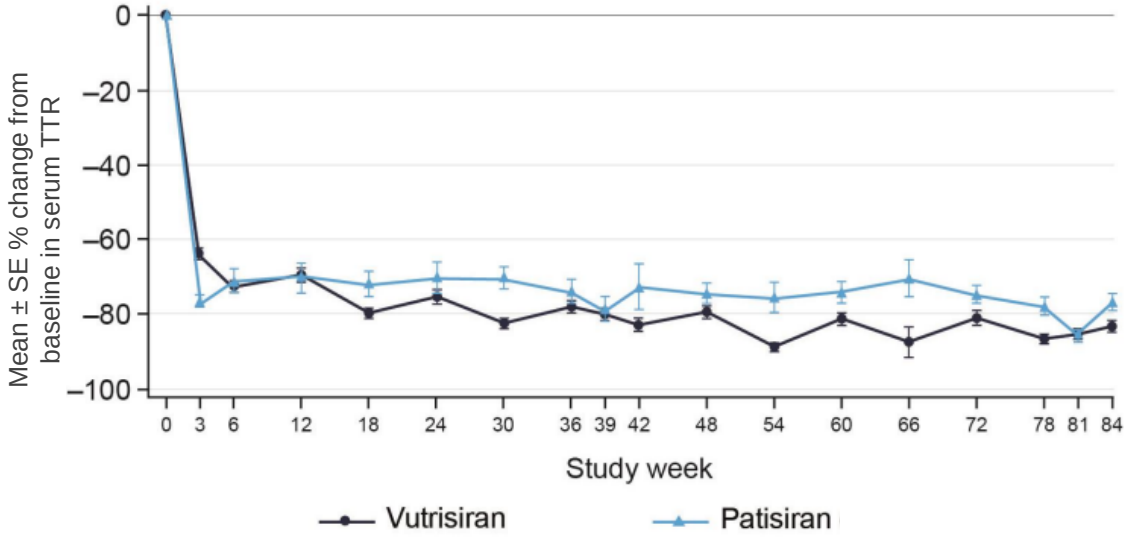
Patisiran-Mediated TTR Knockdown (APOLLO-B)

Change from Baseline in Serum TTR Levels



Vutrisiran-Mediated TTR Knockdown (HELIOS-A)

Change from Baseline in Serum TTR Levels



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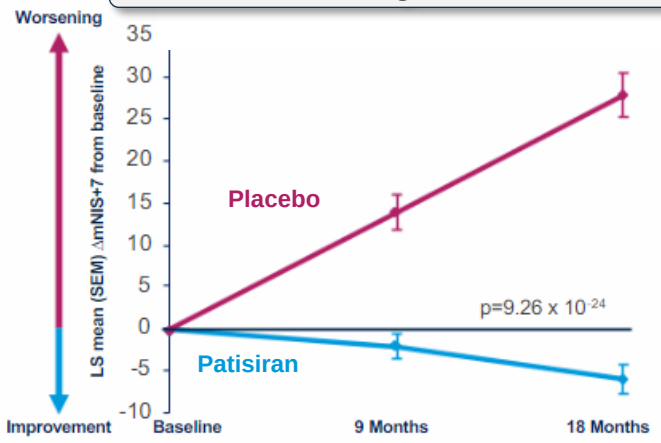
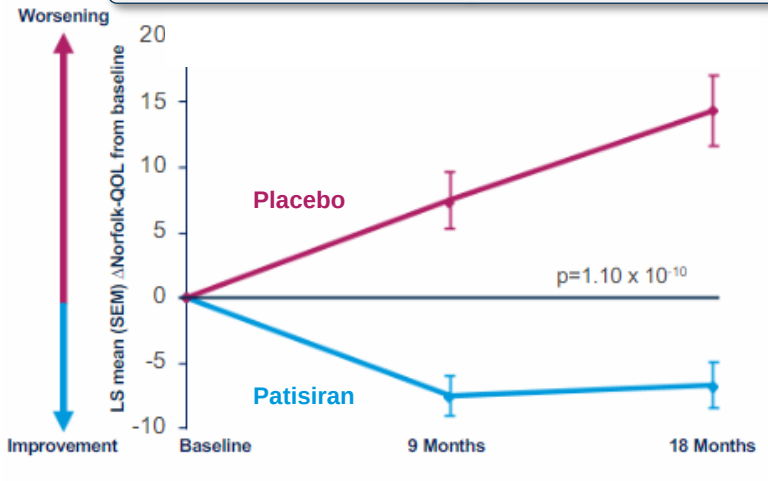
RNAi Achieves Halting and Reversal of Progression in Polyneuropathy Impairment and QOL in hATTR Amyloidosis with Polyneuropathy

APOLLO

mNIS+7 Change from Baseline

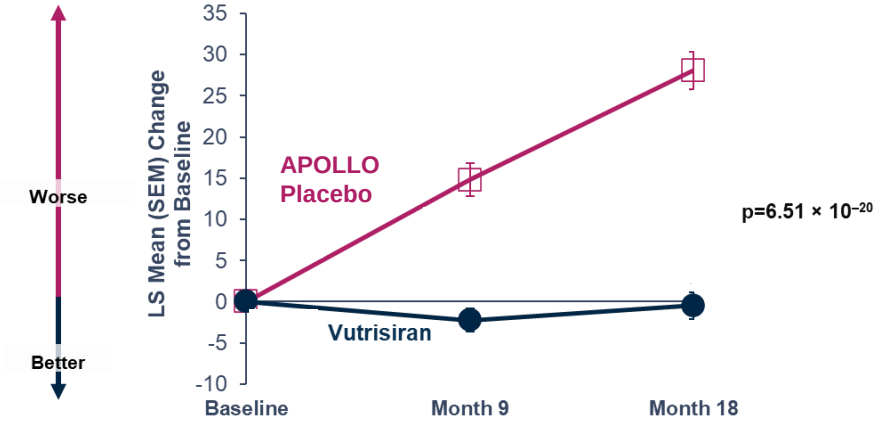


Norfolk QoL Change from Baseline

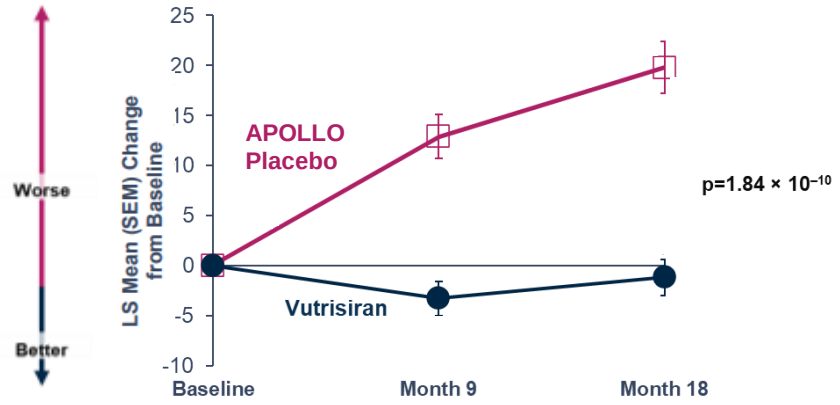


HELIOS-A

mNIS+7 Change from Baseline



Norfolk QoL Change from Baseline



mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; LS, least squares; SEM, standard error of the mean; LSMD, LS mean difference. The figures show LS mean change over time based on MMRM analysis in the overall population

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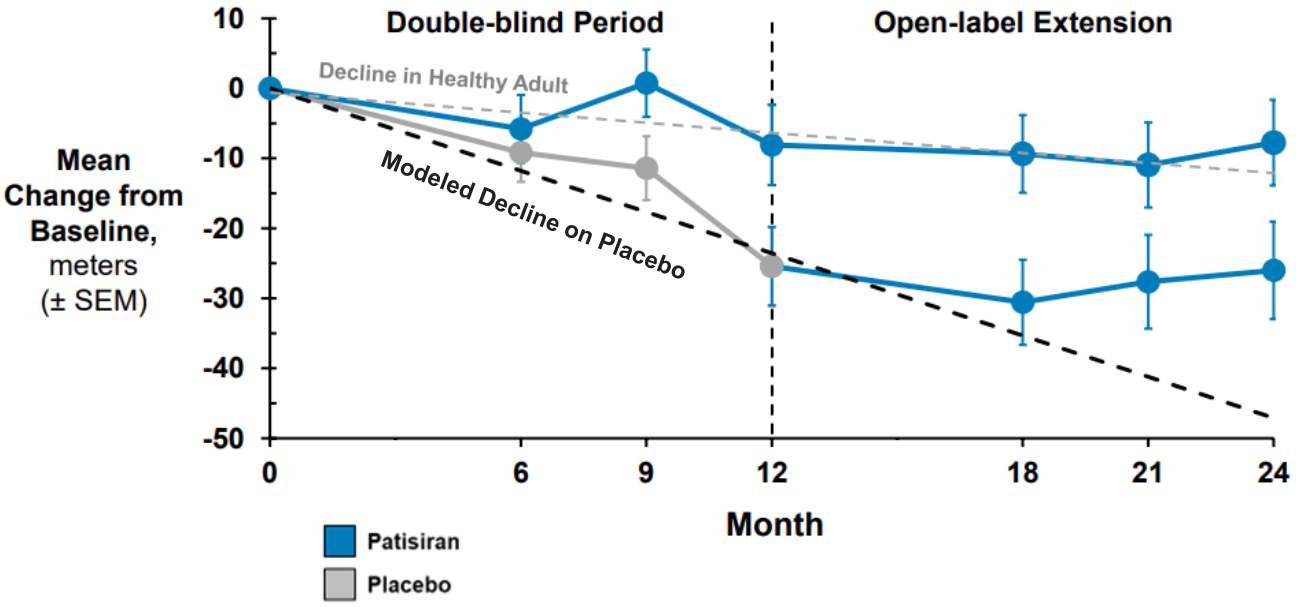
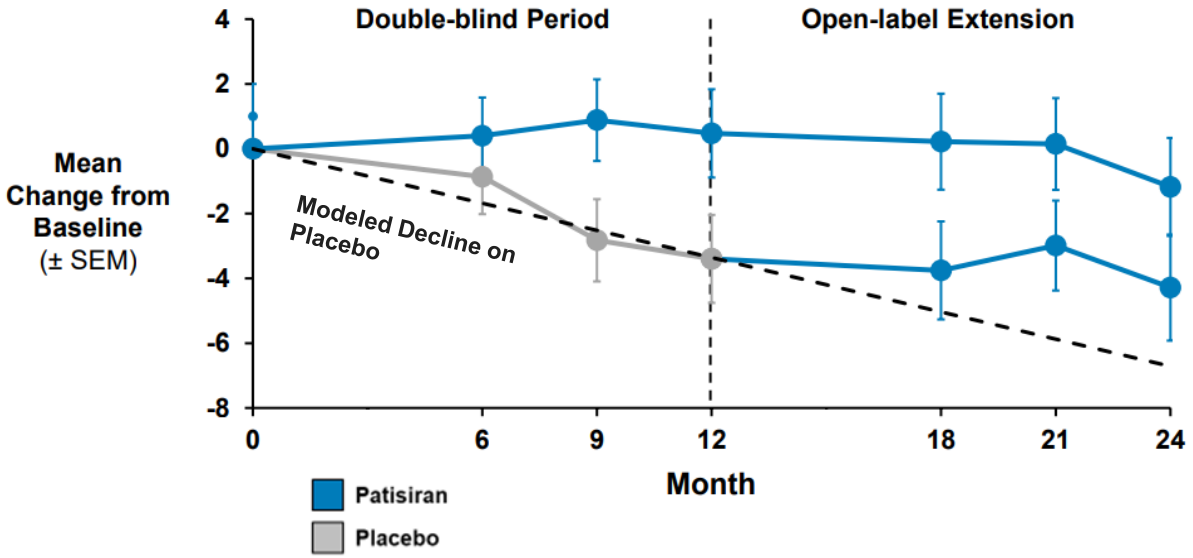
Therapeutic Potential of RNAi Therapeutics in ATTR Amyloidosis with Cardiomyopathy First Demonstrated in APOLLO-B

