Alnylam R&D Day 2022

December 15, 2022

Alnylam®@20

Agenda

Time	Topic	Speaker(s)
8:30 – 8:35am	Welcome	Christine Lindenboom *SVP, Investor Relations & Corporate Communications*
8:35 – 8:45am	Building a Top-Tier Biopharmaceutical Company	Yvonne Greenstreet, MBChB, MBA *Chief Executive Officer*
8:45 – 8:55am	RNAi Therapeutics: The Next Chapter	Akshay Vaishnaw, M.D., Ph.D. *President*
8:55 – 9:55am	TTR Franchise: Addressing Polyneuropathy, Cardiomyopathy, and Beyond	John Vest, M.D. *SVP, Clinical Research* Nitasha Sarswat, M.D. *University of Chicago Hospitals*
9:55 – 10:25am	Reimagining Hypertension Care to Impact Cardiovascular Morbidity and Mortality	Dion Zappe, Ph.D. *Executive Director, Clinical Research*
10:25 – 10:55am	Q&A	Pushkal Garg, M.D. – Moderator *Chief Medical Officer*
10:55 – 11:05am	Break	
11:05 – 11:35am	Early and Mid-Stage Programs: Impacting New Areas of High Unmet Need	Weinong Guo, M.D., Ph.D., FAAC *SVP, Clinical Research*
11:35am – 12:00pm	RNAi Platform: Driving to New Targets and Tissues	Aimee Deaton, Ph.D. *Associate Director, Human Genetics* Vasant Jadhav, Ph.D. *SVP, Research*
12:00 – 12:30pm	Q&A	Kevin FitzGerald, Ph.D. – Moderator *Chief Scientific Officer*

Reminders

- Event scheduled to end at ~12:30 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 our expectations beliefs, goals, plans or prospects, including without limitation expectations regarding our aspiration to become a top-tier biotech company, the potential for us to identify new potential drug development candidates and advance our research and development programs, and our ability to obtain approval for new commercial products or additional indications for our existing products, 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: the direct or indirect impact of the COVID-19 global pandemic or any future pandemic on our business, results of operations and financial condition and the effectiveness or timeliness of our efforts to mitigate the impact of the pandemic; the potential impact of the January 2022 leadership transition on our ability to attract and retain talent and to successfully execute on our “Alnylam P5x25” strategy; our ability to discover and develop novel drug candidates and delivery approaches, including using our IKARIA and GEMINI platforms, and successfully demonstrate the efficacy and safety of our product candidates; the pre-clinical and clinical results for our product candidates, including ALN-APP; actions or advice of regulatory agencies and our ability to obtain and maintain regulatory approval for our product candidates, including vutrisiran and patisiran, as well as favorable pricing and reimbursement; successfully launching, marketing and selling our approved products globally; delays, interruptions or failures in the manufacture and supply of our product candidates or our marketed products; obtaining, maintaining and protecting intellectual property; our ability to successfully expand the indication for ONPATTRO or AMVUTTRA in the future; our ability to manage our growth and operating expenses through disciplined investment in operations and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to maintain strategic business collaborations; our dependence on third parties for the development and commercialization of certain products, including Novartis, Sanofi, Regeneron and Vir; the outcome of litigation; the potential impact of a current government investigation and the risk of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the “Risk Factors” filed with our most recent Quarterly Report on Form 10-Q filed with the SEC and in our other SEC filings. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance, timelines or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.

Acknowledgements and Disclosures

All speakers are employees of Alnylam Pharmaceuticals except for Dr. Nitasha Sarswat, who is a paid consultant 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.

Nathan (USA)
Diagnosed with AHP

Building a Top-Tier Biopharmaceutical Company

Yvonne Greenstreet, MBChB, MBA
Chief Executive Officer

Alnylam®@20

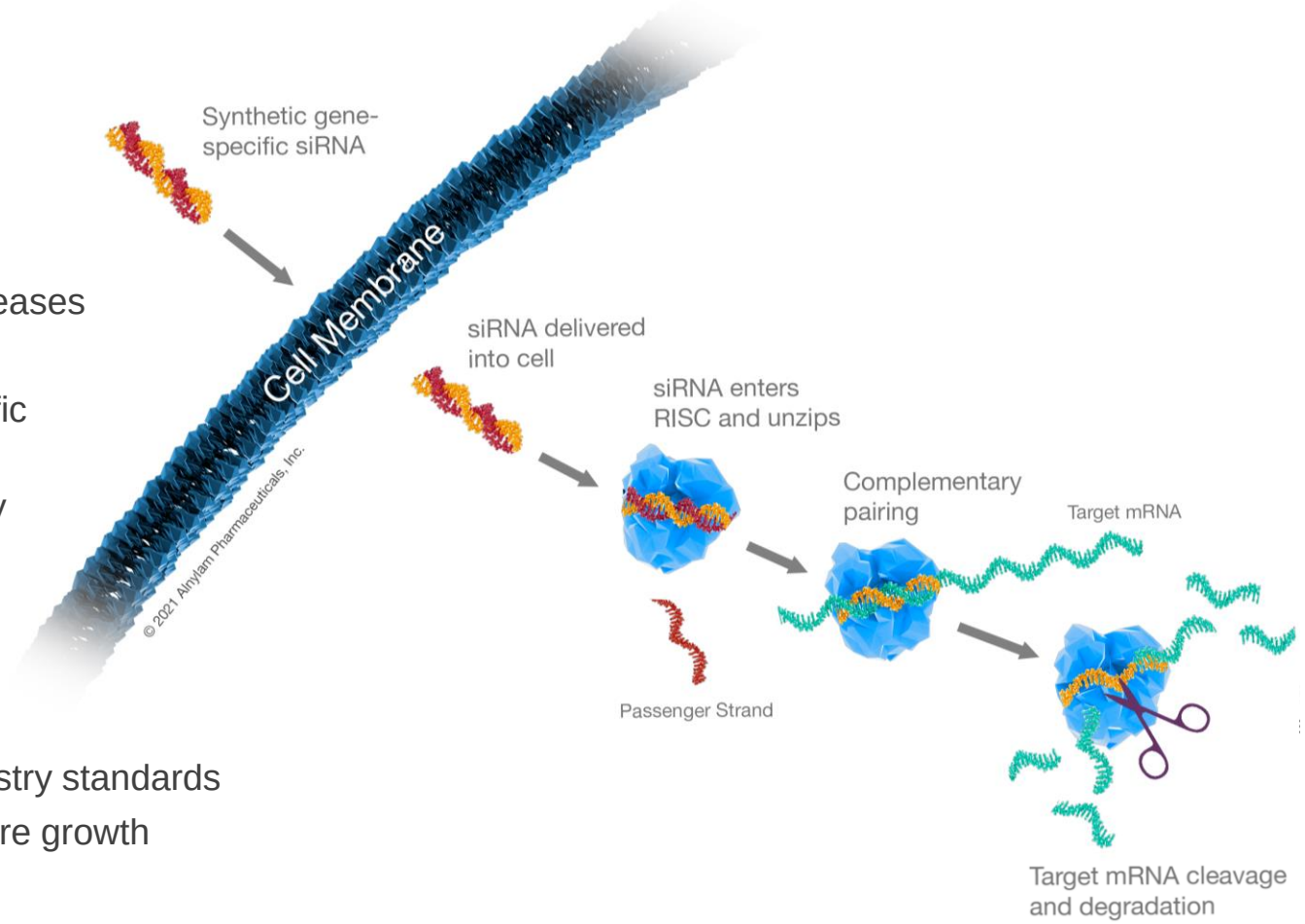
Building a Top-Tier Biopharmaceutical Company

Leader in RNAi Therapeutics

- Pioneered new class of innovative medicines
- 5 medicines approved in < 4 years
- Robust clinical pipeline across rare, specialty, and prevalent diseases
- Global footprint with strong commercial capabilities
- Leading IP estate with fundamental, delivery, and product-specific patent protection
- Strong balance sheet, on path toward financial self-sustainability

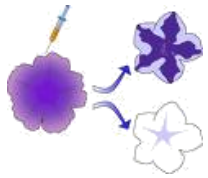
Highly differentiated with proven track record and derisked platform

- Modular and reproducible approach to drug development
- Historic probability of clinical success multiples higher than industry standards
- Organic product engine capable of sustaining innovation for future growth
- Track record of setting and exceeding 5-year goals



RNAi Therapeutics Timeline

From Observation to Nobel Prize to Five Innovative Medicines in Two Decades



Napoli and Jorgensen report that violet petunias turned white instead of deeper violet[1]

1990

Fire and Mello report potent gene silencing effect in worms coined RNAi interference[2]

1998

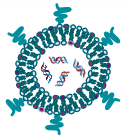
Alnylam® PHARMACEUTICALS

Alnylam founded

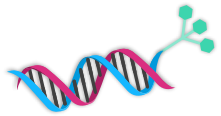
2002

2006
Fire and Mello awarded Nobel Prize in Physiology or Medicine

2004
first in vivo silencing of a gene after systemic administration



2006
First silencing of a gene using LNPs



2013
First silencing of a liver gene using GalNAc conjugate

2018
Improved off target safety with ESC+

RNAi Platform Technology

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

amvuttra® (vutrisiran) injection 25 mg/0.5 mL

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

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

LEQVIO® (inclisiran) injection 284 mg/1.5 mL

2018-2022

1. Napoli C et al. Plant Cell. 1990;2(4):279-289;
2. Fire A et al. Nature. 1998;391(6669):806-811

Fully Integrated Biotech Company

Commercial Portfolio

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

Global Market Presence

- Customer-facing organization with strong track record in launches & organic growth
- Clinical development & regulatory expertise in all key markets including U.S., EU & Japan
- Robust manufacturing & supply chain capabilities

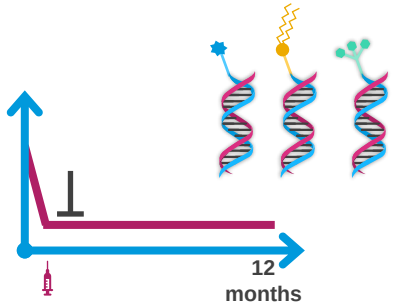
23 Direct

24 Distributor

High-Yield Pipeline

OXLUMO® (lumasiran)	*Primary Hyperoxaluria Type 1*[4]		●	Global
LEQVIO® (inclisiran)	*Hypercholesterolemia*[5]		●	Milestones & up to 20% Royalties[6]
amvuttra® (vutrisiran)	*hATTR Amyloidosis with PN*[7]		●	Global
Patisiran	*ATTR Amyloidosis with CM*		●	Global
Vutrisiran	*ATTR Amyloidosis with CM*	●		Global
ALN-TTRsc04*	*ATTR Amyloidosis*	●		Global
Fitusiran*	*Hemophilia*	●		15-30% Royalties
Cemdisiran (+/- Pozelimab)[8]*	*Complement-Mediated Diseases*	●		Global; Milestone/Royalty
Belcesiran[9]*	*Alpha-1 Liver Disease*	●		Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)[10]*	*Hepatitis B Virus Infection*	●		50-50 option post-Phase 2
Zilebesiran*	*Hypertension*	●		Global
ALN-HSD*	*NASH*	●		Royalty
ALN-APP*	*Alzheimer's Disease; Cerebral Amyloid Angiopathy*	●		50-50

Self-Sustainable Platform



IKARIA™

Alnylam® HUMAN GENETICS

+ Our Future Health

biobank uk

Alnylam Clinical Development Pipeline

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] (OLE/Phase 4/IIS/registries)	COMMERCIAL RIGHTS
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GIVLAARI (givosiran)	*Acute Hepatic Porphyria[3]*			Global
OXLUMO (lumasiran)	*Primary Hyperoxaluria Type 1[4]*			Global
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Zilebesiran*	*Hypertension*			Global
ALN-HSD*	*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] Approved in the U.S. and Canada for the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; [3] Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU and Japan for the treatment of AHP in adults and adolescents aged 12 years and older; [4] Approved in the U.S. for the treatment of PH1 to lower urinary oxalate and plasma oxalate levels in pediatric and adult patients; [5] Approved in the U.S. for the treatment of heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) and in the EU for the treatment of hypercholesterolemia or mixed dyslipidemia; [6] 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; [7] Approved in the U.S. for the PN of hATTR amyloidosis in adults, and in the EU and Japan for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; [8] Alnylam and Regeneron are evaluating potential combinations of the investigational therapeutics cemdisiran and pozelimab; [9] Dicerna is leading and funding development of belcesiran; [10] Vir is leading and funding development of ALN-HBV02; * Not approved for any indication and conclusions regarding the safety or efficacy of the drug have not been established.

As of December 2022

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

Multiple Drivers of Future Growth

TTR Franchise Leadership

Expansion into Prevalent Diseases

Engine for Sustainable Innovation

Andreas (Sweden)
Diagnosed with hATTR amyloidosis

Nurturing a Culture to Ensure Future Success

Commitment to People

The Boston Globe TOP PLACES TO WORK 2015-2022

FAST COMPANY BEST WORKPLACES FOR INNOVATORS 2022

FAST COMPANY BEST WORKPLACES FOR INNOVATORS 2021

2022 BEST PLACES to WORK PRESENTED BY BioSpace

2023 BEST PLACES to WORK PRESENTED BY BioSpace

Science 2019 TOP EMPLOYER

Science 2021 TOP EMPLOYER

Science 2022 TOP EMPLOYERS

Diversity, Equity, & Inclusion

FORTUNE BEST WORKPLACES FOR WOMEN 2022

Bloomberg Gender-Equality Index 2021

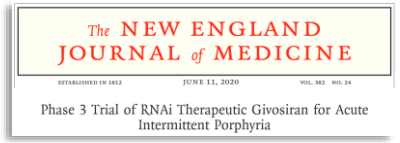
Bloomberg Gender-Equality Index 2022

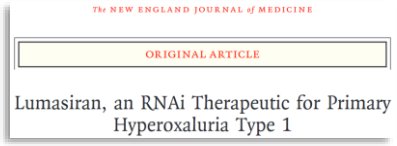
Best Workplaces™ For Women Medium Organisations Great Place To Work. UK 2021

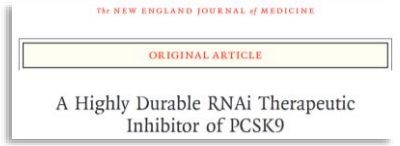
Best Workplaces™ for Women Medium Organisations Great Place To Work. UK 2022