24 Month Open-Label Extension (OLE)

6MWT[1]



KCCQ-OS[2]



Patisiran treatment preserved functional capacity and health status through 24 months in APOLLO-B OLE, consistent with observations in patients with hATTR amyloidosis with PN, underscoring the potential of RNAi for the treatment of ATTR amyloidosis

[1] Assessments where the timer was stopped after ≤4 minutes or conducted using unapproved walking aid are excluded from the analysis. Assessments through Month 24 are presented. Baseline is defined as the last non-missing value available prior to first dose of study drug in the DB period. All patients received patisiran after Month 12. [2] Assessments through Month 24 are presented. Baseline is defined as the last non-missing value available on or before the date of first dose of study drug in the DB period. All patients received patisiran after Month 12. The FDA issued a Complete Response Letter to the sNDA for patisiran for treatment of the cardiomyopathy of ATTR amyloidosis. Patisiran 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. Abbreviations: 6MWT, 6-minute walk test; DB, Double-blind; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; SEM, standard error of the mean.

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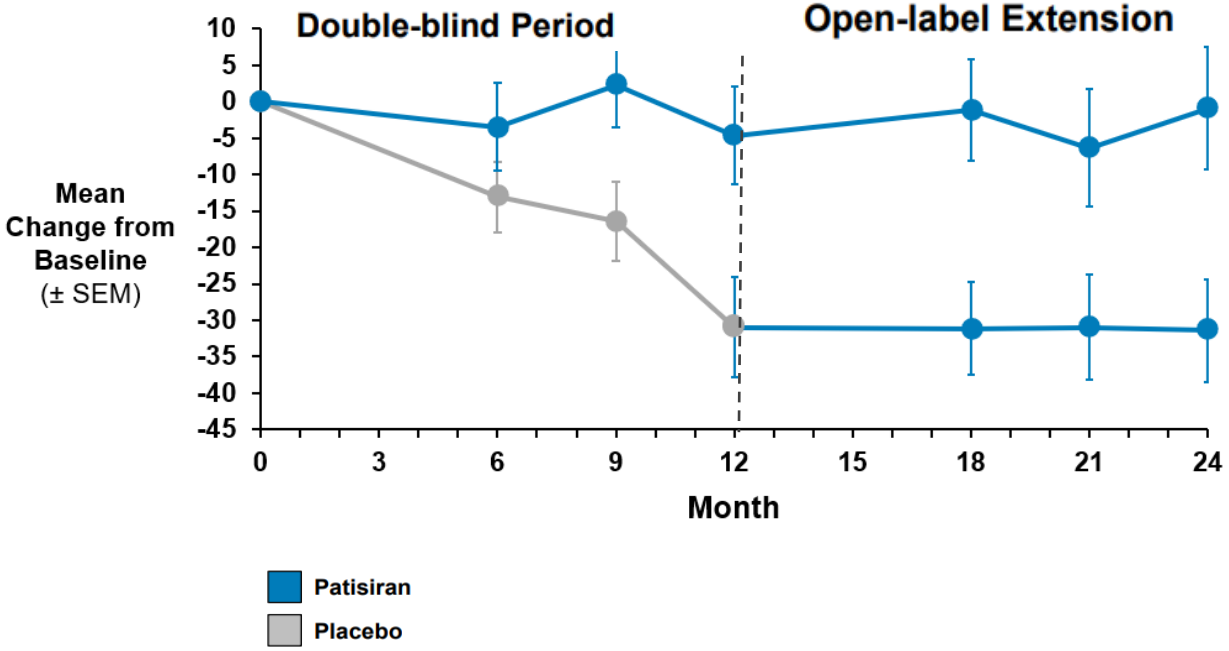
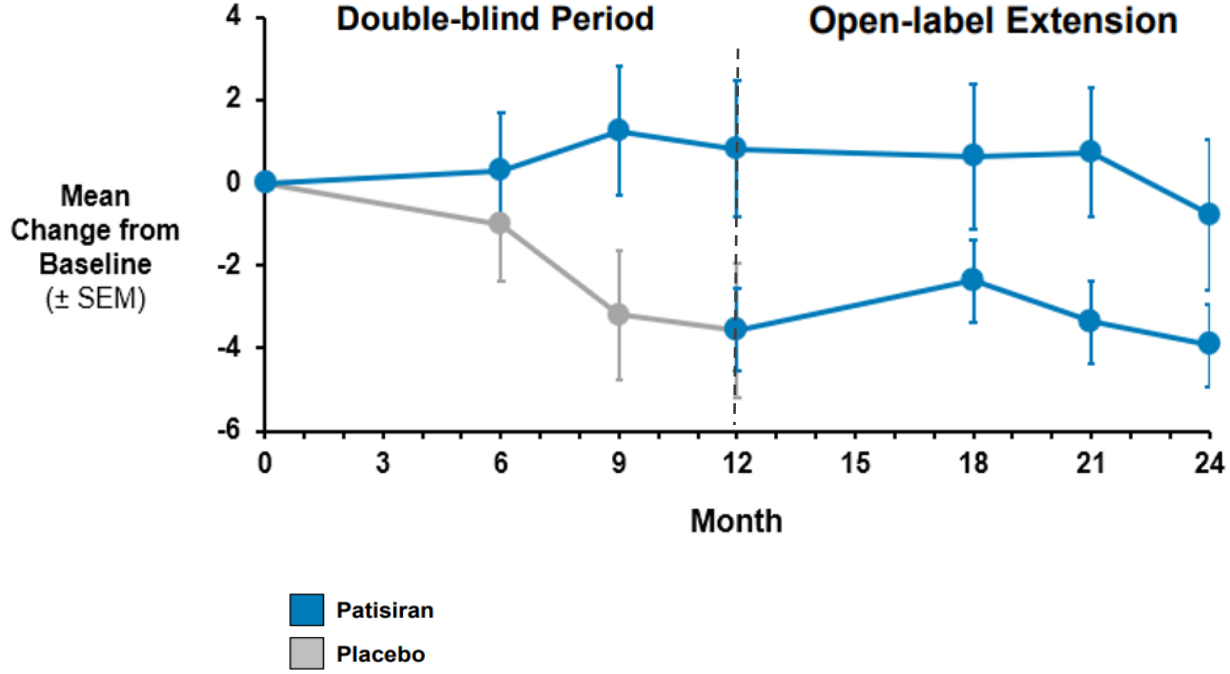
Magnitude of Treatment Effect on Both Function and Quality of Life Enhanced in Monotherapy Setting in APOLLO-B

6MWT[1]



KCCQ-OS[2]



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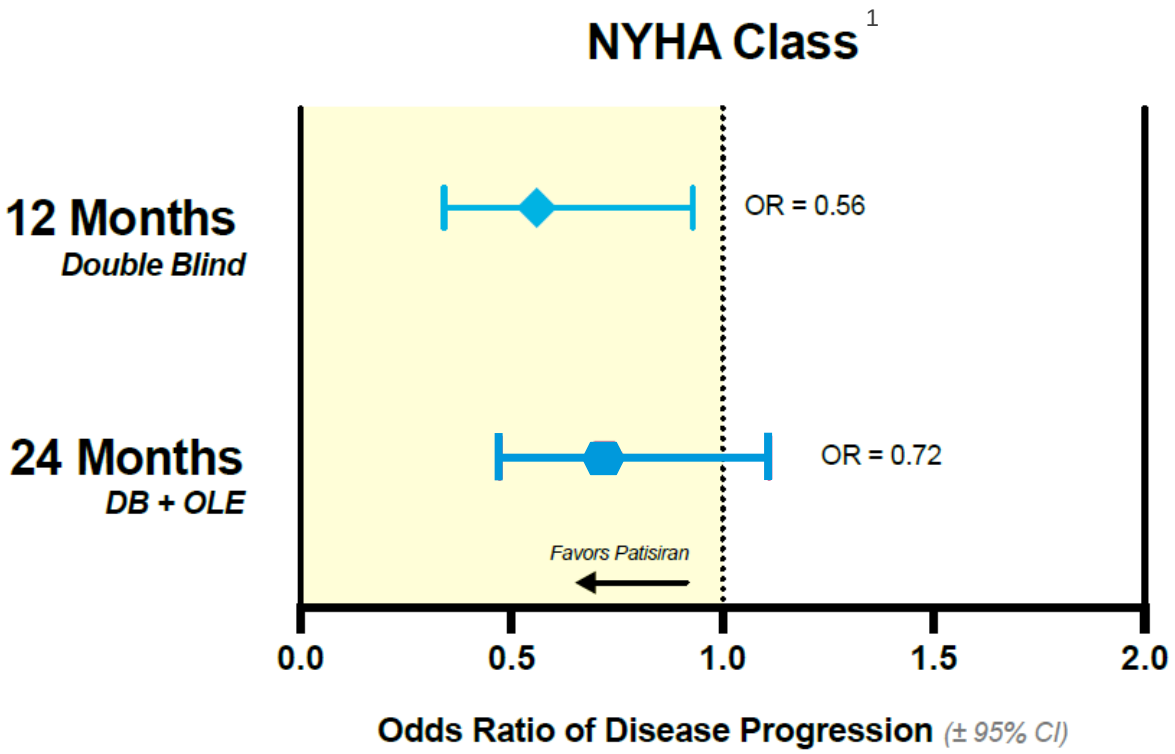
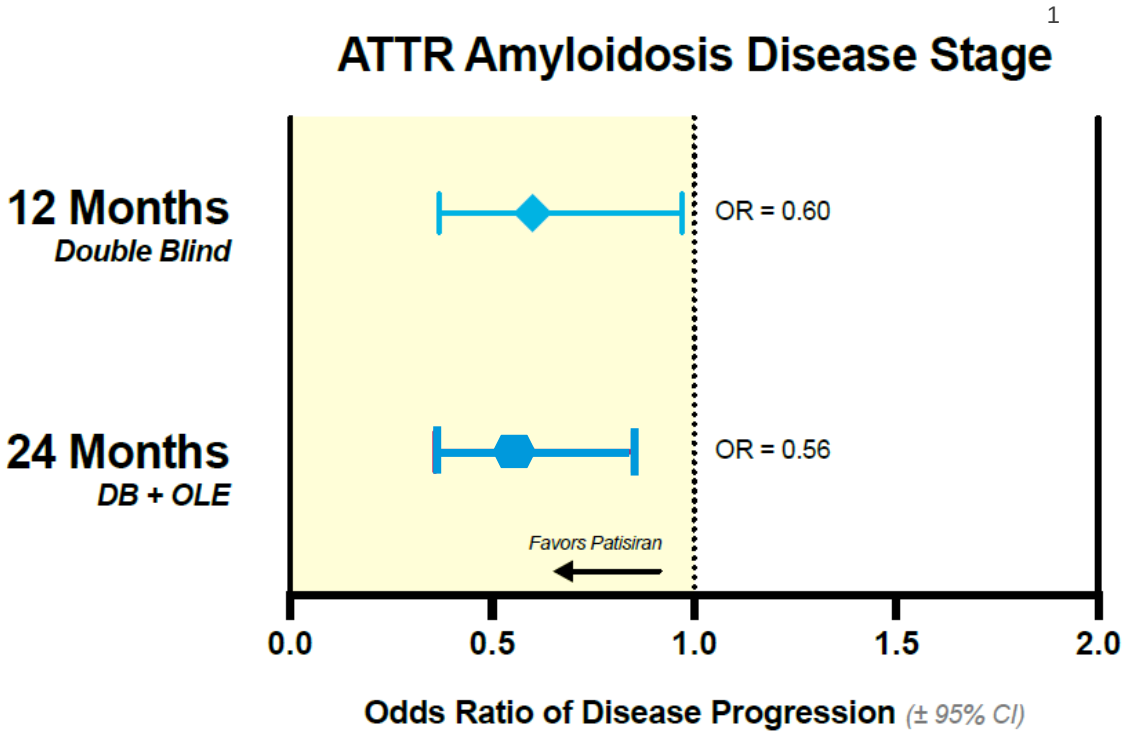
Patisiran Decreased Odds of Heart Failure Progression in APOLLO-B





[1] APOLLO-B post-hoc analysis.The FDA issued a Complete Response Letter to the sNDA for patisiran for treatment of the cardiomyopathy of ATTR amyloidosis. Patisiran 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. Abbreviations: ATTR, transthyretin-mediated; CI, confidence interval; DB, double-blind; OLE, open-label extension.

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RNAi Therapeutics: Broad Effects on the Heart Begin Early

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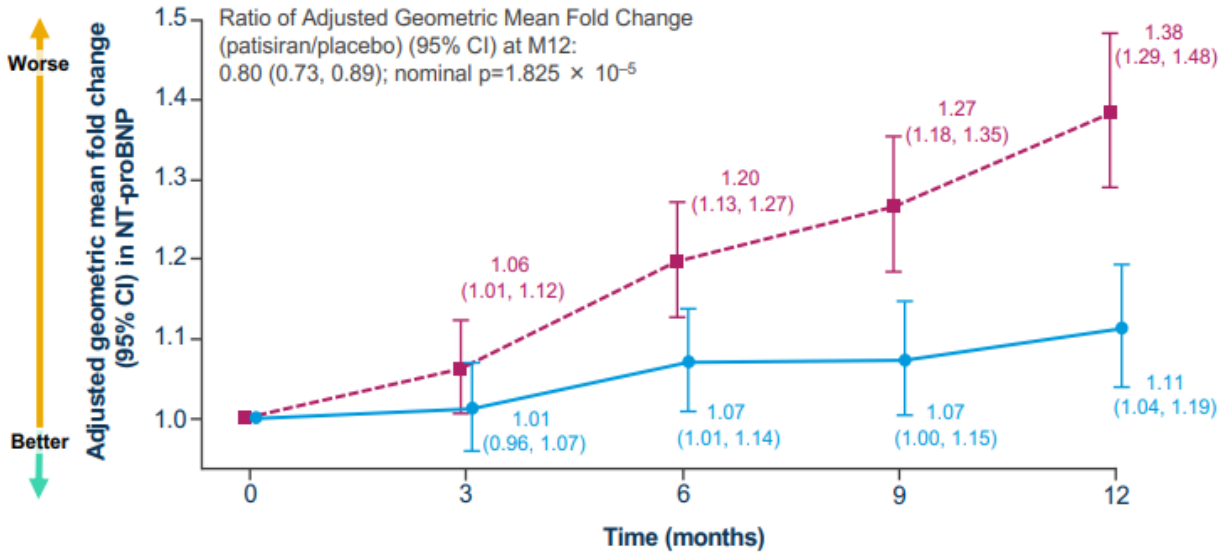
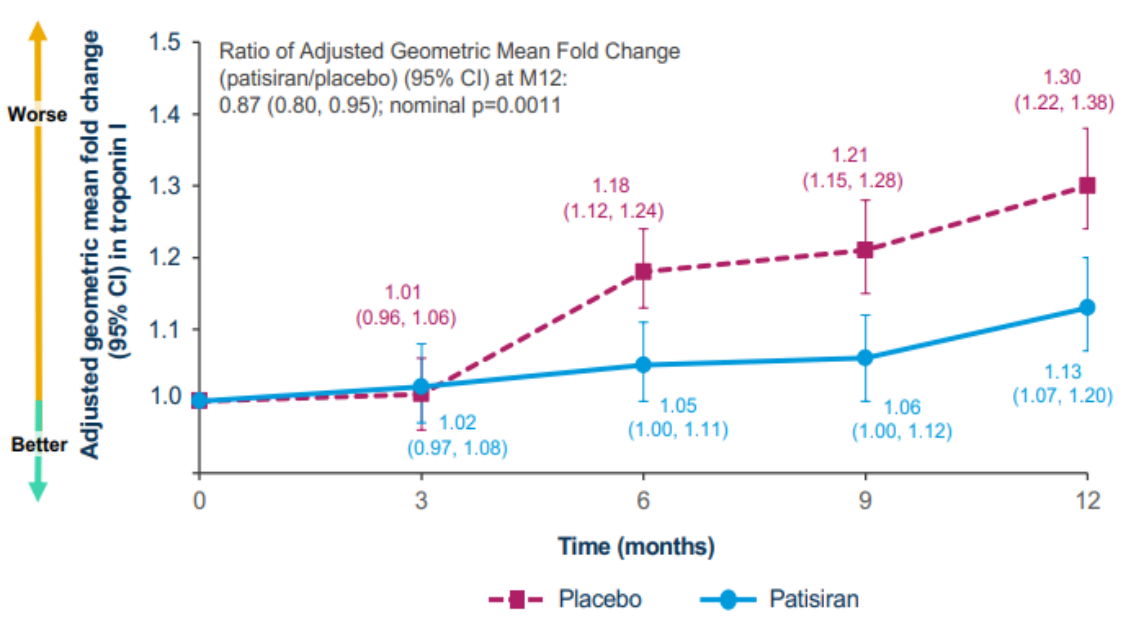
Change from Baseline in NT-proBNP and Troponin I

APOLLO-B

Change from Baseline in NT-proBNP[1] at Month 12



Change from Baseline in Troponin I[2] at Month 12



[1] NT-proBNP is a measure of cardiac stress, with higher values indicating a greater level of cardiac stress. [2] Troponin I is a measure of myocardial injury, with higher values indicating a greater level of myocardial injury. The FDA issued a Complete Response Letter to the sNDA for patisiran for treatment of the cardiomyopathy of ATTR amyloidosis. Patisiran has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population.

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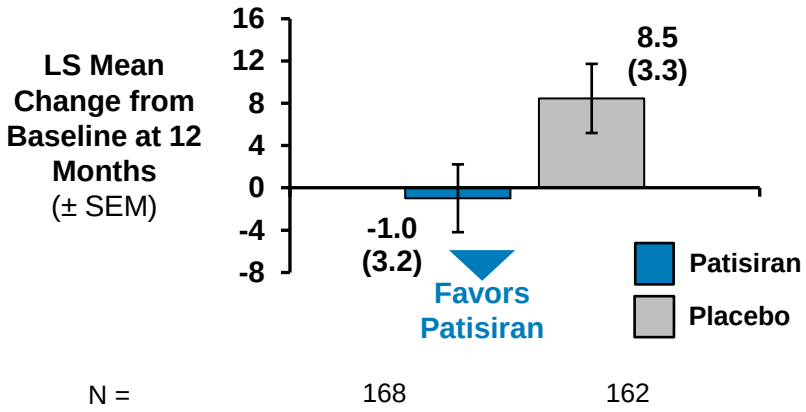
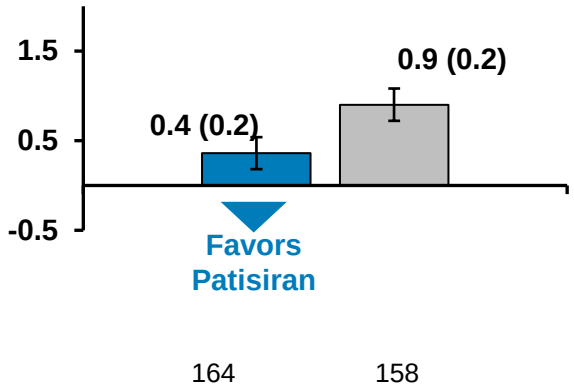
Treatment Effect on Cardiac Structure and Function in APOLLO-B

Exploratory Echocardiographic Parameters and Tc Scintigraphy Imaging

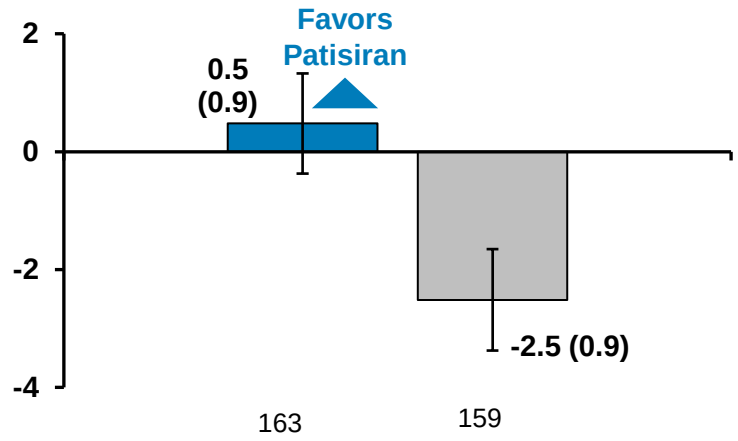
LV Mass (g)
Nominal p = 0.0402



Global Longitudinal Strain (%)
Nominal p = 0.0324



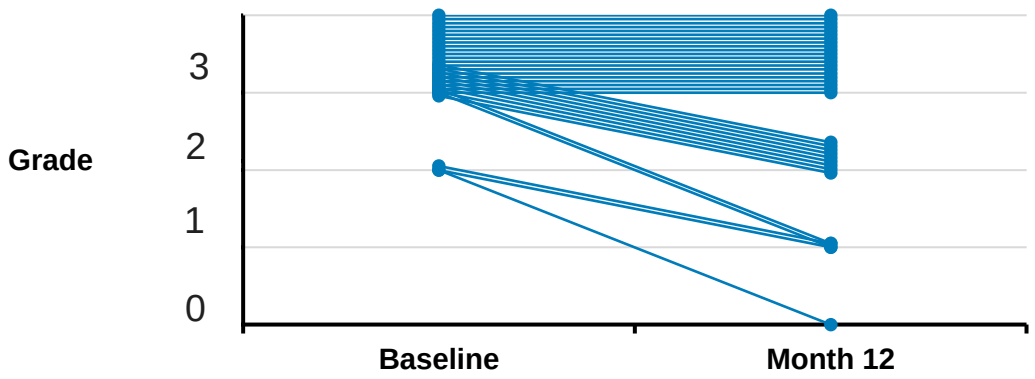
LV Stroke Volume (mL)
Nominal p = 0.0140