Best Workplaces™ For Wellbeing Medium Organisations Great Place To Work. UK 2022

Scientific Innovation



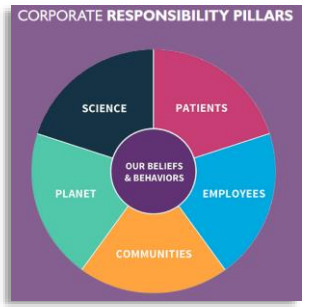


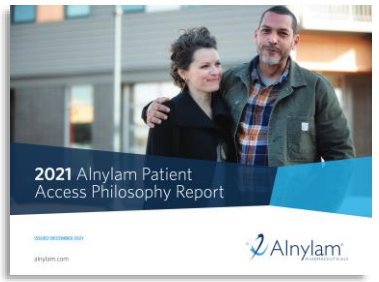


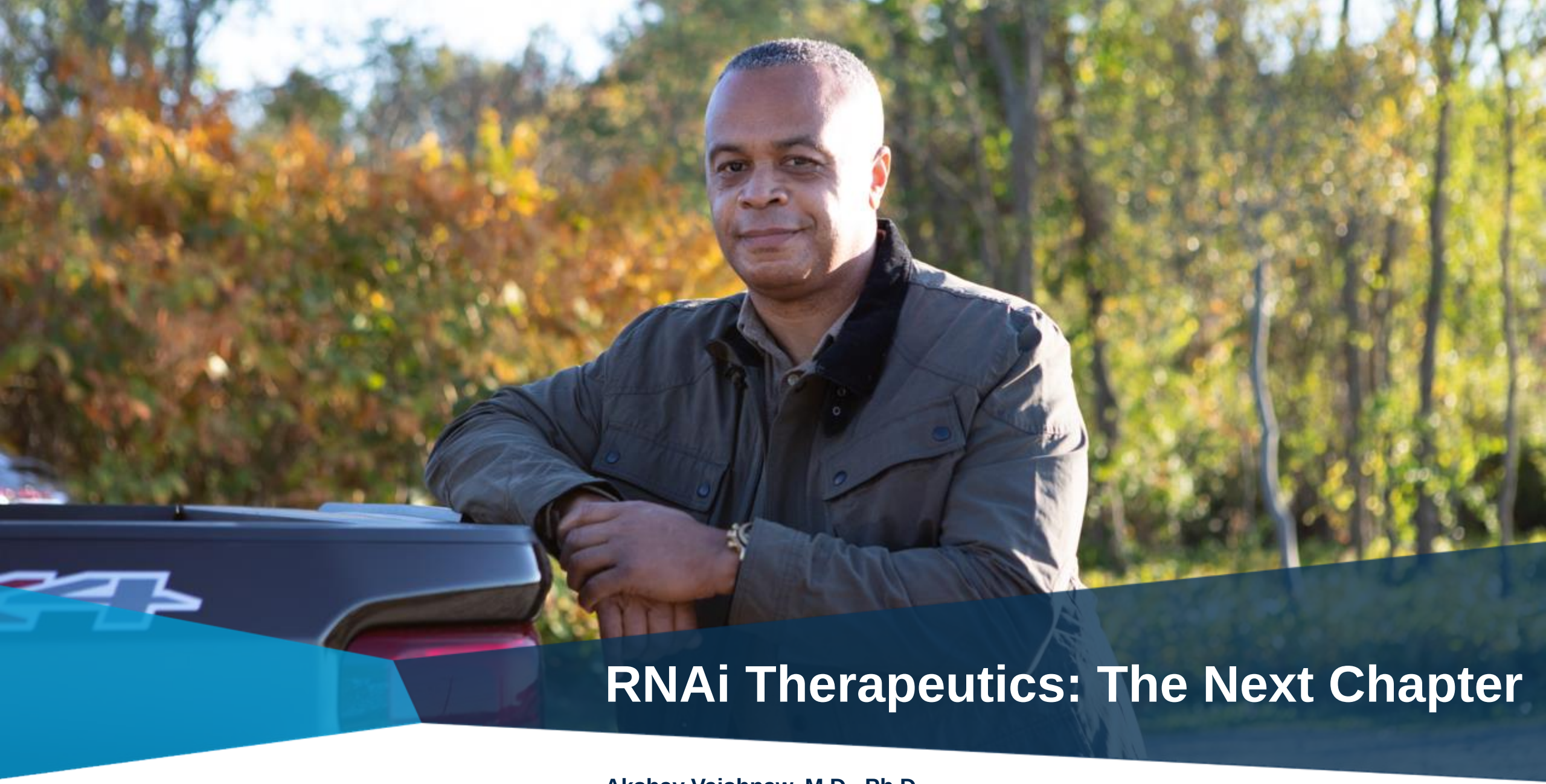
PRIX GALIEN

OTS Paper of the Year 2022
Expanding RNAi therapeutics to extrahepatic tissues with lipophilic conjugates
Brown, et al.

Social Responsibility







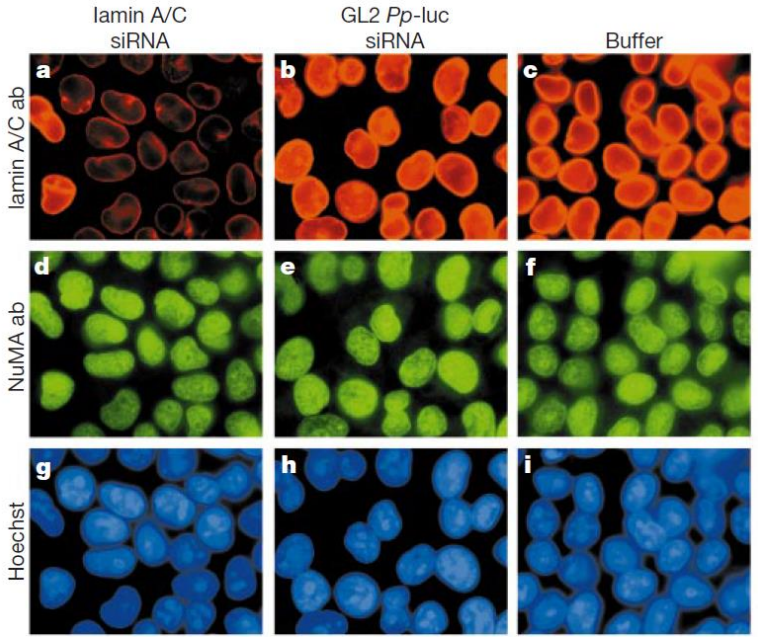
RNAi Therapeutics: The Next Chapter

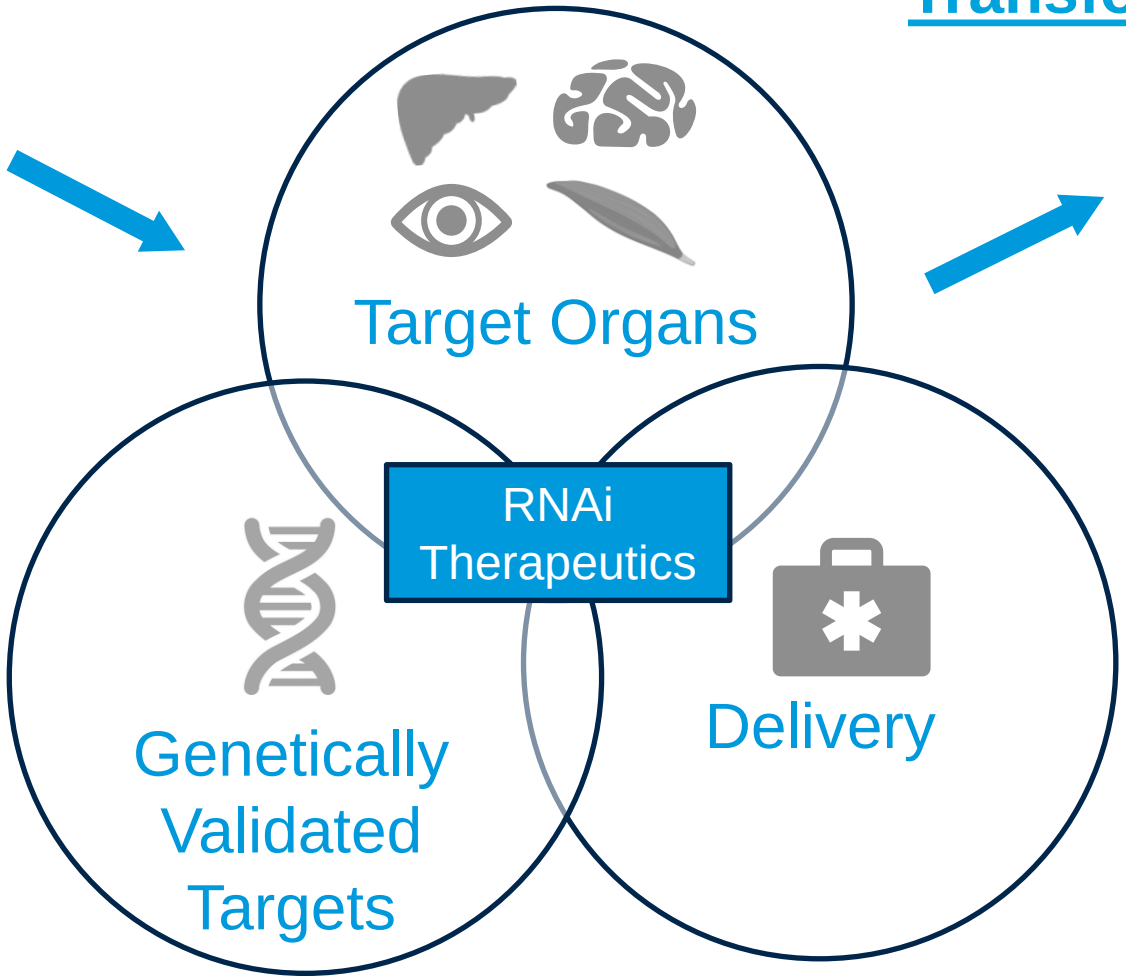
Akshay Vaishnaw, M.D., Ph.D.
President

Alnylam®@20

Focused R&D Strategy

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





Transformative Medicines

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

Alnylam Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

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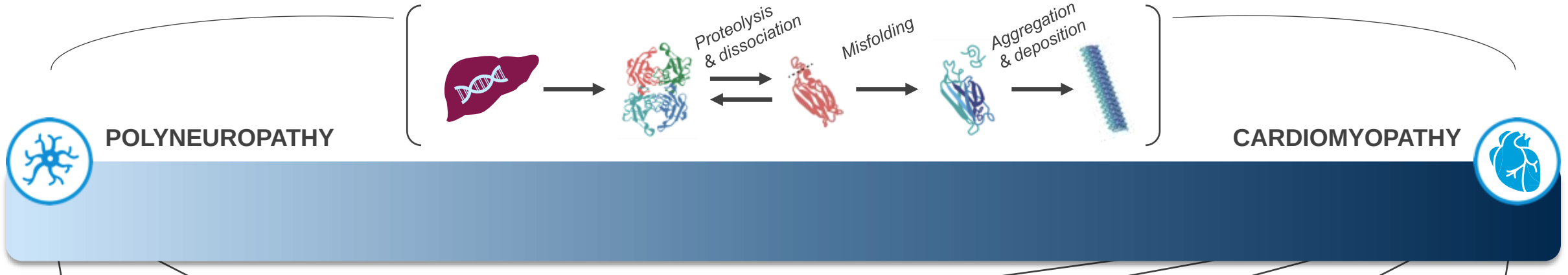
As of December 2022

RNAi Therapeutics Opportunity for ATTR Amyloidosis

Potential for Broad Impact of TTR Silencing Across Disease Spectrum



ONPATTRO
Primary endpoint
- mNIS+7

All secondary endpoints

APOLLO

AMVUTTRA
Primary endpoint
- mNIS+7

HELIOS·A

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

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

APOLLO

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

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

HELIOS·A

PATISIRAN
Primary endpoint
- 6-minute walk test

APOLLO·B

VUTRISIRAN
Primary endpoint
- Mortality & CV events

Enrollment complete

Topline results early 2024

HELIOS·B

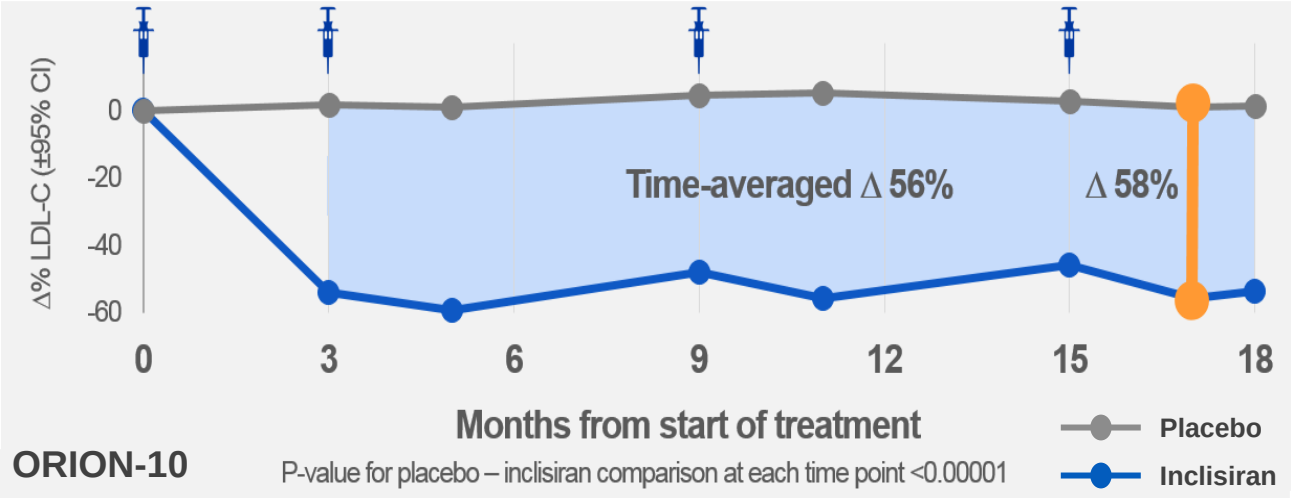
[1] Solomon S, et al. Circulation 2018

[2] Fontana, et al. J Am Coll Cardiol Cardiovasc Imaging. Oct 28, 2020. Epublished DOI: 10.1016/j.jcmg.2020.07.043t