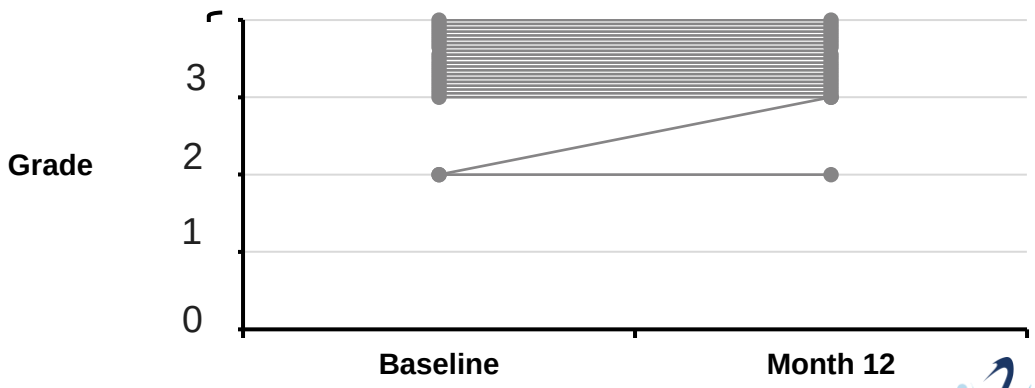
Perugini grade (0 – 3) widely used in diagnosis (≥ grade 2) of ATTR amyloidosis

Visually assesses ^{99m}Tc uptake in myocardium compared to bones; centrally read by assessor blinded to treatment and timepoint

Patisiran (N = 37)



Placebo (N = 28)



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Data from RNAi Therapeutics: Potential for Mortality Benefit

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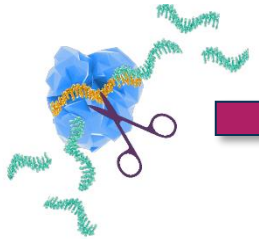
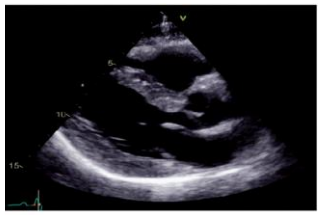
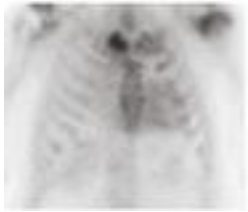
RNAi Therapeutics Demonstrate Consistent Effects Across Multiple Disease Manifestations

Supports Confidence in Potential for Outcomes Benefit

Rapid and Potent Reduction in TTR [1]	Slowed Increase in Cardiac Biomarkers[1]	Reduced Decline in Cardiac Structure and Function[2]	Stability/ Improvement in ^{99m}Tc Uptake[2]	Reduced Decline in Functional Capacity[1]	Stability in Patient Reported Health Status and QoL[1]
					
Rapid Knockdown with TTR Reduction > 85 %	**NT-proBNP Troponin I**	• **LV Mass** • **Global Longitudinal Strain** • **LV Stroke Volume**	**Improved Perugini Grade**	**6MWT**	**KCCQ-OS**

[1] Maurer, et al. New England Journal of Medicine 2023 [2] Patisiran AdCom Briefing Documents - https://www.fda.gov/media/172043/download. The FDA issued a Complete Response Letter to the sNDA for patisiran for treatment of the cardiomyopathy of ATTR amyloidosis. Patisiran has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population.

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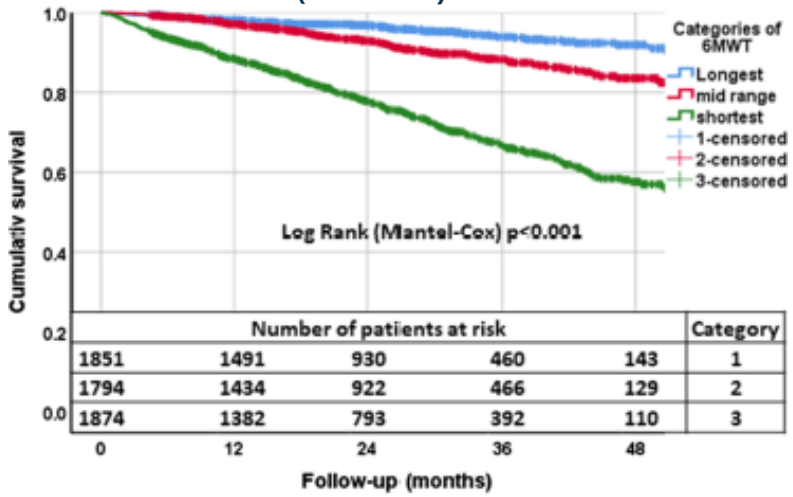
Benefits in Key Cardiac Endpoints Support Potential for Outcomes Benefit

Data from Heart Failure & ATTR-CM Literature

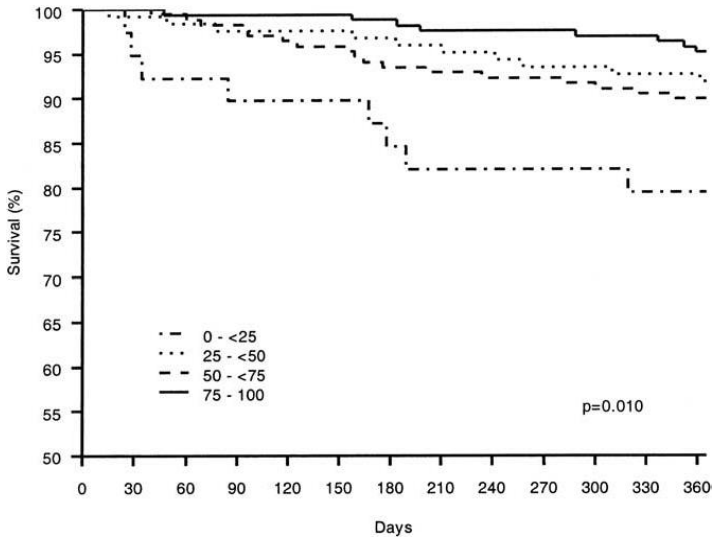
6MWT[1]

(HF Patients)



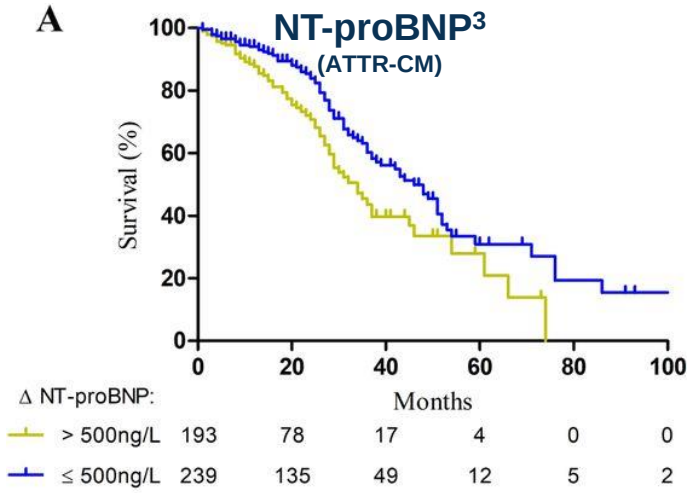
KCCQ[2]

(HF Patients)



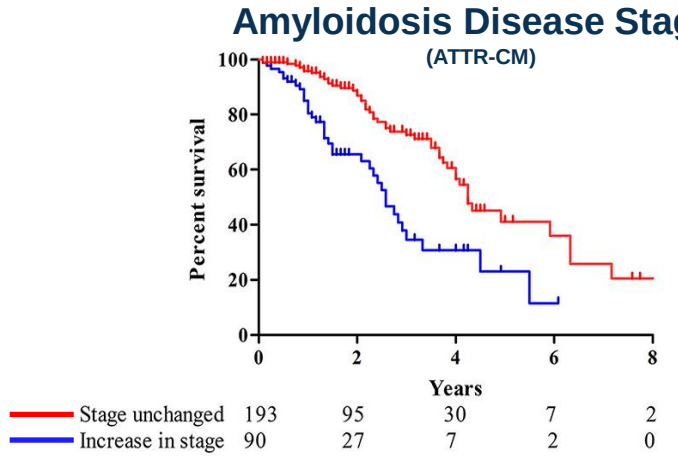
NT-proBNP[3]

(ATTR-CM)



Amyloidosis Disease Stage[4]

(ATTR-CM)



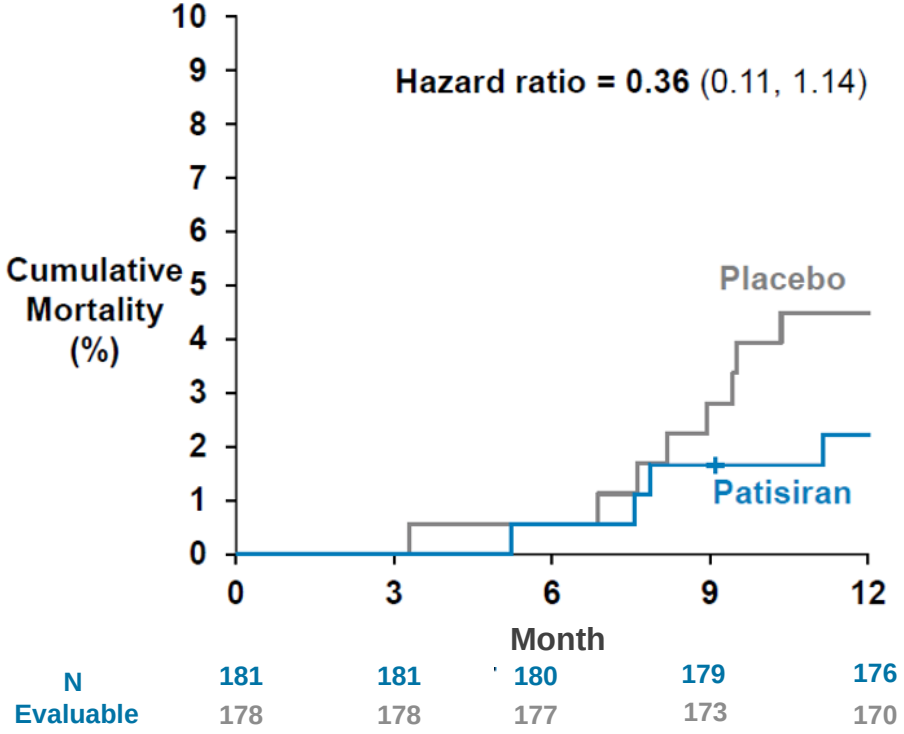
[1] Grundtvig, et al, ESC Heart Failure 2020. [2] Heidenreich, et al, J Am Coll Cardiol 2006. [3] Law, S. Heart 2022. [4] Law, S. ESC Heart Failure 2020.