Inclisiran Demonstrates Benefit of RNAi Therapeutics in Prevalent Diseases

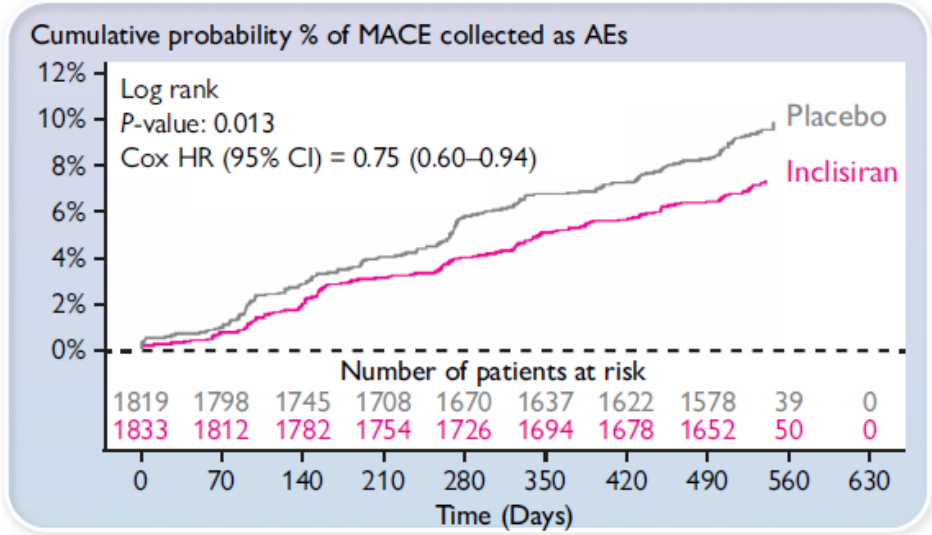
Durable, Potent, and Consistent LDL-C Lowering Over 18 Months with Semiannual Doses

Percent change in LDL-C over time – observed values in ITT patients



- Inclisiran safety profile **similar to placebo**, with no adverse changes in laboratory markers
- Injection site events 2.6-4.7% - predominantly mild and none persistent
- ORION-9+10+11: Numerically fewer CV events reported for inclisiran than placebo (prespecified exploratory endpoint)

Kaplan-Meier curves showing cumulative event rate for MACE-related safety events[2]



[1] Wright et al., AHA 2019; Ray et al., ESC Congress 2019; All 95% confidence intervals are less than ±2% and therefore are not visible outside data points

[2] Ray et al, EHJ 2022

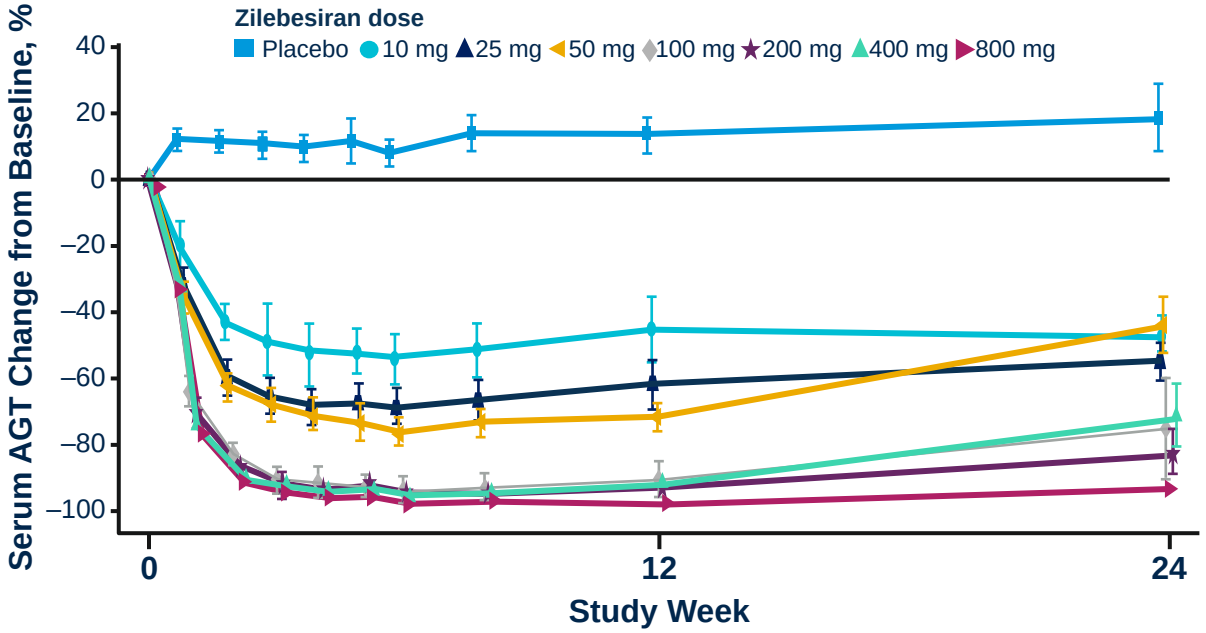
Note: Novartis has obtained global rights to develop, manufacture and commercialize inclisiran; 50% of inclisiran royalty revenue from Novartis will be payable to Blackstone by Alnylam.

Zilebesiran Interim Phase 1 Results

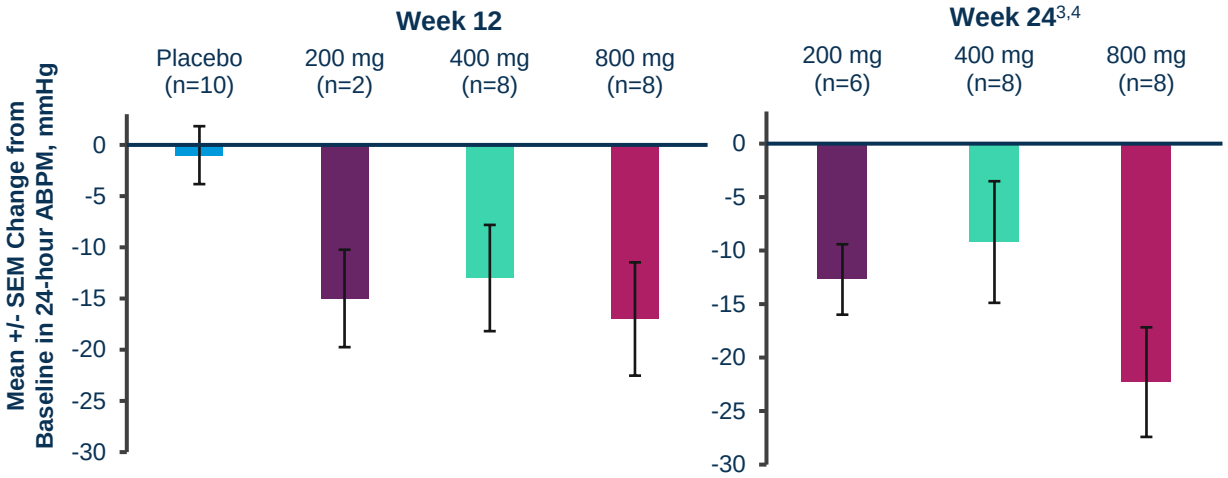
Results for Investigational Therapy Presented at AHA Scientific Sessions[1]

Serum AGT Lowering

≥90% reduction in serum AGT from baseline was observed with single doses of zilebesiran ≥100 mg from Week 3 and sustained to Week 12



Mean Change From Baseline in Mean 24-Hour Ambulatory SBP[2]



Encouraging safety and tolerability profile

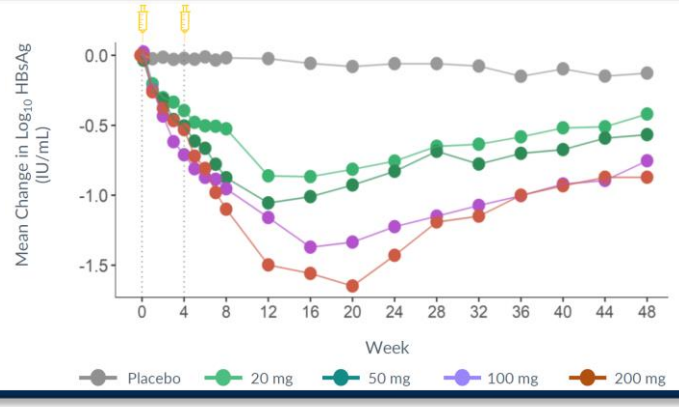
- Most AEs mild or moderate in severity
- ISRs in 5 of 56 patients (8.9%) were all mild and transient
- No treatment-related SAEs
- No patients required intervention for low blood pressure

[1] Huang et al, AHA, November 2021; Data cutoff date: 28 May 2021

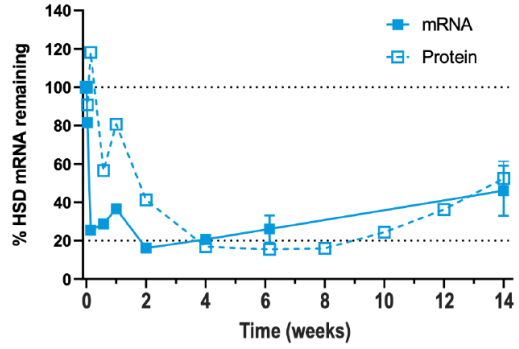
[2] Median baseline SBP/DBP: Placebo – 142/88 mmHg; 200 mg – 139/83 mmHg; 400 mg – 138/90 mmHg; 800 mg – 142/88 mmHg; [3] After Week 12, patients on placebo were not required to be followed; [4] Two patients in the 200 mg dose group, one patient in 400 mg, and two patients in 800 mg received add-on antihypertensive therapy.

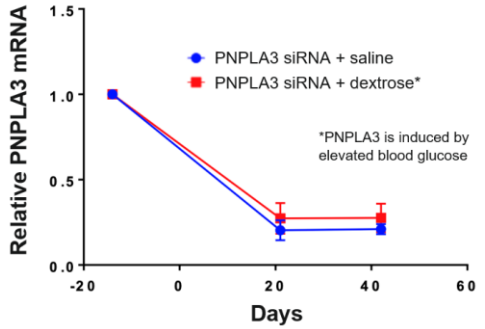
Additional Opportunities from Investigational RNAi Therapeutics Pipeline

ALN-HBV02 (VIR-2218) | *Hepatitis B Virus Infection*

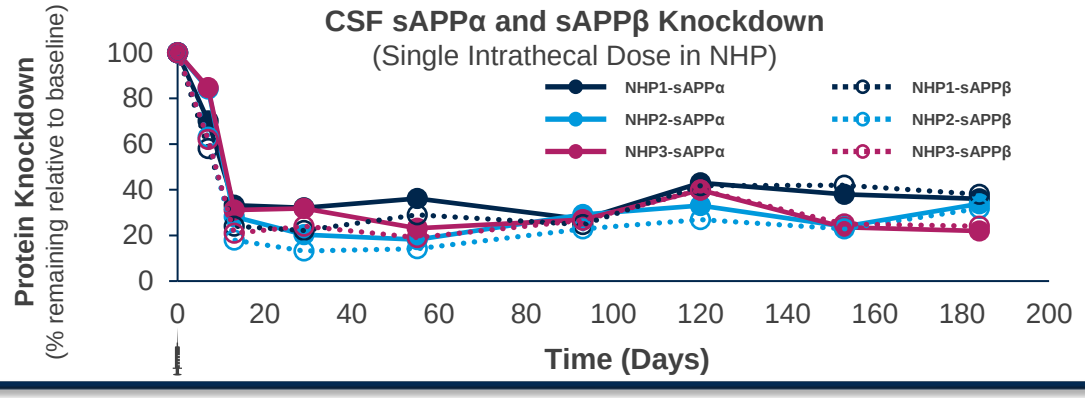


ALN-HSD & ALN-PNP | *NASH*

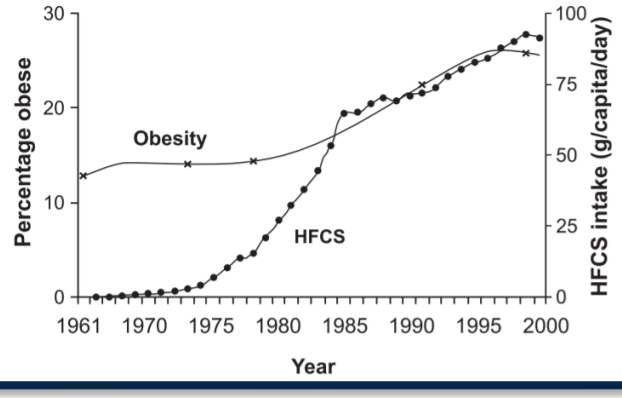




ALN-APP | *Alzheimer's Disease & CAA*

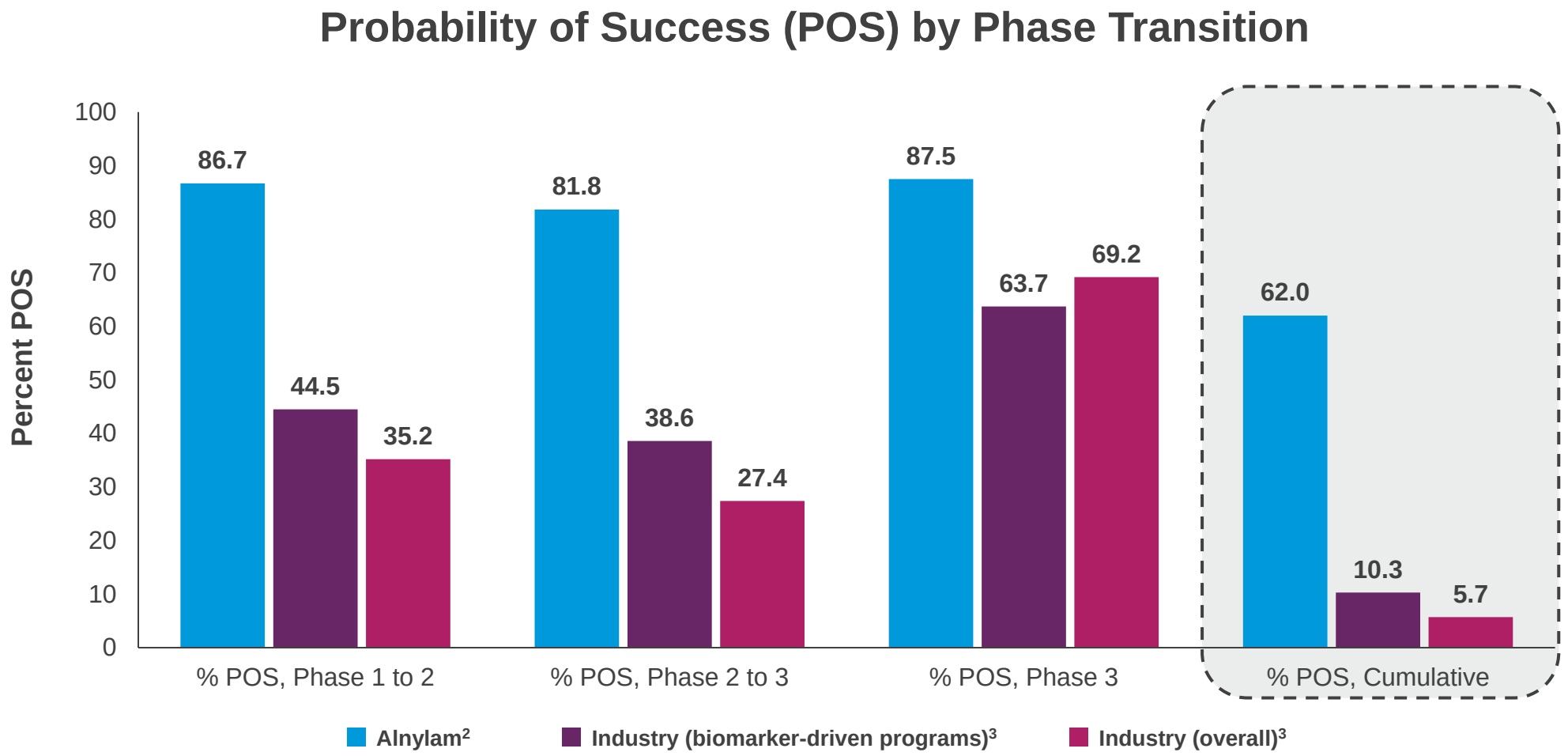


ALN-KHK | *Type 2 Diabetes*



High-Yield Productivity of Alnylam RNAi Therapeutics Platform

Comparison of Historical Metrics to Alnylam Portfolio[1]