Favorable Trends with Patisiran

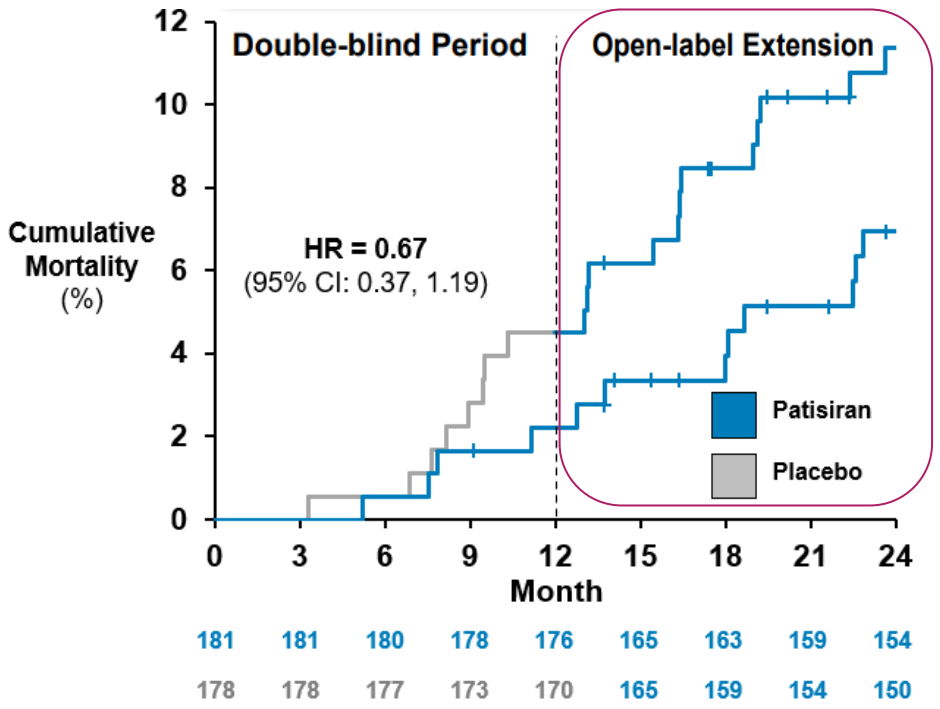
APOLLO-B – Mortality Curves Separating as Early as 9 Months

- Mortality analyses across the double-blind and OLE periods did not show statistically significant differences; however, favorable trends were observed
- Supports potential for favorable impact on outcomes in HELIOS-B with up to 36 months of follow up

All-Cause Mortality at Month 12



All-Cause Mortality at Month 24



The FDA issued a Complete Response Letter to the sNDA for patisiran for treatment of the cardiomyopathy of ATTR amyloidosis. Patisiran has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population.

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Early Evidence Suggests Encouraging Trends for Potential Mortality Benefit with RNAi Therapeutics

Study	Hazard Ratio (95% CI)
APOLLO [1]	0.53 (0.18 - 1.59)
APOLLO-B [2]	0.36 (0.11 - 1.14)
APOLLO-B Monotherapy [2]	0.40 (0.10 – 1.54)
APOLLO-B Baseline Tafamidis [2]	0.30 (0.03 – 2.86)

[1] APOLLO post-hoc analyses; hazard ratio not statistically significant. [2] APOLLO-B 12-month DB period; hazard ratios not statistically significant. The FDA issued a Complete Response Letter to the sNDA for patisiran for treatment of the cardiomyopathy of ATTR amyloidosis. Patisiran has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population.

HELIOS-B Poised to Address Remaining Unmet Need in ATTR Amyloidosis with Cardiomyopathy

Stabilizer Landscape

Continued disease progression across multiple endpoints

Delayed impact on mortality

Greater benefit in **NYHA Class I / II** patients

RNAi Therapeutics Offer Differentiated Profile

Rapid knockdown drives potential for early clinical benefit

Halting or reversal of disease progression demonstrated across multiple studies in PN; potential in CM

Market-leading profile of vutrisiran in PN including efficacy, safety, and infrequent dosing

Beneficial effect of RNAi across multiple important predictors of CV outcomes

HELIOS-B Positioned for Success

Powered to deliver outcomes; overenrolled and enriched for patients most likely to benefit

Potential for **robust data package** with follow-up to 36M and analyses for consistency of effect across key subgroups

>10 years of experience in ATTR amyloidosis trials

Promising Foundation for ATTR Amyloidosis Market Leadership

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Vutrisiran HELIOS·B Phase 3 Study

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

N = 655
Patient Population

- ATTR amyloidosis; wild-type or any TTR mutation
- Confirmed cardiomyopathy and medical history of symptomatic heart failure
- NYHA ≤ III; minimum walk and NT-proBNP limits at baseline

1:1 RANDOMIZATION

Vutrisiran
SC q3M
25 mg

or

Placebo
SC q3M

Primary Endpoint

- Composite outcome of all-cause mortality and recurrent CV events (when last patient reaches Month 30)

Select Secondary Endpoints

- 6-MWT distance
- Kansas City Cardiomyopathy Questionnaire (KCCQ OS) score
- Echocardiographic parameters
- All-cause mortality & recurrent all-cause hospitalizations & urgent HF visits
- All-cause mortality
- Recurrent CV events
- NT-proBNP

ClinicalTrials.gov Identifier: NCT04153149

HELIOS·B

Topline results expected **early 2024**

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HELIOS-B Positioned for Success

Design

Designed and powered to deliver **outcomes;** ~2x as large and ~3x as long as APOLLO-B

Enriched for patients most likely to benefit, excluding advanced NYHA III and IV

Potential for robust data package with follow-up to 36M in most patients

Analyses planned to demonstrate **consistency of effect across key subgroups**

Execution

Overenrolled by ~10%

Tafamidis baseline sub-group **lower than target of 50%**

Low rate of tafamidis drop-ins, well within expectations

Rapid knockdown with vutrisiran

Supportive data from patisiran in APOLLO-B

Potential for **Positive HELIOS-B** with Outcomes Benefit in ATTR Amyloidosis with CM Patients

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Upcoming Milestones

Early 2024: HELIOS-B topline data readout

Mid 2024: sNDA submission for vutrisiran label expansion in ATTR amyloidosis with cardiomyopathy[1]

2025: AMVUTTRA commercialization in ATTR amyloidosis with cardiomyopathy[1]

[1] Pending positive HELIOS-B results and regulatory review and approval

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Commitment to ATTR Amyloidosis: Continued Innovation with ALN-TTRsc04

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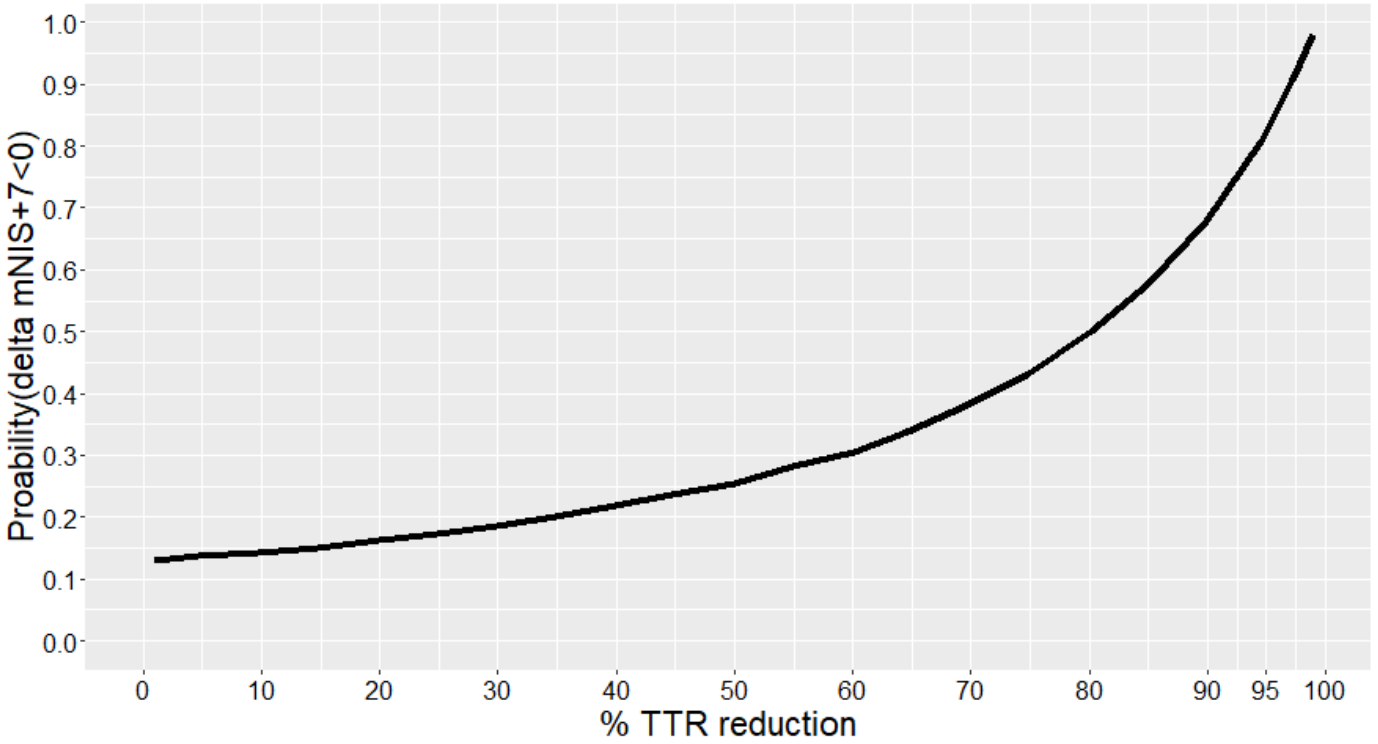
Modeling from APOLLO Supports Hypothesis that Greater Serum TTR Knockdown Leads to Improved Clinical Outcomes in ATTR Amyloidosis

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



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

Source: APOLLO Phase 3 Data; Internal Alnylam modeling

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ALN-TTRsc04 Demonstrates Alnylam's Continuing Innovation in TTR

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

An Approved RNAi Therapeutic for Treatment of Polyneuropathy of hATTR Amyloidosis*

About ONPATTRO

- Based on APOLLO data, commercially available in >30 countries for hATTR amyloidosis with polyneuropathy
- Positive results from APOLLO-B‡
- 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†