[1] Analysis as of December 2022; Past rates of Alnylam and industry respectively may not be predictive of the future

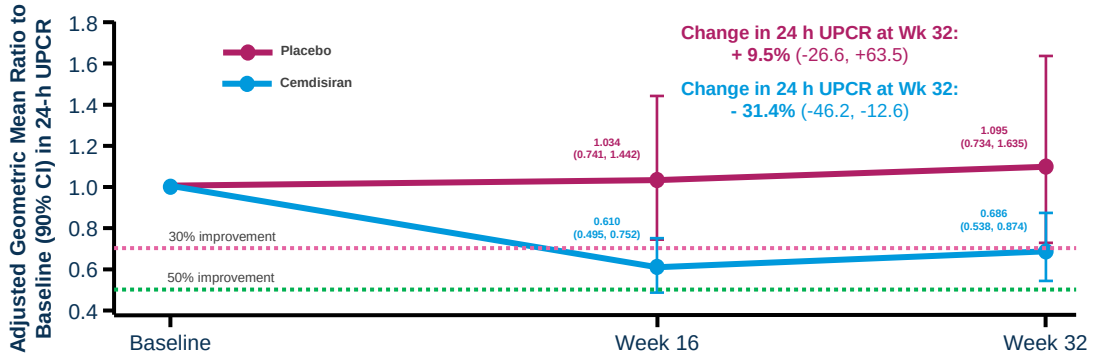
[2] Alnylam programs biomarker-driven at all stages of development (100%); figures include Alnylam-originated molecules now being developed by partners

[3] Wong et al., Biostatistics (2019) 20, 2, pp. 273–286

Pipeline Prioritization

Program Updates

Cemdisiran | *IgA Nephropathy*

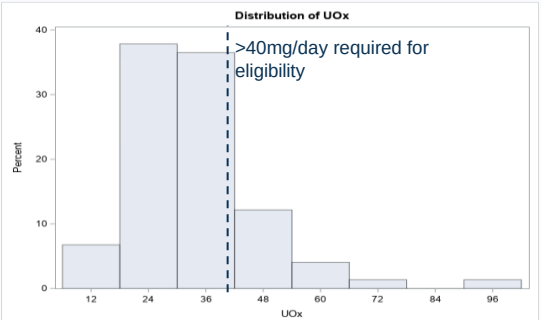


ALN-XDH | *Gout*

- SAD Cohort 5: 600 mg (N=12)
- SAD Cohort 4: 300 mg (N=12)
- SAD Cohort 3: 150 mg (N=8)
- SAD Cohort 2: 75 mg (N=8)
- SAD Cohort 1: 25 mg (N=4)

Phase 1 pharmacodynamic data suggest extrahepatic contributes significantly to serum urate in humans

Lumasiran | *Recurrent Renal Stones*

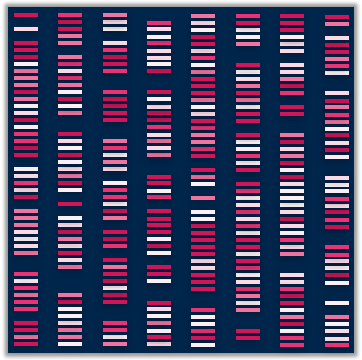


24-Hour Urine Oxalate data from all screened patients in ALN-GO1-008
If more than 1 24-hour urine collected, mean UOx used

Pre-randomization screening showed urinary oxalate not elevated to degree suggested by literature and expert community

Sources of Sustainable Innovation

Human Genetics

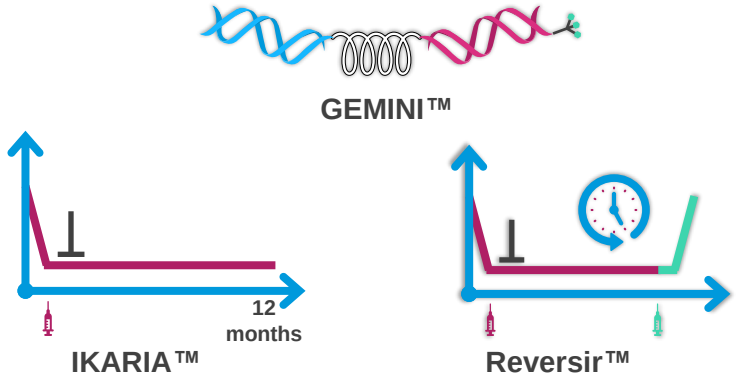


+ Our Future Health

biobank uk

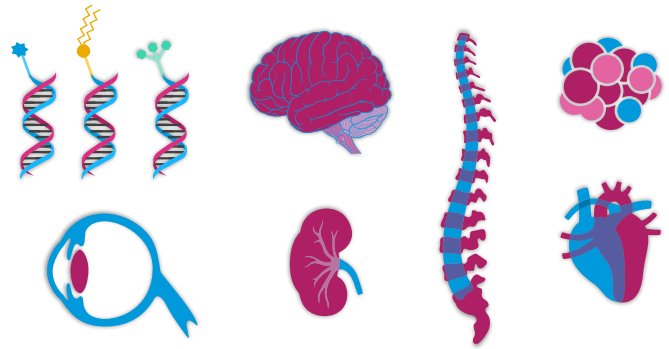
- Sourcing novel, genetically validated targets
- Secured access to large PheWAS databases
- Proven ability to uncover novel gene targets (e.g., *HSD17B13*, *INHBE*, and more)

Platform Innovation



- Two-decade track record of industry leadership in RNAi
- IKARIA™ enables robust target knockdown with annual dosing potential
- GEMINI™ combines siRNAs for simultaneous silencing of two transcripts
- Reversir™ provides tailored control of RNAi pharmacology

Extrahepatic Delivery



- Novel conjugates with variety of ligands for delivery beyond liver
- C16 conjugate provides robust CNS knockdown with wide biodistribution and long duration of action
- Peptide and antibody-based approaches being explored for targeted siRNA delivery to new tissues

Addressing Patient Needs in an Evolving Ecosystem

Alnylam Innovation Extension Strategy

Platform innovation drives product development and differentiation

Patisiran (ONPATTRO)

*hATTR-PN; ATTR-CM**

IV q3W

Vutrisiran (AMVUTTRA)

hATTR-PN

SC q3M

Vutrisiran (AMVUTTRA)

hATTR-PN

SC potentially q6M

(filing planned early 2023)

Vutrisiran

*ATTR-CM**

SC potentially q6M

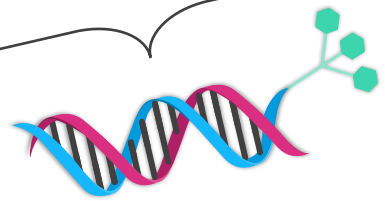
Phase 3 data 2024

ALN-TTRsc04

ATTR

SC potentially q12M

Phase 1 data 2023



* Patisiran and vutrisiran have 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 their safety or effectiveness in this population

Alnylam 2023 Goals

			Early	Mid	Late
onpattro (patisiran) · GIVLAARI (givosiran) · OXLUMO (lumasiran) · amvuttra (vutrisiran)		*Combined Net Product Revenue Guidance to be Provided at Q4/YE 2022 Earnings*			●
PATISIRAN	ATTR Amyloidosis	FDA Approval of sNDA			●
VUTRISIRAN	ATTR Amyloidosis	Biannual Dosing Regimen Data	●		
		Submit sNDA for Biannual Dosing Regimen	●		
ALN-TTRsc04*	ATTR Amyloidosis	Phase 1 Topline Results			●
ZILEBESIRAN*	Hypertension	Complete KARDIA-2 Enrollment	●		
		KARDIA-1 Phase 2 Topline Results		●	
		KARDIA-2 Phase 2 Topline Results (at or around year-end)			●
ALN-APP*	Alzheimer's Disease	Phase 1 Topline Results	●		
ALN-KHK*	Metabolic Liver Disease	Initiate Phase 1 Study	●		
		Phase 1 Topline Results			●
ADDITIONAL PROGRAMS		File 2-4 New INDs			●
PARTNERED PROGRAM MILESTONES					
FITUSIRAN* (Sanofi)	Hemophilia	ATLAS Phase 3 Topline Results			●
ALN-HBV02* (Vir)	Chronic HBV/HDV Infection	Phase 2 Results	●		●
ALN-PNP* (Regeneron)	NASH	Initiate Phase 1 Study	●		

* 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

TTR Franchise: Addressing Polyneuropathy, Cardiomyopathy, and Beyond

John Vest, M.D.
SVP, Clinical Research

Alnylam@20

Alnylam TTR Franchise

Approved Treatment Options and Investigational Clinical Programs

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 CTA submitted
- Potential for annual dosing and >90% serum TTR reduction
- No third-party royalties; exclusivity expected beyond 2040

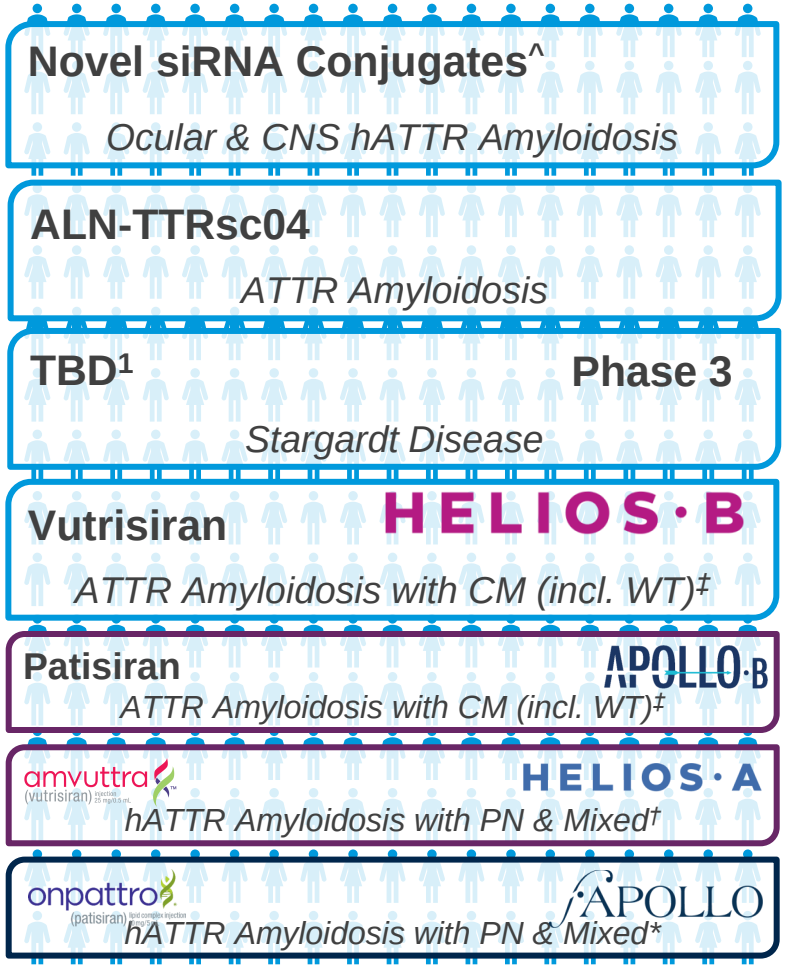
* ONPATTRO is approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU, Switzerland and Brazil for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis 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

Alnylam TTR Franchise

Potential to Expand Value to Patients Globally for Many Years to Come

2018 – 2022

2022 – 2024



2024 & Beyond

* ONPATTRO is approved in the U.S. and Canada for the treatment of the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or 2 PN; ‡ ONPATTRO and AMVUTTRA have 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; † 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; ^ Novel siRNA conjugate development candidates for ocular or CNS hATTR amyloidosis not yet selected; [1] The Company is considering options for the best path forward to bring an RNAi therapeutic to patients with Stargardt Disease; Intended to be illustrative and not intended to represent specific estimates of patient numbers

Cece
Living with hATTR Amyloidosis

ATTR Amyloidosis

Rare, Progressively Debilitating, and Often Fatal Disease

Description

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

Hereditary ATTR (hATTR) Amyloidosis

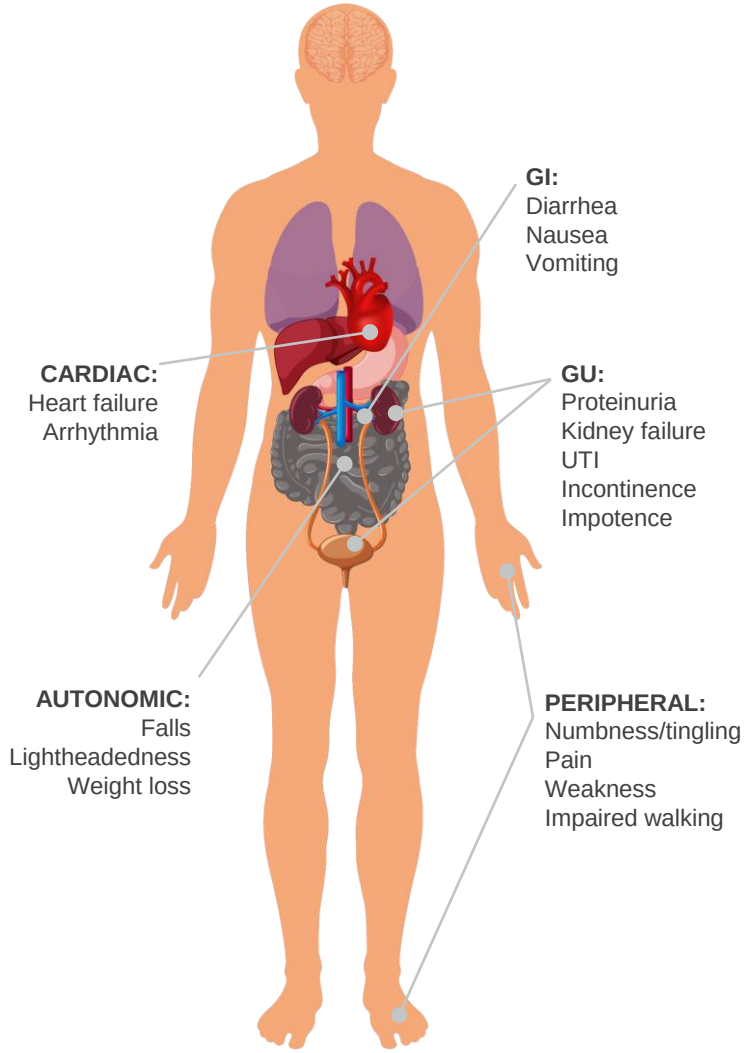
~50,000

patients worldwide*

Wild-Type ATTR (wtATTR) Amyloidosis

~200,000 – 300,000

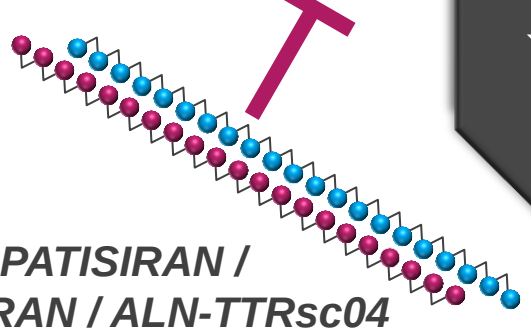
patients worldwide



1 Coelho T, et al. N Engl J Med. 2013;369(9):819-829
* Ando, et al. Orphanet J Rare Dis, 2013; Ruberg, et al. Circulation, 2012

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

Production of variant and wild-type TTR in liver*

Reduce circulating TTR

Prevent or clear tissue amyloid deposits

Halt or improve progressive manifestations of disease

* >95% of TTR in circulation produced in liver

Vutrisiran HELIOS·A Phase 3 Study

Randomized, Open-Label Study in Patients with Hereditary ATTR Amyloidosis with Polyneuropathy

HELIOS·A

Patient Population N=164

- 18–85 years old
- hATTR amyloidosis; any *TTR* mutation
- NIS of 5–130 and PND ≤IIIB
- KPS ≥60%
- Prior tetramer stabilizer use permitted

ClinicalTrials.gov Identifier: NCT03759379

3:1 RANDOMIZATION

Stratification:
TTR V30M vs non-V30M
Baseline NIS <50 vs ≥50

N=122

Vutrisiran
25 mg
SC Q3M

or

N=42

Reference comparator
(patisiran)
0.3 mg/kg
IV Q3W

9-Month Efficacy Assessment

Vutrisiran vs APOLLO Placebo

Primary Endpoint
- Change from baseline in mNIS+7*

Secondary Endpoints
Change from baseline in:
- Norfolk QOL-DN†
- 10-MWT‡

Selected Exploratory Endpoints
Change from baseline in:
- mBMI
- R-ODS
- NT-proBNP

18-Month Efficacy Assessment

Randomized Treatment Extension (RTE)

1:1 RANDOMIZATION

Vutrisiran 25 mg Q3M

or

Vutrisiran 50 mg Q6M

Topline data expected **early 2023**

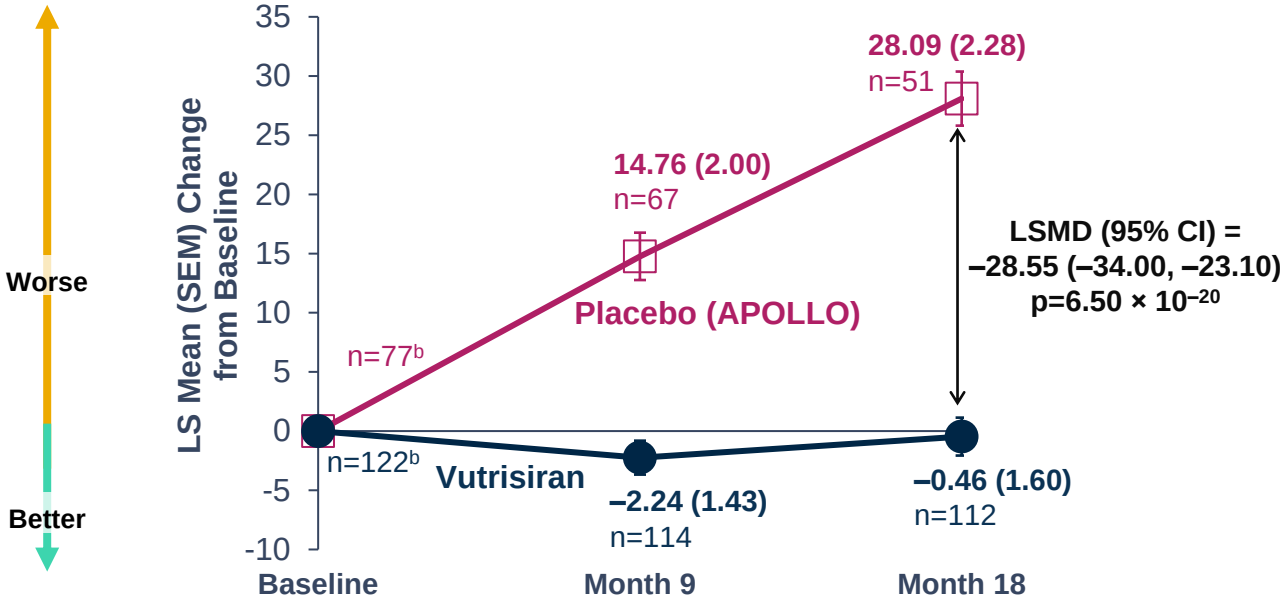
sNDA submission expected **early 2023**

*Higher scores of mNIS+7 indicate more neurologic impairment (range, 0 to 304). †Higher scores of Norfolk QOL-DN indicate worse quality of life (range, -4 to 136). ‡10-meter walk test speed (m/s) = 10 meters/mean time (seconds) taken to complete two assessments at each visit, imputed as 0 for patients unable to perform the walk; lower speeds indicate worse ambulatory function.
10-MWT, 10-meter walk test;; IV, intravenous; KPS, Karnofsky performance status; mBMI, modified body mass index; mNIS+7, modified Neuropathy Impairment Score +7; NIS, Neuropathy Impairment Score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP, N-terminal pro–brain natriuretic peptide; PND, polyneuropathy disability; Q3M, every 3 months; Q3W, every 3 weeks; R-ODS, Rasch-built overall disability scale; SC, subcutaneous; TTR, transthyretin.

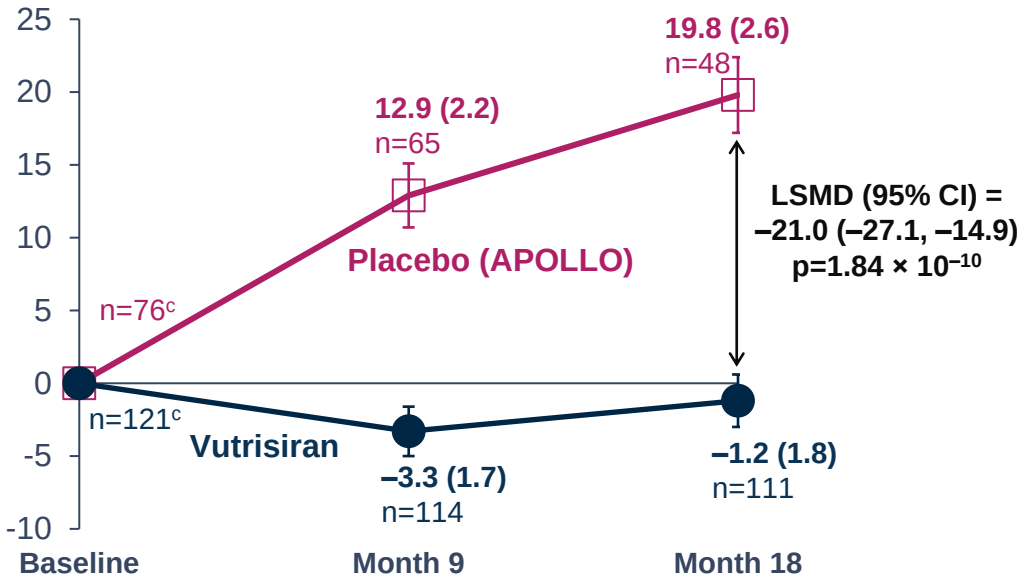
Statistically Significant Improvement in Neuropathy Impairment and Quality of Life with Vutrisiran vs External Placebo at Month 18

- As previously reported, the primary endpoint of change from baseline in mNIS+7 compared with the external placebo group at Month 9 was met[1]
- Improvement in mNIS+7 and Norfolk QOL-DN compared with placebo was consistently observed across all prespecified patient subgroups (data not shown)

mNIS+7 LS Mean Change from Baseline[a]



Norfolk QOL-DN LS Mean Change from Baseline[a]



[a]mITT population (all randomized patients who received any amount of study drug). Value of n is the number of evaluable patients at each timepoint. Data plotted for mNIS+7 and Norfolk QOL-DN at Month 9 are ANCOVA/multiple imputation model data and data plotted at Month 18 are MMRM model data. **[b]At baseline, the mean (±SD) mNIS+7 was 60.6 (36.0) in the vutrisiran group and 74.6 (37.0) in the external placebo group. [c]At baseline, the mean (±SD) Norfolk QOL-DN score was 47.1 (26.3) in the vutrisiran group and 55.5 (24.3) in the external placebo group.**

ANCOVA, analysis of covariance; CI, confidence interval; LS, least squares; LSMD, LS mean difference; mITT, modified intent-to-treat; MMRM, mixed model for repeated measures; mNIS+7, modified Neuropathy Impairment Score +7; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; SD, standard deviation; SEM, standard error of the mean.

1. Adams D et al. *Neurology* 2021;96(15 Supplement):1234.

HELIOS-A Safety Summary[a]

The majority of AEs were mild or moderate in severity

- No drug-related discontinuations or deaths
- Three study discontinuations (2.5%) due to AEs in the vutrisiran arm (two due to death, as previously reported; one due to a non-fatal heart failure event), none of which were considered related to study drug
  - One death due to COVID-19 pneumonia and the other due to iliac artery occlusion
- As previously reported, two SAEs deemed related to vutrisiran by investigators:
  - Dyslipidemia and urinary tract infection
- AEs ≥10% in the vutrisiran group included fall, pain in extremity, diarrhea, peripheral edema, urinary tract infection, arthralgia, and dizziness
  - All except arthralgia and pain in extremity were reported at a similar or lower frequency than external placebo
- Injection-site reactions were reported in 5 patients (4.1%) receiving vutrisiran; all were mild and transient
- No safety signals regarding liver function tests, hematology, or renal function related to vutrisiran

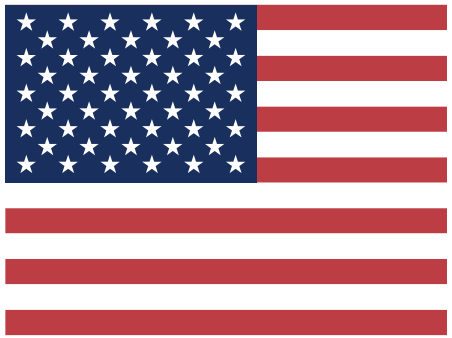
HELIOS-A Safety Summary[a]

	APOLLO	HELIOS-A	
At least one event, n (%)	Placebo (n=77)	Vutrisiran (n=122)	Patisiran (n=42)
AEs	75 (97.4)	119 (97.5)	41 (97.6)
SAEs	31 (40.3)	32 (26.2)	18 (42.9)
Severe AEs	28 (36.4)	19 (15.6)	16 (38.1)
AEs leading to treatment discontinuation	11 (14.3)	3 (2.5)	3 (7.1)
AEs leading to stopping study participation	9 (11.7)	3 (2.5)	2 (4.8)
Deaths	6 (7.8)	2 (1.6)	3 (7.1)

[a]Data reported during 18-month treatment period.
AE, adverse event; SAE, serious AE.

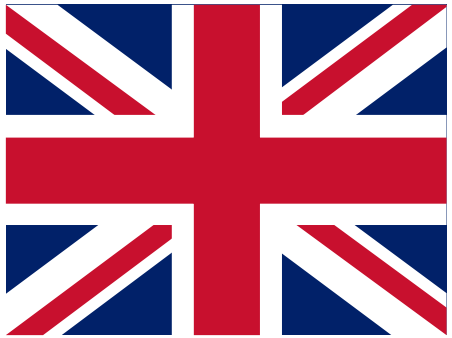
amvuttra™
(vutrisiran) injection 25 mg/0.5 mL

NOW APPROVED

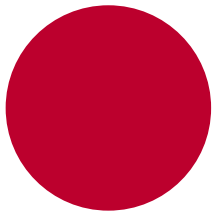


JUNE 2022

SEPTEMBER 2022



SEPTEMBER 2022



SEPTEMBER 2022

DECEMBER 2022

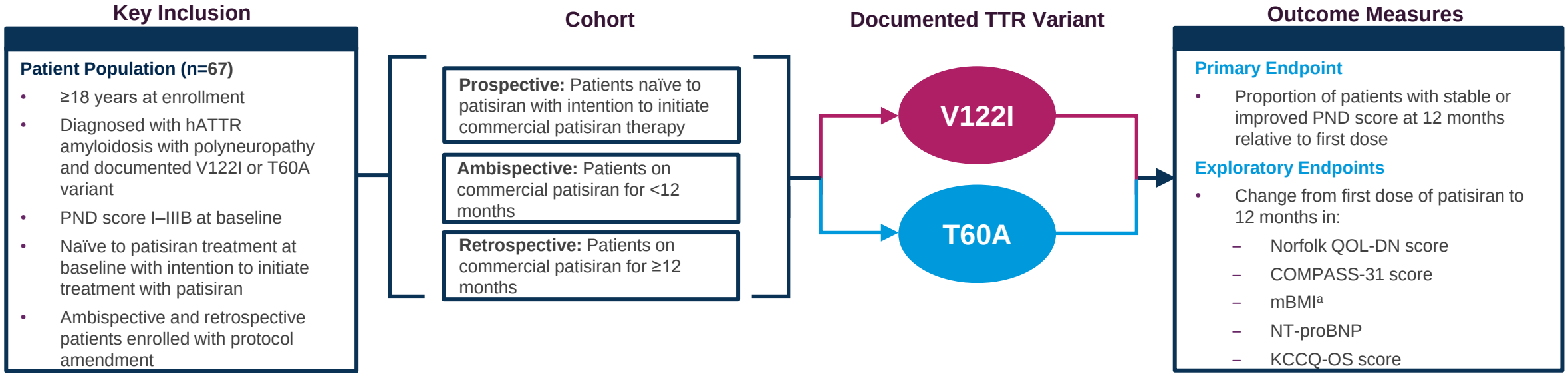
Phase 4 Study of Patisiran

Phase 4 Study: Multicenter Observational Study to Evaluate Effectiveness of Patisiran in Patients With Polyneuropathy of ATTRv Amyloidosis With a V122I or T60A Mutation