About AMVUTTRA

- Based on HELIOS-A data, approved in US, EU, UK, JP, and BR
- HELIOS-B ongoing in ATTR amyloidosis with CM††
- Subcutaneous administration, once quarterly, potential for biannual dosing

ALN-TTRsc04

An Investigational RNAi Therapeutic for Potential Treatment of ATTR Amyloidosis

About ALN-TTRsc04

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

* 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; † 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; ‡ Patisiran 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; †† Vutrisiran has not been approved by the FDA, EMA, or any other regulatory agency for cardiac manifestations of amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in this population

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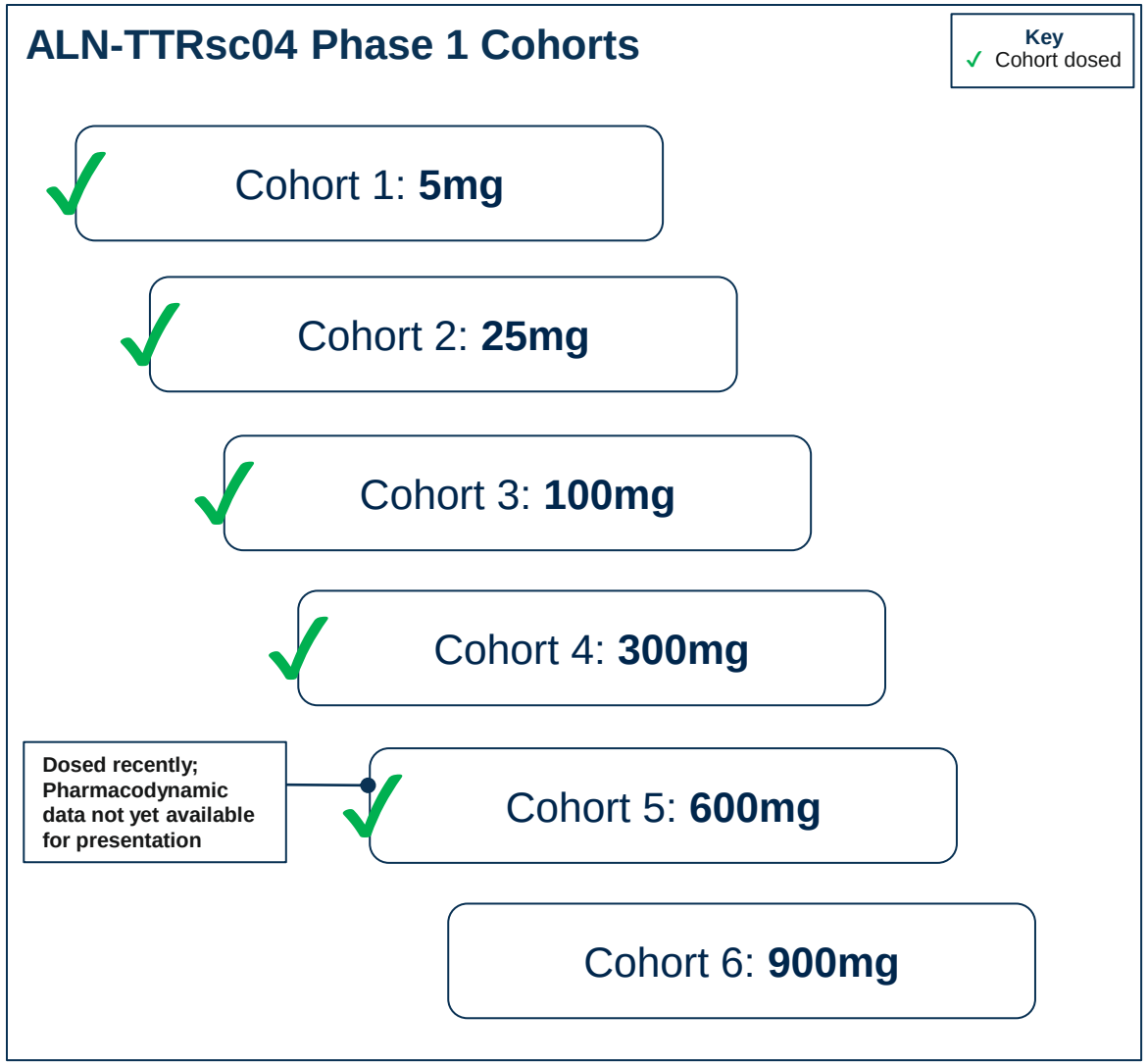
ALN-TTRsc04 Healthy Volunteer Phase 1 Study



- Randomized, **double-blind, placebo controlled, single-ascending dose** study design
- **Cohorts of 8 healthy volunteers**
- Endpoints include **safety, tolerability and pharmacodynamic effects** (e.g., TTR knockdown)

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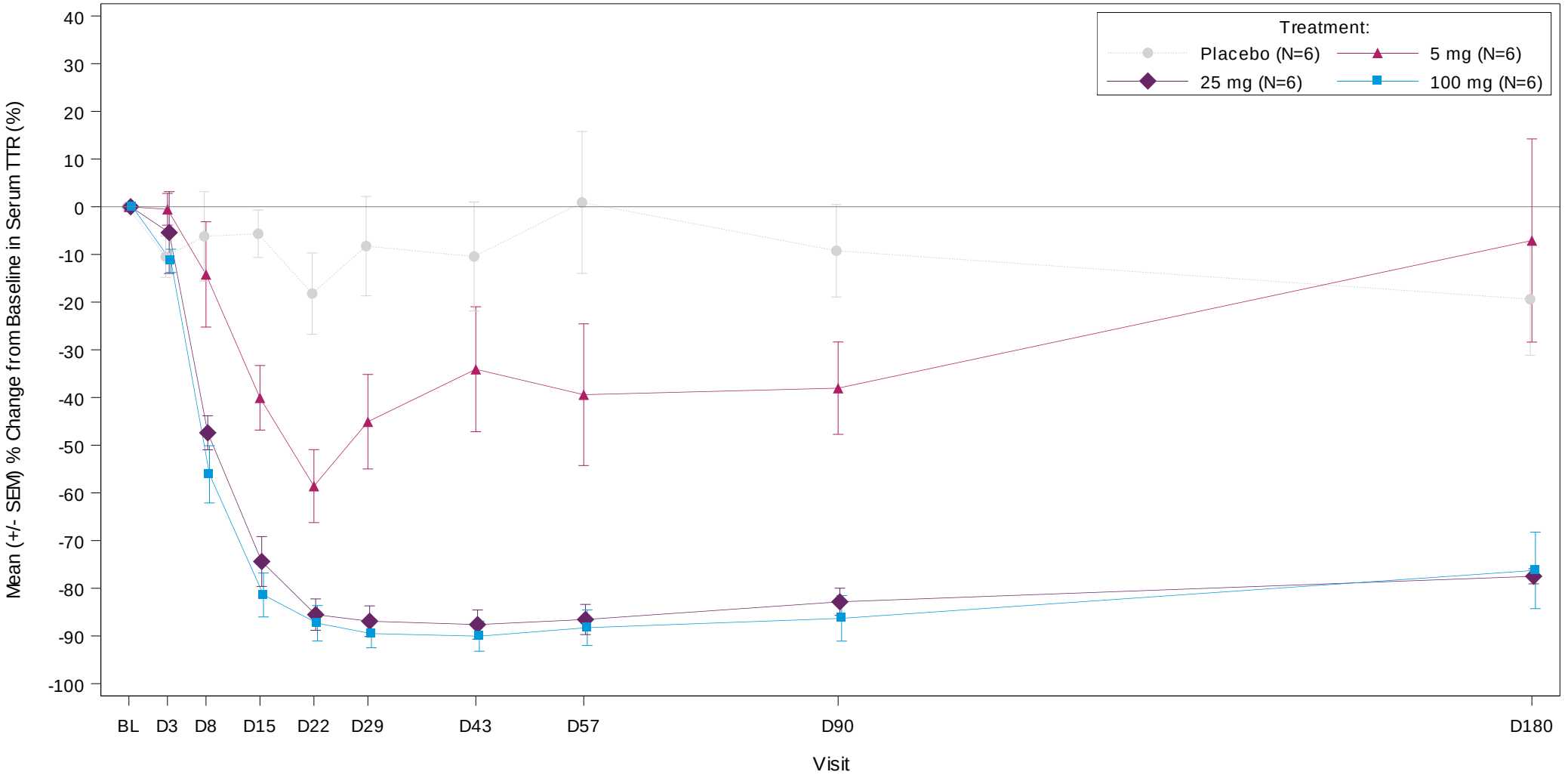
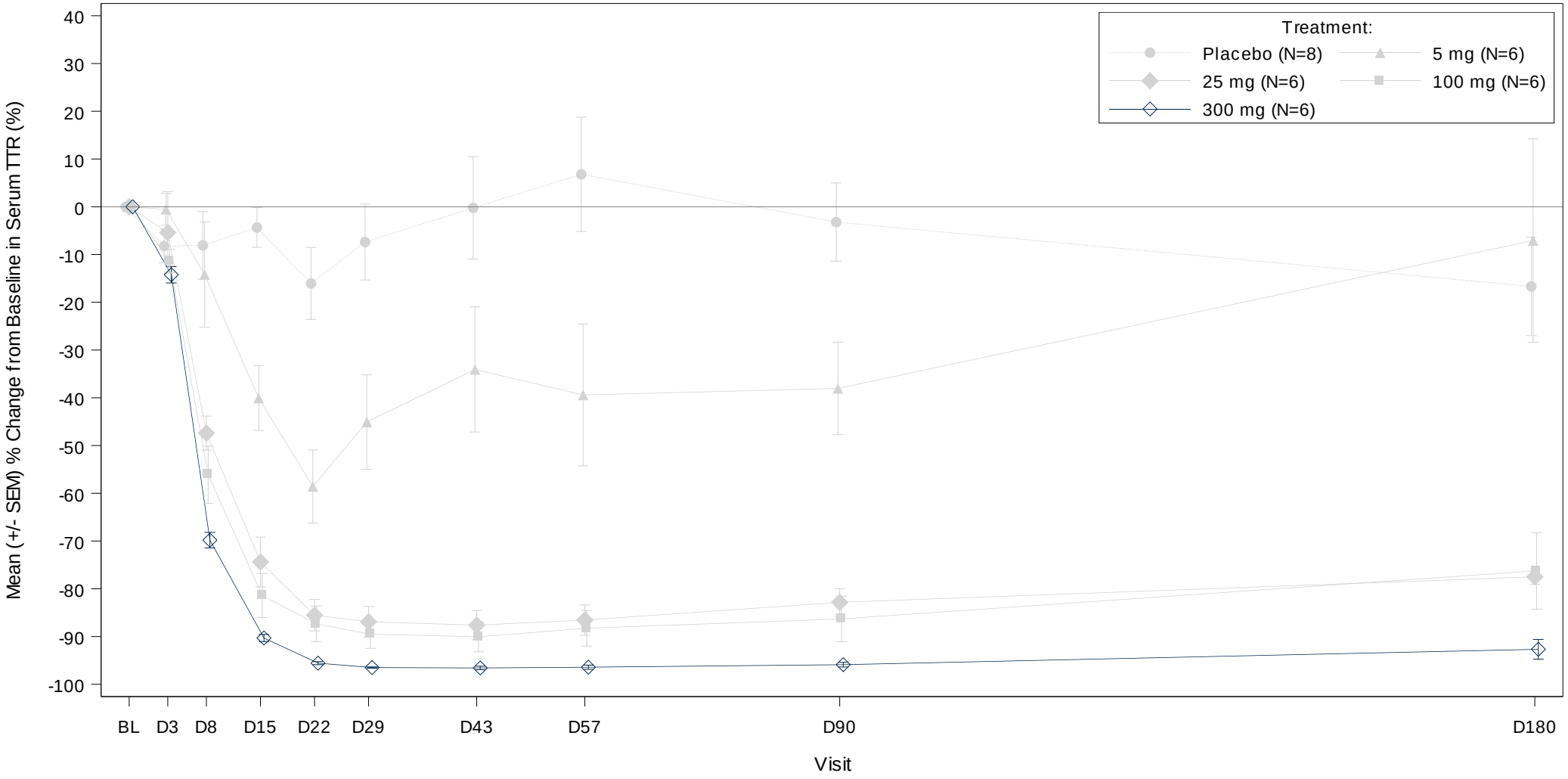
ALN-TTRsc04 Achieves Rapid and Sustained Serum TTR Knockdown