Study Design

- Patients in U.S. with hATTR amyloidosis with polyneuropathy and documented V122I or T60A variant were enrolled into one of three cohorts (prospective, ambispective, retrospective) based on prior patisiran exposure
- Primary endpoint was proportion of patients with stable or improved polyneuropathy disability (PND) score after 12 months of patisiran treatment relative to first dose

Patisiran Phase 4 Study Design



NCT04201418

[a]If albumin was collected as routine care, mBMI was calculated as BMI × albumin programmatically in the clinical database

Abbreviations: BMI, body mass index; COMPASS-31, Composite Autonomic Symptom Scale 31-item questionnaire; hATTR, hereditary transthyretin mediated; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP, N-terminal pro-brain natriuretic peptide; mBMI, modified body mass index; PND, polyneuropathy disability

Primary Endpoint: PND Score at Month 12 Relative to First Dose of Patisiran

- 42/45 (93.3%) patients demonstrated stabilization or improvement in PND score from baseline to Month 12 of patisiran treatment
- Of the 3 patients that worsened, 2 had diabetes and 1 had small-fiber neuropathy associated with Ehlers–Danlos syndrome

PND Score from Baseline to Month 12 (Efficacy Population)

PND Score at Baseline	PND Score at Month 12[a]				
	0	I	II	IIIA	IIIB
I: Preserved walking, sensory disturbances	**4**	**20**	**2**	0	0
II: Impaired walking, but can walk without stick/crutch	0	**7**	**6**	**1**	0
IIIA: Walk with 1 stick/crutch	0	0	**1**	**2**	0
IIIB: Walk with 2 sticks/crutches	0	0	0	**1**	**1**

Improved (n=13, 28.9%) Stabilized (n=29, 64.4%) Worsened (n=3, 6.7%)

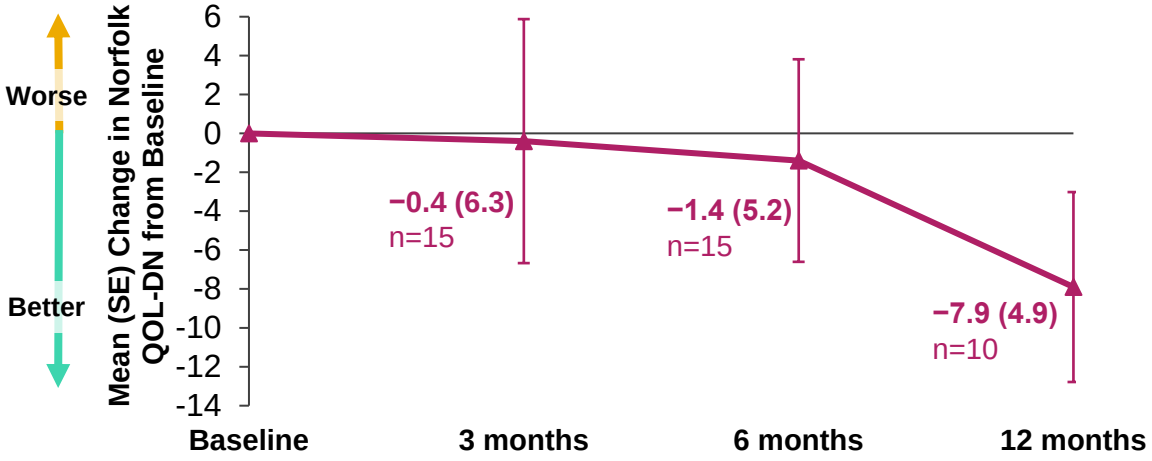
[a]In the V122I population (n=32), 13 patients (40.6%) improved, 17 (53.1%) stabilized, and 2 (6.3%) worsened. In the T60A population (n=13), no patients improved, 12 (92.3%) stabilized, and 1 (7.7%) worsened

Abbreviations: PND, polyneuropathy disability

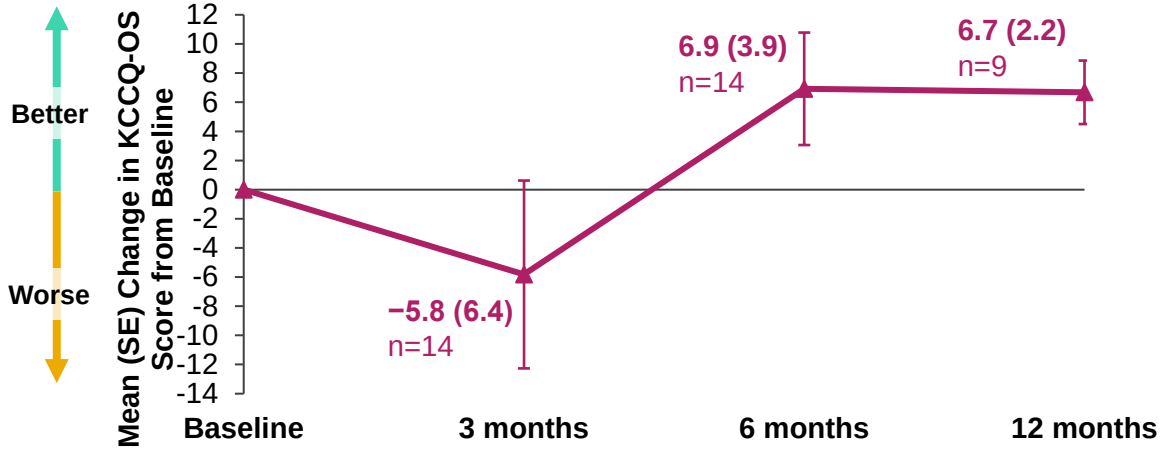
Exploratory Endpoints: Quality of Life and Health Status as Measured by Norfolk QOL-DN and KCCQ-OS

- Patients demonstrated an improvement in Norfolk QOL-DN from baseline to Month 12 of patisiran treatment, with the trend towards improvement evident as early as Month 3
- Patients demonstrated an improvement in KCCQ-OS from baseline, starting at Month 6 of patisiran treatment

Norfolk QOL-DN Total Score



KCCQ-OS Score



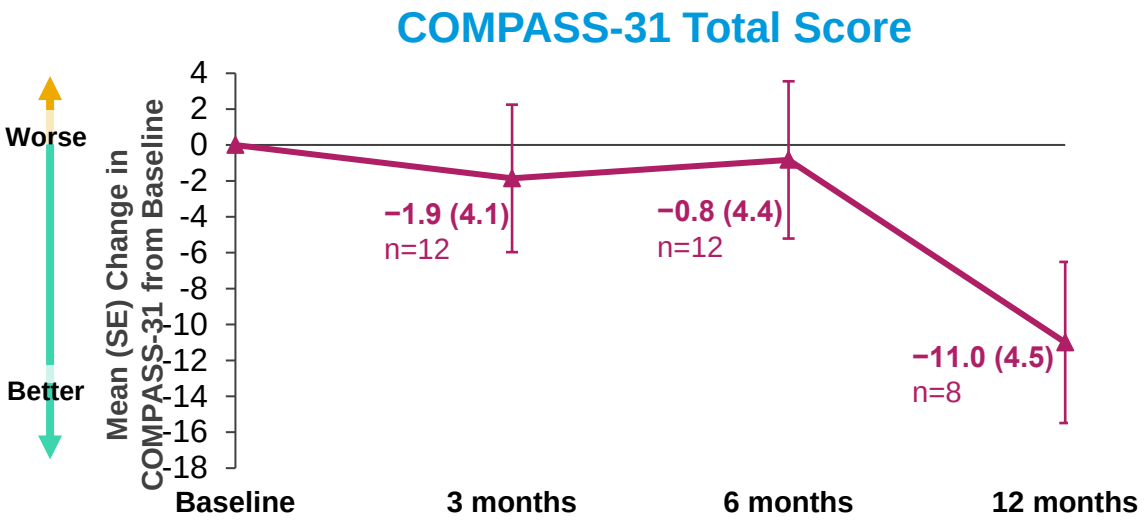
Mean (SE) Norfolk QOL-DN score at baseline was 28.44 (5.08), with a range of −2.0 to 78.0. Higher scores of Norfolk QOL-DN indicate worse QOL (range: −4 to 136)

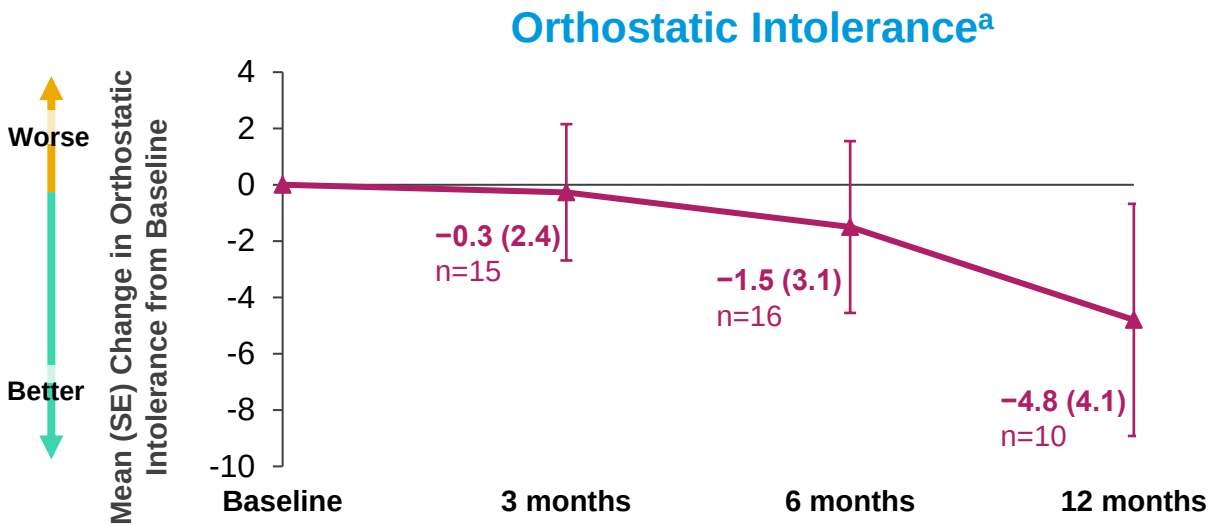
Mean (SE) KCCQ-OS score at baseline was 63.97 (5.22). Lower KCCQ-OS scores indicate worse health status (range: 0–100)

Abbreviations: KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy; SE, standard error

Exploratory Endpoints: Autonomic and Nutritional Status as Measured by COMPASS-31, Orthostatic Intolerance, and mBMI

- Patients demonstrated improvements in COMPASS-31 and orthostatic intolerance[a] from baseline to Month 12 of patisiran treatment





- Nutritional status, measured by modified body mass index, improved from baseline to Month 6 of patisiran treatment, and this improvement was maintained to Month 12 (mean [SE] change from baseline: Month 6, +118.9 [105.9], n=6; Month 12, +201.8 [139.0], n=5)

Mean (SE) COMPASS-31 score at baseline was 22.40 (3.09), with a range of 0.0–45.7. Mean (SE) orthostatic intolerance score at baseline was 9.38 (1.93), with a range of 0.0–32.0
Higher scores of COMPASS-31 total (range: 0–100) and orthostatic intolerance (range: 0–40) indicate worse autonomic symptoms
[a]Orthostatic intolerance is a domain of COMPASS-31

Abbreviations: COMPASS-31, Composite Autonomic Symptom Scale 31-item questionnaire; SE, standard error

Safety

- 11 patients were hospitalized during the study
  - 4 of the 11 hospitalizations were associated with congestive heart failure
  - 3 of the 11 hospitalized patients subsequently died
  - All hospitalizations and deaths were unrelated to patisiran

Overall Summary of Selected Safety Events

Selected Safety Event	Patients with Event (n=42)[a]	Patient-Years of Exposure	Exposure-Adjusted Incidence Rate (Rate/Patient-Year)
≥1 serious treatment-emergent AE[b]	9	25.19	0.357
≥1 severe treatment-emergent AE[b]	8	25.19	0.318
≥1 treatment-emergent AE leading to study withdrawal[b]	2	25.19	0.079
Death[c]	4	25.19	0.159

The most common treatment-emergent AE was infusion-related reaction (n=2)

Selected safety event includes events occurring or worsening on or after the first dose of patisiran are reported. Selected safety event includes death, SAEs, significant AEs that led to an intervention, marked laboratory abnormalities, overdose, pregnancy, and ADR. Selected safety events with missing causality are considered related. Selected safety events with missing severity are considered severe

[a]Patients in the prospective cohort and mixed cohort are summarized. [b]AEs considered unrelated to the study drug. [c]All deaths are reported as serious selected safety events, including those not treatment-emergent. Causes of death were: acute respiratory failure (n=1), exacerbation of heart failure not otherwise specified (n=1), cardiogenic shock (n=1), unknown (died at home, n=1). All deaths were considered unrelated to patisiran

Abbreviations: ADR, adverse drug reaction; AE, adverse event; SAE, serious adverse event

Summary

- In this patisiran Phase 4 study, patients with a V122I or T60A variant of hereditary transthyretin-mediated (hATTR) amyloidosis, historically associated with cardiomyopathy, also experienced polyneuropathy at baseline, as demonstrated by impaired quality of life (QOL), autonomic dysfunction, and a wide range of ambulatory dysfunction

- The primary endpoint of the study was met and 93.3% of patients demonstrated stabilization or improvement from baseline in polyneuropathy disability (PND) score after 12 months of patisiran treatment

- Patients also demonstrated evidence of improvement from baseline in QOL, autonomic symptoms, and health status after 12 months of patisiran treatment

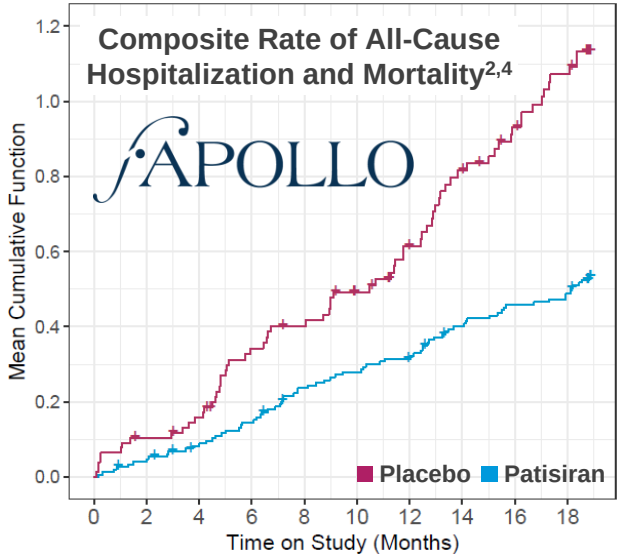
- Patisiran demonstrated an acceptable safety profile, consistent with existing data

Abbreviations: hATTR, hereditary transthyretin mediated; PND, polyneuropathy disability; QOL, quality of life

ATTR Amyloidosis with Cardiomyopathy

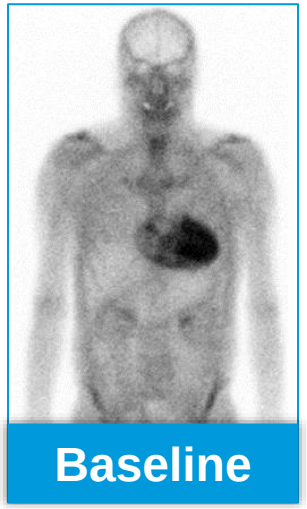
Evidence for Investigational RNAi Therapeutics in ATTR Cardiomyopathy[1]

Exploratory & Post-hoc Data from APOLLO[2]



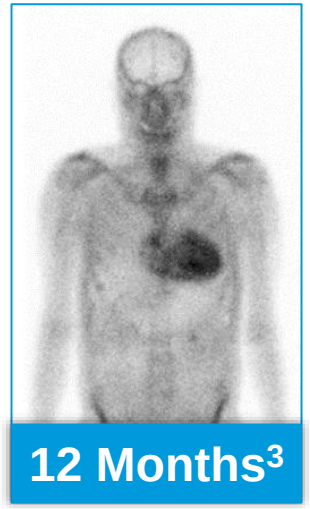
- **55%** Relative reduction in **NT-proBNP** vs. placebo[2,†]
- **0.9mm** Mean reduction in **LV wall thickness** vs. placebo[2,‡]
- **-1.4%** Improvement in **global longitudinal strain** vs. placebo[2,‡]
- **0.35m/s** Improvement in **10-MWT** vs. placebo[2,†]

Investigator-Sponsored Study from National Amyloidosis Centre, UK[3]



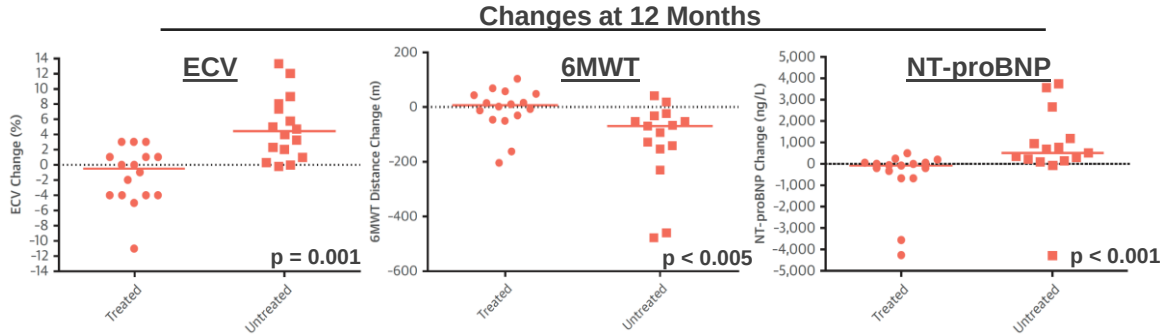
Patient with hATTR and CM, receiving patisiran and diflunisal

Example Tc-DPD Bone Scintigraphy & Image Analysis conducted as part of study, in this patient showing "unequivocal reduction in cardiac and soft tissue uptake"[3]



Cardiac Safety Data in Entire APOLLO Study Population:

	Placebo[5] (n=77)	Patisiran[5] (n=148)
Rates of Death/Hospitalization, per 100 py (95% CI)		
Death	6.2 (2.5 – 12.7)	3.2 (1.4 – 6.2)
All-cause hospitalization	69.7 (54.3 – 87.7)	32.9 (25.9 – 41.1)
Cardiac hospitalization	15.6 (9.0 – 24.9)	8.2 (5.0 – 12.6)
Hospitalization and/or death	71.8 (56.1 – 90.1)	34.7 (27.5 – 43.1)
Cardiac hospitalization and/or death	18.7 (11.4 – 28.8)	10.1 (6.4 – 14.9)



[1] Patisiran has not been approved by the FDA, EMA, or any other regulatory agency for treatment of cardiac amyloidosis. No conclusions can or should be drawn regarding its safety or effectiveness in treating CM in this population; [2] Solomon S, et al. Circulation 2018;

[3] Fontana, et al. J Am Coll Cardiol Cardiovasc Imaging. Oct 28, 2020. Epublished DOI:10.1016/j.jcmg.2020.07.043; [4] Analysis of hospitalization/death data was conducted post-hoc based on data collected from AE CRFs; hospitalization/death events caused by SAEs within 28 days of last dose of study drug were included; hospitalization events caused by SAEs within SOC of cardiac disorder were classified as cardiac hospitalization; [5] For any hospitalization/death analysis: negative binomial regression rate ratio (RR) 0.49 [0.30, 0.79]; Anderson-Gill hazard ratio (HR) 0.48 [0.34, 0.69]; † nominal p<0.01; ‡ nominal p<0.05

TTR Franchise Phase 3 Program

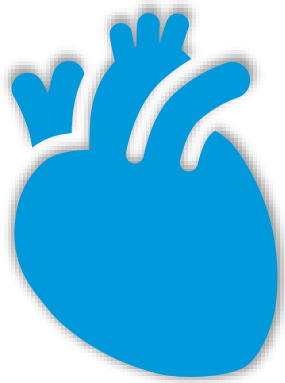
Randomized, Double-Blind, Placebo-Controlled Studies in ATTR Amyloidosis Patients with Cardiomyopathy

APOLLO-B

patisiran

N = 360
hereditary & wild-type
6-minute walk test
12 months

Results presented at
ISA and HFSA – September 2022



HELIOS-B

vutrisiran

N = 655
hereditary & wild-type
mortality & cardiovascular events
30 months

Enrollment **complete**

Topline results on 30-month endpoint expected **early 2024**

THE UNIVERSITY OF CHICAGO MEDICINE

Heart and Vascular Center

The State of ATTR Amyloidosis with Cardiomyopathy

Nitasha Sarswat, MD

Assistant Professor of Medicine

Director, Cardiac Amyloid Program

University of Chicago Hospitals

Disclosures

I am consultant of Alnylam and my institution is receiving compensation for this presentation

I am an investigator on the Apollo-B and Helios-B studies, sponsored by Alnylam

Patient MD

- 76 yo Caucasian male who has been very active throughout his life and loves traveling
- Developed worsening dyspnea and fatigue and could not keep up with his wife on a hike
- History of spinal stenosis, carpal tunnel disease and had a R carpal tunnel release 8 years ago
- History of atrial fibrillation, hypertension and foot numbness
- On exam, JVP 8 cm, irregularly irregular heart beat, extremities warm and perfused with 1+ edema bilaterally
- Elevated proBNP and troponin
- Echocardiogram and cardiac MRI consistent with amyloidosis
- Has been reading on the internet that amyloid is a ‘death sentence’ and discussion regarding the disease and recent changes/hope on the horizon

Patient MD

- Has an “AL ruleout” that’s negative
- Sent for a PYP that returns grade 3 with heart/lung ratio of 1.8
- Genetics negative for a TTR mutation
- Returns to clinic for discussion
- Discussion regarding diagnostic algorithm and his diagnosis of wild type TTR
- Review of medication options and data behind them: an informed discussion

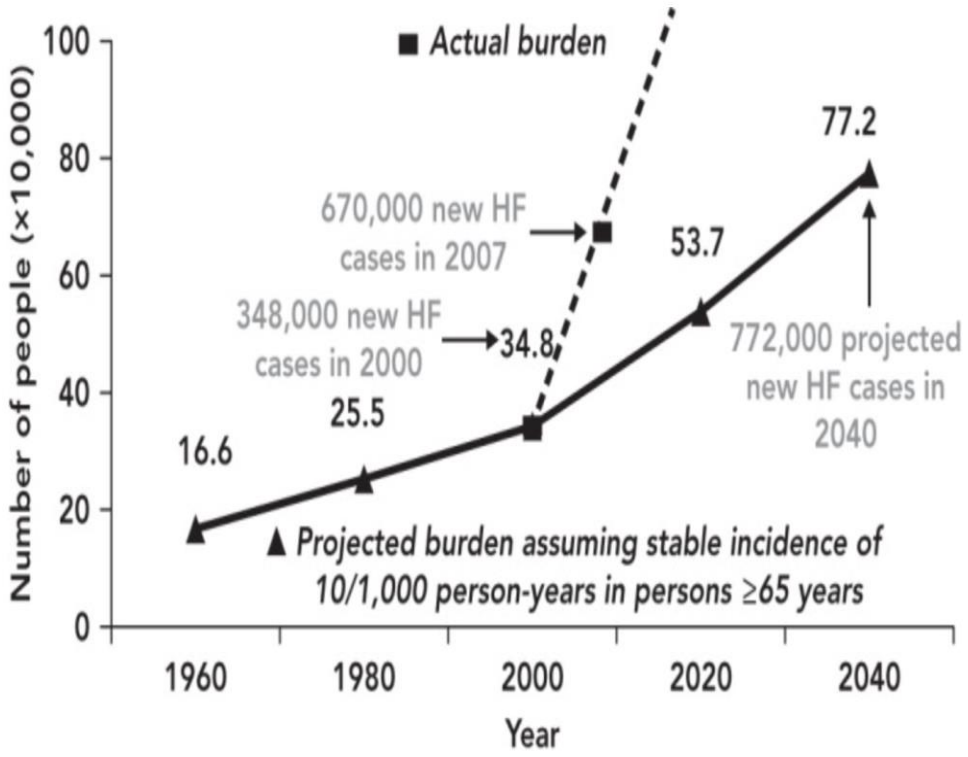
Outline of Discussion

- How big is the population that is impacted by the disease that would potentially benefit?
- What is the unmet need in terms of ATTR amyloidosis treatment?
- A patient that whose life is affected by these discussions

Why is HF so important?

- Affects nearly 6.2 million Americans
- Primary diagnosis for hospital discharge in about 1 million
- Secondary diagnosis in about 2 million hospitalizations annually
- By 2030, more than 8 million people in the United States (1 in every 33) will have HF

An Epidemic…



Burden of Heart Failure

The actual annual incidence of heart failure (HF) reported in the US (squares and dotted line) exceeded the projected annual incidence (triangles and solid line) calculated based on a stable incidence of 10 per 1,000 person-years in persons aged ≥65 years. Source: Lam et al., 2011.[69] Reproduced with permission, © 2011 John Wiley & Sons.

Understanding the Population

- Of patients with heart failure, slightly more than half have heart failure with preserved ejection fraction (HFPEF)
- Of those with HFPEF, its estimated that 13 to 29% actually have cardiac amyloidosis
- AbouEzzeddine et al. Of 1235 patients with LV wall thickness > 12 mm, 10% of men and 2.2% of women had ATTR-CM
- Autopsy study[1]:
  - 25% of patients >80 years old had TTR deposition
  - 2/3 of those had left ventricular involvement -> significant cardiac involvement in 8-16% of people >80 years old
- Recent study of 151 patients undergoing TAVR for aortic stenosis: 16% of the patients[2] were PYP+
- Emerging data using nuclear scintigraphy has suggested that 13% (95% confidence interval, 7.2% -19.5%) of patients hospitalized with heart failure with preserved ejection fraction may have ATTR with cardiac involvement

1. AbouEzzedine et al. *JAMA Cardiol.* 2021;6(11):1267-1274. doi:10.1001/jamacardio.2021.3070
JAMA Cardiol. 2021;6(11):1267-1274. doi:10.1001/jamacardio.2021.3070

1. Cornwell et al. Am J Med. 1983;75:618–623.
2. Castano et al. Eur Heart J. 2017 Oct 7;38(38):2879-2887.
3. Gonzalez-Lopez et al. Eur Heart J. 2015 Oct 7;36(38):2585-94.

Understanding the Population

- At least 155,000 people (5% of estimated HFpEF prevalence) have ATTR, but milder deposition is probably playing a role in many others with HFpEF
- Val122Ile mutation has been found in 10% of African Americans over the age of 65 years who have severe HF
- Worsening survival among those with ATTRwt-CM has been observed with declining NYHA functional classes
- NYHA functional class III or IV was identified as an independent risk factor for adverse cardiovascular outcomes that include the development of conduction disease, HF hospitalization, and stroke

Focus on Unmet Need of Patients with TTR Cardiac Amyloidosis

Therapeutic Approaches

1. Stabilize the TTR tetramer

    A. Tafamidis: approved for treatment of wild type or hereditary amyloidosis in adults to reduce CV mortality and CV-related hospitalization

    B. Diflunisal

    C. Acoramidis – investigational therapy for potential treatment of cardiomyopathy of ATTTR amyloidosis completed enrolling, phase 3 trial

Therapeutic Approaches

2. Reduce TTR production

A. Patisiran – approved for treatment of polyneuropathy of hereditary ATTR amyloidosis in adults, investigational therapy for potential treatment of cardiomyopathy of ATTR amyloidosis

B. Vutrisiran – approved for treatment of polyneuropathy of hereditary ATTR amyloidosis in adults, investigational therapy for potential treatment of cardiomyopathy of ATTR amyloidosis