ALN-TTRsc04 Serum TTR Change from Baseline by Dose Level in Phase 1 Study



ALN-TTRsc04 Achieves Rapid and Sustained Serum TTR Knockdown

ALN-TTRsc04 Serum TTR Change from Baseline by Dose Level in Phase 1 Study



Single 300mg dose resulted in mean TTR reduction of:

- **>90%** at Day 15
- **97%** at Day 29
- **93%** at Day 180

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ALN-TTRsc04 Demonstrates Encouraging Safety Profile

- All doses of ALN-TTRsc04 have been well-tolerated to date
- No adverse events have been considered related to study drug by the investigator
- All adverse events have been mild or moderate in severity
- No safety signals identified (including no liver related safety signals and no injection site reactions)
- Study is ongoing and remains blinded

Accurate as of most recent data extraction date of 16 November 2023; Study remains ongoing

ALN-TTRsc04 Summary and Next Steps

- A promising profile is emerging for ALN-TTRsc04
  - Potential for annual subcutaneous dosing regimen with >90% serum TTR reduction
  - In ongoing healthy volunteer Phase 1 study, single 300mg dose resulted in:
    - Rapid TTR reduction of >90% at Day 15
    - 97% TTR reduction seen at Day 29
    - 93% TTR reduction sustained through to Day 180
  - Well-tolerated to date

- Alnylam is committed to bringing continued innovation to ATTR amyloidosis patients; Phase 3 study in ATTR amyloidosis with cardiomyopathy expected to initiate at or around year-end 2024.

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Accelerating Alnylam's Leadership in ATTR Amyloidosis

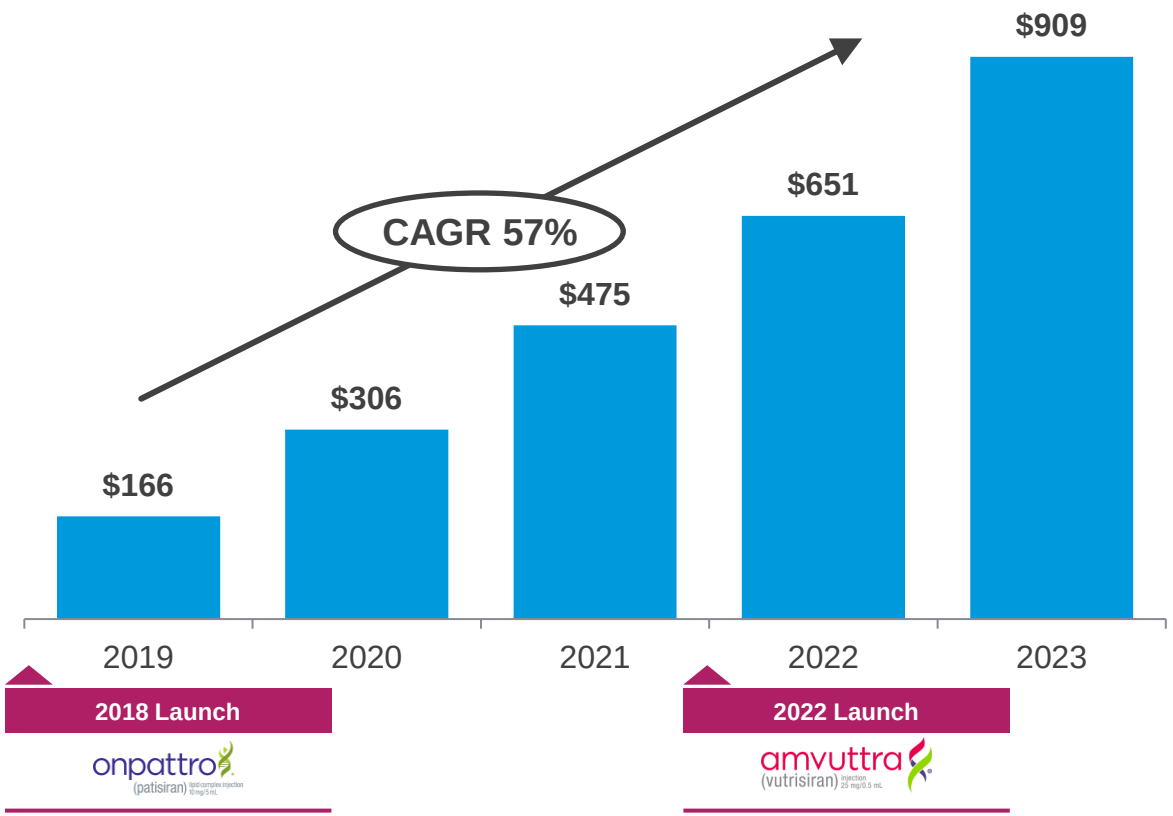
Tolga Tanguler
Chief Commercial Officer

Alnylam®

We Have Built a Strong Growth Engine in our TTR Franchise

57% annual growth in Global TTR franchise

TTR Product Sales Actuals 2019–22 & Consensus '23 ($M)



Strong performance ex-US[1]

>80% Estimated share of PN market in Europe and Japan[1]

Compelling metrics in US[2]

2x Start Forms for AMVUTTRA compared to ONPATTRO

>60% growth in prescribers

>99% of patients have confirmed access

~70% of patients have no out-of-pocket costs

>90% of patients comply with AMVUTTRA dosing regimen and remain on therapy

Source: 2019–2022: Actuals; 2023: Consensus. 1. Internal data and market data estimation; 2. Actuals

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Foundational Capabilities Built Over Past 5 Years to Enable Impressive Growth

Integrated Field Teams

Ensures coordinated approach to delivering across full life cycle

Advanced Lead Generation

Best-in-class analytics backbone enables high-quality lead generation

Comprehensive Patient Services

Optimizes time to therapy initiation and enables strong compliance

Strong Payer and Health Systems Partnerships

Exceptional patient access achieved due to excellence in account management and clinical education

Well Positioned For Success Along Each Step of Patient Journey in ATTR-CM, Assuming Approval

Awareness & Diagnosis

AMVUTTRA launching into rapidly growing ATTR-CM market

Treatment Selection

AMVUTTRA expected to have highly competitive profile in ATTR-CM

Access

AMVUTTRA has obtained favorable coverage across various payer platforms

Adherence & Compliance

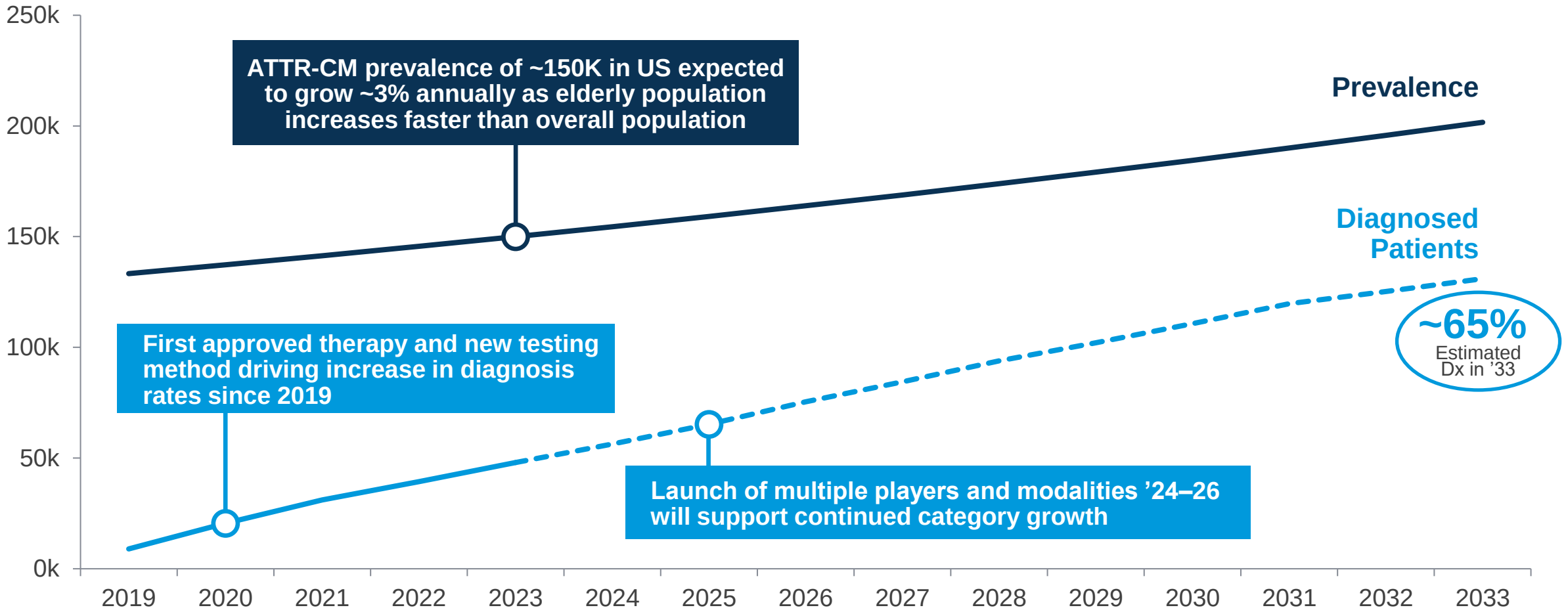
AMVUTTRA's quarterly, HCP dosing supports high patient compliance

CM: cardiomyopathy; PN: polyneuropathy; HCP: healthcare professional.

Note: The safety and efficacy of AMVUTTRA (vutrisiran) for the treatment of the cardiomyopathy of ATTR have not been established or evaluated by the FDA, EMA or any other health authority.

ATTR-CM is a Rapidly Evolving Category, with Significant Unmet Patient Need and Growth Potential

of U.S. ATTR-CM Patients



Note: The safety and efficacy of AMVUTTRA (vutrisiran) for the treatment of the cardiomyopathy of ATTR have not been established or evaluated by the FDA, EMA or any other health authority.
Source: Internal Market research.

If Approved, AMVUTTRA Expected to Have Market Leading Profile in ATTR-CM

RAPID KNOCKDOWN

- **Rapid knockdown** of TTR means therapeutic effects may start sooner
- TTR knockdown expected to result in **functional** and **quality of life** improvements
- Well established **strong safety profile**

Unique MOA

- Highly **targeted** double-stranded RNA works upstream of pathological protein development, **reducing production of disease-causing protein** at its source

Only 4 Doses per Year

- **Quarterly dosing** that aligns with doctor visits and promotes strong adherence
- Based on internal market research, nearly **twice** as many patients indicated they would prefer quarterly HCP-administration vs. monthly self-administration[1]

1. Internal Market research with TTR patients (N=205).

Note: The safety and efficacy of AMVUTTRA (vutrisiran) for the treatment of the cardiomyopathy of ATTR have not been established or evaluated by the FDA, EMA or any other health authority. The information is intended to provide an overview of the potential clinical profile of vutrisiran in ATTR-CM

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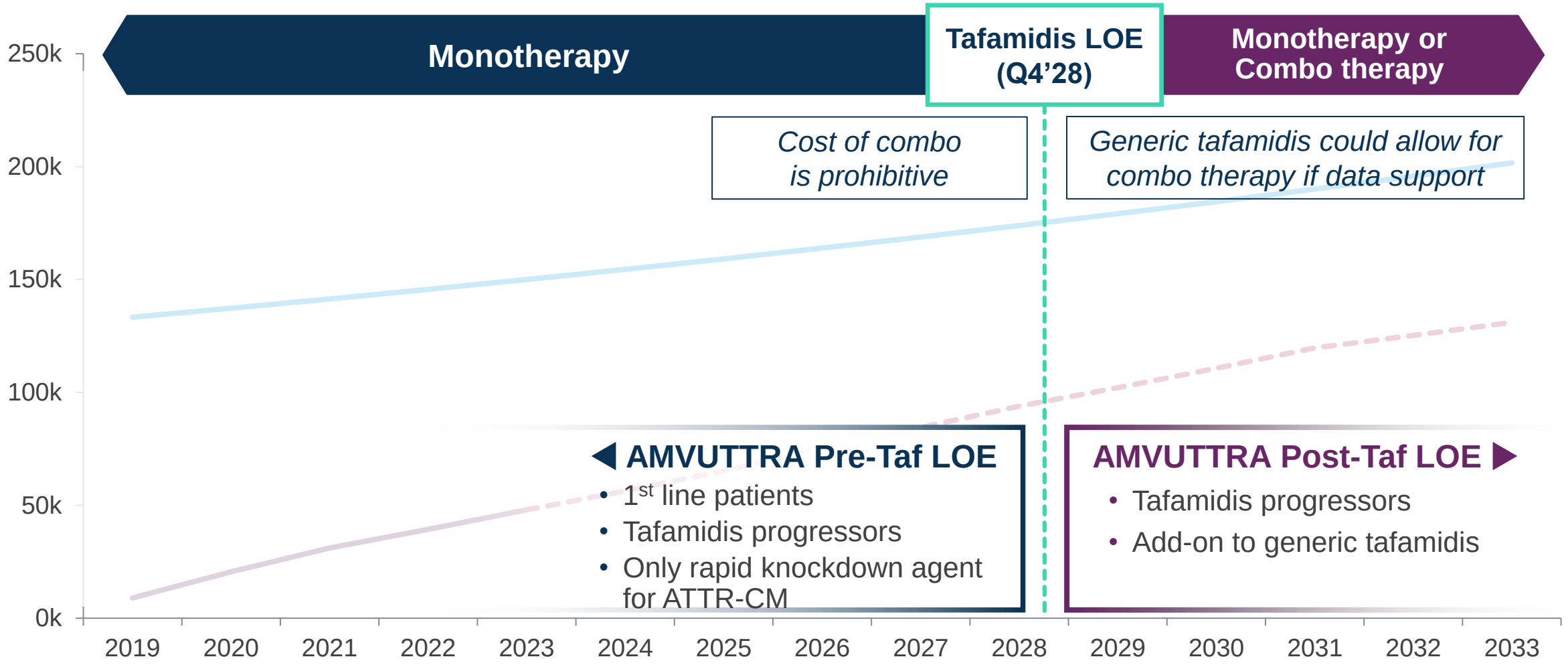
Profile of AMVUTTRA Expected to Support First-Line Positioning and Significantly Grow our TTR Business



Note: The safety and efficacy of AMVUTTRA (vutrisiran) for the treatment of the cardiomyopathy of ATTR have not been established or evaluated by the FDA, EMA or any other health authority. Pending positive HELIOS-B study results and regulatory approval

Source: Internal Market research. LOE: loss of exclusivity

Continuous Evidence Generation to Support Customers and Patients Globally

Today

amvuttra (vutrisiran) injection 25 mg/0.5 mL HELIOS-A

hATTR-PN & Mixed Phenotype[1]

- Rapid knockdown of TTR
- Reversal of neuropathy impairment
- Convenient dosing every 3 months
- Global approvals

2024 & Beyond

amvuttra (vutrisiran) injection 25 mg/0.5 mL HELIOS-B

ATTR-CM[2]

- Potential rapid knockdown agent for ATTR-CM[3]
- Potential agent for both hATTR-PN and ATTR-CM
- Primary endpoint: composite of all-cause mortality and recurrent CV events

amvuttra (vutrisiran) injection 25 mg/0.5 mL Evidence Generation

ATTR-CM[2]

- ConTTRibute registry and innovative real-world evidence generation
- Imaging studies to investigate halting and reversal of disease
- Switch data to inform treatment decisions for progressing patients

ALN-TTRsc04

hATTR-PN & ATTR-CM

- 3rd generation RNAi therapeutic with improved potency
- Potential for rapid knockdown with >90% TTR reduction
- Potential for annual dosing

[1]AMVUTTRA is approved in the U.S. for the treatment of the PN of hATTR amyloidosis in adults and in the EU and Japan for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with stage 1 or stage 2 polyneuropathy; [2]AMVUTTRA 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. [3]Pending positive HELIOS-B results and regulatory review

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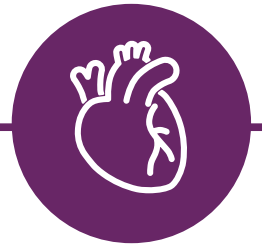
Well Positioned for Market Leadership in ATTR Amyloidosis



Potential for compelling **product profile** with robust **data generation** plan

Deep experience with **ATTR amyloidosis patient community**

Global capabilities and footprint in **60+** markets

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Q&A

Moderator:

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

Panelists:

- David Werring, M.D. – *Professor of Clinical Neurology, Stroke Research Centre, UCL Queen Square Institute of Neurology*
- Rhian Touyz, MBBCh, Ph.D. – *Executive Director & Chief Scientific Officer, Research Institute of the McGill University Health Centre*
- Simon Fox, Ph.D. – *VP, Zilebesiran Program Lead*
- John Vest, M.D. – *SVP, Clinical Research*
- Ali Murad, M.D. – *Senior Director, Clinical Research*
- Tolga Tanguler – *Chief Commercial Officer*

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Closing Remarks

Yvonne Greenstreet, MBChB
Chief Executive Officer

Alnylam 2024 Goals

			Early	Mid	Late
onpattro (patisiran) amvuttra (vutrisiran) GIVLAARI (givosiran) OXLUMO (lumasiran)		*Combined Net Product Revenue Guidance to be Provided at Q4/YE 2023 Earnings*			●
VUTRISIRAN	ATTR Amyloidosis	HELIOS-B Topline Results	●		
		sNDA Submission		●	
ALN-TTRsc04*	ATTR Amyloidosis	Initiate Phase 3 ATTR-CM Study			●
ZILEBESIRAN*	Hypertension	KARDIA-2 Phase 2 Topline Results	●		
		Initiate KARDIA-3 Phase 2 Study	●		
ALN-APP*	Alzheimer's Disease	Interim Phase 1 Part B Multi-Dose Results			●
		Initiate Phase 2 Study			●
	Cerebral Amyloid Angiopathy	Initiate Phase 2 Study	●		
ALN-KHK*	Type 2 Diabetes	Initiate Phase 1 Part B	●		
ALN-BCAT*	Hepatocellular Carcinoma	Initiate Phase 1 Study	●		
ADDITIONAL PROGRAMS		File 3 New INDs			●
KEY PARTNER-LED PROGRAM MILESTONES					
FITUSIRAN* (Sanofi)	Hemophilia	Submit NDA Filing	2024		
ALN-HBV02* (Vir)	Chronic HBV/HDV Infection	Phase 2 Results	Q2, Q4		

* Not approved for any indication and conclusions regarding the safety or effectiveness of these drugs have not been established.
Early is Q1-Q2, Mid is Q2-Q3, and Late is Q3-Q4

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Additional Growth Opportunities via Partnered Programs

FITUSIRAN

Hemophilia

Innovative approach to hemophilia A and B, with or without inhibitors

Demonstrated reduction in annualized bleeding rate

NDA submission expected **2024**

sanofi

ALN-HBV02 (VIR-2218)

Hepatitis B/D Virus Infection

Potential for functional cure of chronic HBV infection

Additional Phase 2 HBV/HDV readouts expected in **2024**

Alnylam opt-in right to VIR-2218 prior to Phase 3

VIR

CEMDISIRAN/POZELIMAB

Complement-Mediated Diseases

Novel approach providing potent C5 inhibition

Phase 3 Myasthenia Gravis study **ongoing**

Phase 2 and 3 Paroxysmal Nocturnal Hemoglobinuria studies **ongoing**

REGENERON

Alnylam®

R&D Day Key Takeaways

Significant Progress with Platform Innovation and Clinical Pipeline

- **Extending Alnylam's leadership in RNAi platform innovation with novel extrahepatic delivery systems**
- **Fueling pipeline with next wave of RNAi therapeutics**
- **Encouraging positive initial Phase 1 results with ALN-TTRsc04 and ALN-KHK**
- **Establishing new frontiers in CNS with RNAi**
- **Opportunity to reimagine the treatment of hypertension with zilebesiran**
- **Building ATTR amyloidosis market leadership**

Anticipate by end of 2025:

9+ Alnylam-led INDs
including
5 liver targets, 2 CNS, and 2 new tissues (adipose and muscle)

plus
6+ additional INDs for partner-led programs

Alnylam®

Ambitious Five-Year Strategy to Drive Growth

Alnylam P5x25

Patients: Over 0.5 million on Alnylam RNAi therapeutics globally

Products: 6+ marketed products in rare and prevalent diseases

Pipeline: Over 20 clinical programs, with 10+ in late stages and 4+ INDs per year

Performance: ≥40% revenue CAGR through YE 2025

Profitability: Achieve sustainable non-GAAP profitability within period

Alnylam®