C. Inotersen - approved for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults

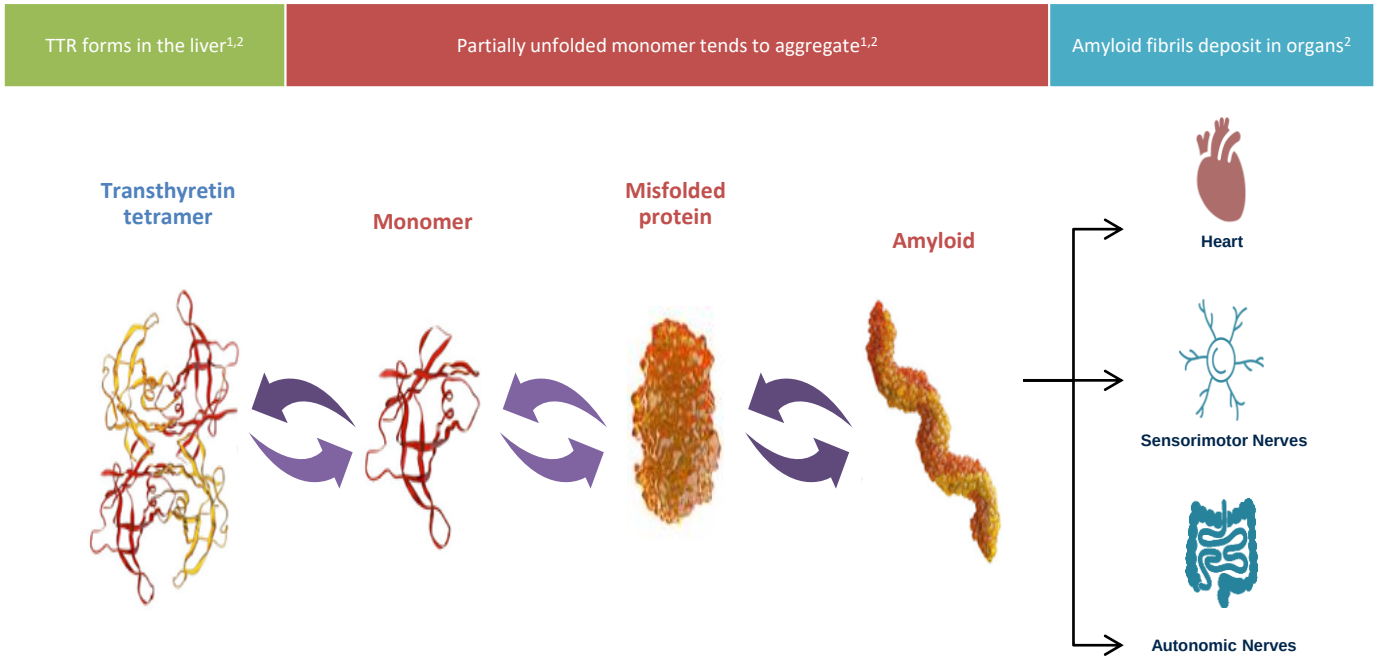
D. Eplonotersen: investigational therapy for potential treatment of polyneuropathy of hereditary ATTR amyloidosis in adults; investigational therapy for potential treatment of cardiomyopathy of ATTR amyloidosis

Therapeutic Approaches

3. Breakdown TTR protein
    Doxycycline + TUDCA (tauroursodeoxcholic acid)

4. CRISPR Gene Editing?

Amyloid Formation in ATTR Amyloidosis: One disease with multiple manifestations



Therapeutic Approaches

Back to our patient:

Only current option is a stabilizer

Cannot afford his tafamidis copay
and does not quality for assistance

Therapeutic Approaches

1. There are patients whose needs remain unmet by current treatments
   - Affordability
   - Access
2. Current TTR silencer therapies are only approved for hereditary neuropathy
3. What about stabilizer non-responders – those who progress despite a stabilizer?
4. Quality of life remains a significant issue

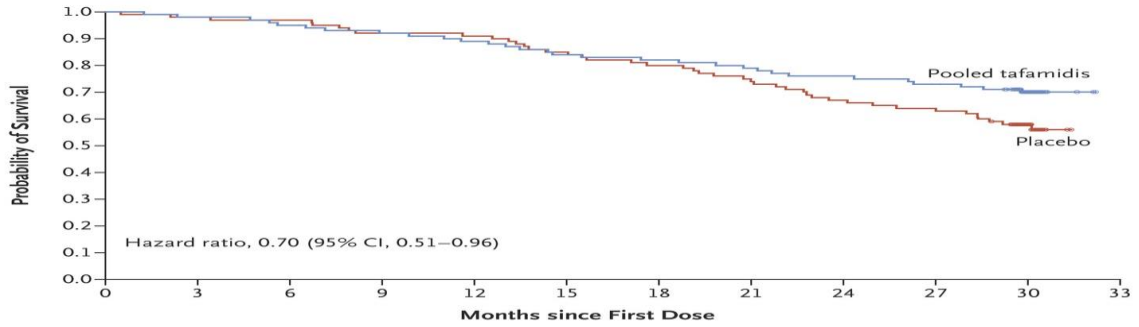
Tafamidis

ATTR-ACT: Primary Analysis and Components

A Primary Analysis, with Finkelstein–Schoenfeld Method

	No. of Patients	P Value from Finkelstein–Schoenfeld Method	Win Ratio (95% CI)	Patients Alive at Mo 30 *no. (%)*	Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30 *per patient per yr*
Pooled Tafamidis	264	<0.001	1.70 (1.26–2.29)	186 (70.5)	0.30
Placebo	177			101 (57.1)	0.46

B Analysis of All-Cause Mortality



No. at Risk (cumulative no. of events)

Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)

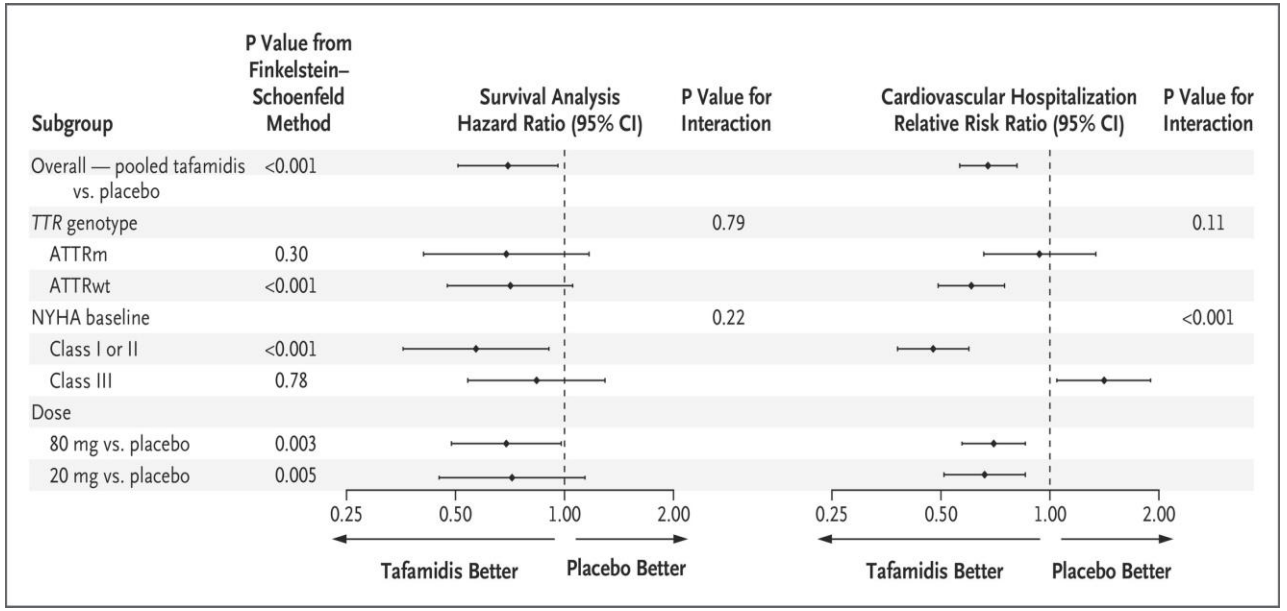
C Frequency of Cardiovascular-Related Hospitalizations

	No. of Patients	No. of Patients with Cardiovascular- Related Hospitalizations *total no. (%)*	Cardiovascular- Related Hospitalizations *no. per yr*	Pooled Tafamidis vs. Placebo Treatment Difference *relative risk ratio (95% CI)*
Pooled Tafamidis	264	138 (52.3)	0.48	0.68 (0.56–0.81)
Placebo	177	107 (60.5)	0.70	

The NEW ENGLAND JOURNAL of MEDICINE

Tafamidis

ATTR-ACT: Overall and Subgroup Results as Calculated with the Use of the Finkelstein–Schoenfeld Method, All-Cause Mortality, and Cardiovascular-Related Hospitalizations.



The NEW ENGLAND JOURNAL of MEDICINE

Tafamidis is still unavailable to large group of patients: Access

- 107 ATTR patients, median age was 83.9 years, 79% were men, and 63 (59%) of them were on tafamidis

- Demographics and baseline cardiovascular risk factors did not differ significantly between those on vs off tafamidis
  - Higher proportion of NYHA class III or IV heart failure in those off tafamidis (76% vs 57%, $P < 0.01$)

- The most common reasons patients were not on tafamidis included:
  1. delays in obtaining the drug or financial barriers (59%)
  2. NYHA class IV heart failure (19.5%)

- Patients taking tafamidis had a significantly higher median survival compared to those not on tafamidis (median survival 6.70 vs 1.43 years, $P < 0.0001$). Our study demonstrates significantly improved survival in ATTR patients taking tafamidis

Hussain…Sarswat et al.
https://doi.org/10.1016/j.cpcardiol.2022.101358

Diflunisal

Generic nonsteroidal anti-inflammatory drug (NSAID)

Binds to and stabilizes TTR tetramer in a manner similar to tafamidis

Use of diflunisal is controversial as an NSAID with possible adverse effects

- gastrointestinal bleeding
- renal dysfunction
- fluid retention
- hypertension that may precipitate heart failure

Unmet Need: Sicker patients

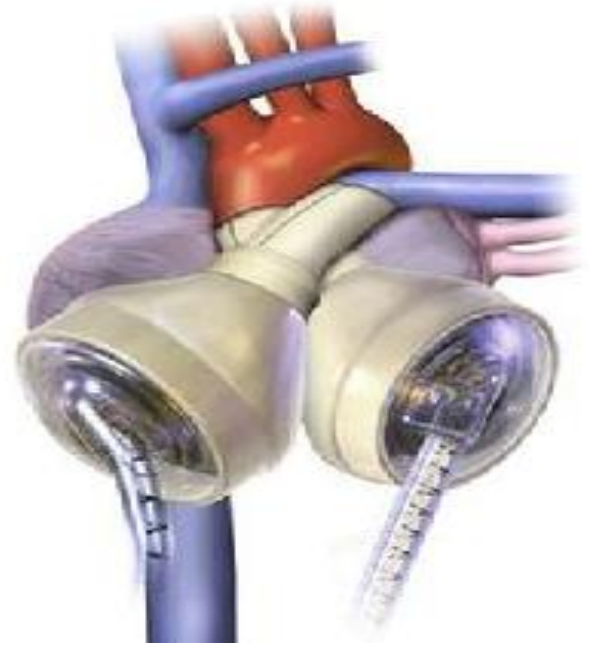
Table 2. Clinical Classifications of Heart Failure Severity.*

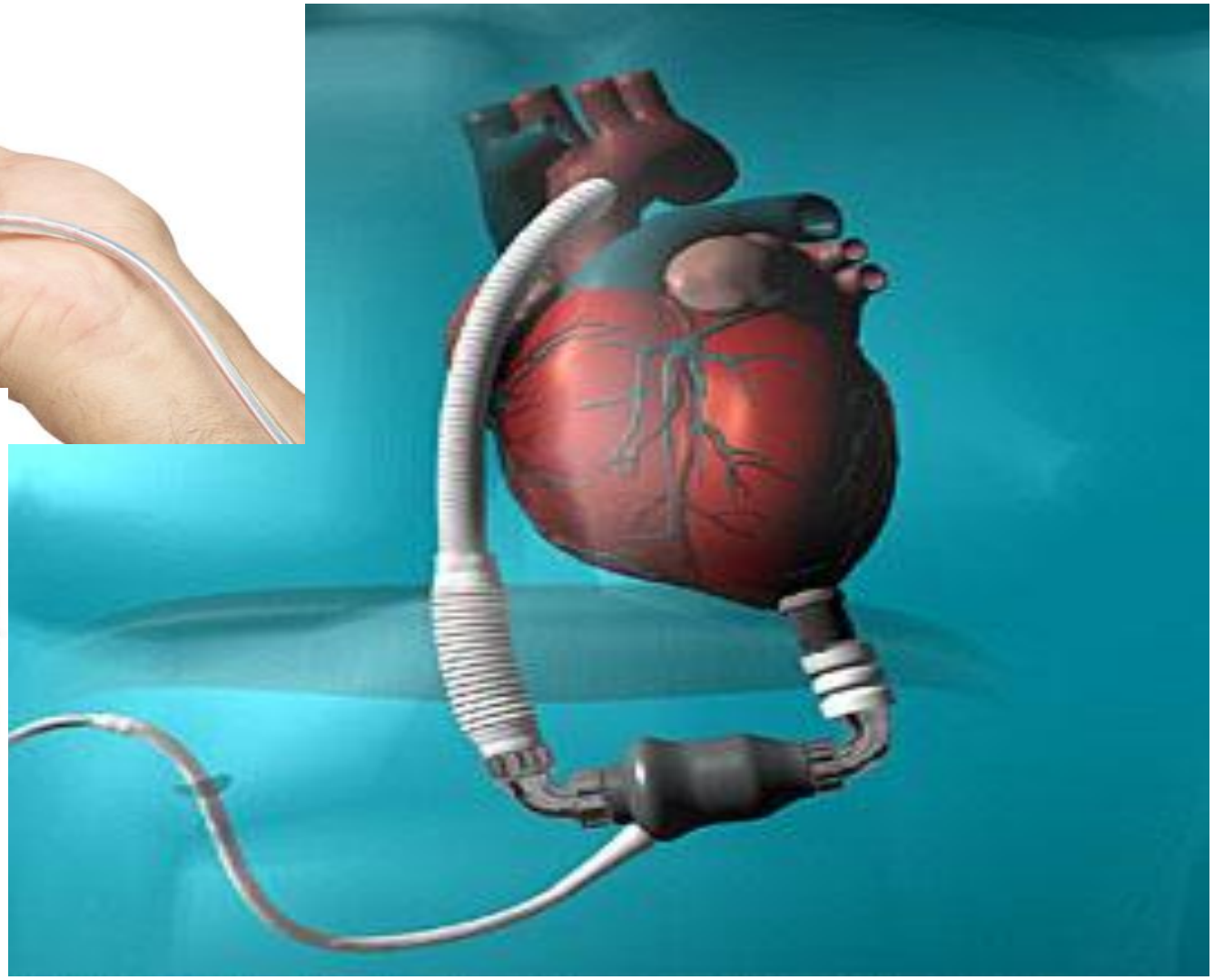
NYHA Functional Classification		ACC–AHA Stages of Heart Failure	
Class I	No limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea	Stage A	At high risk for heart failure; no identified structural or functional abnormality; no signs or symptoms
Class II	Slight limitation of physical activity; comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea	Stage B	Developed structural heart disease that is strongly associated with the development of heart failure but without signs or symptoms
Class III	Marked limitation of physical activity; comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnea	Stage C	Symptomatic heart failure associated with underlying structural heart disease
Class IV	Unable to carry on any physical activity without discomfort; symptoms present at rest; if any physical activity is undertaken, discomfort is increased	Stage D	Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy

* The American College of Cardiology (ACC)–American Heart Association (AHA) classification is from Hunt et al.[8] The New York Heart Association (NYHA) functional classification is from the Criteria Committee of the New York Heart Association.[12]

Other new promising therapies are not studied in this population such as Barostim, CCM, entresto, vericiguat, omecamtiv

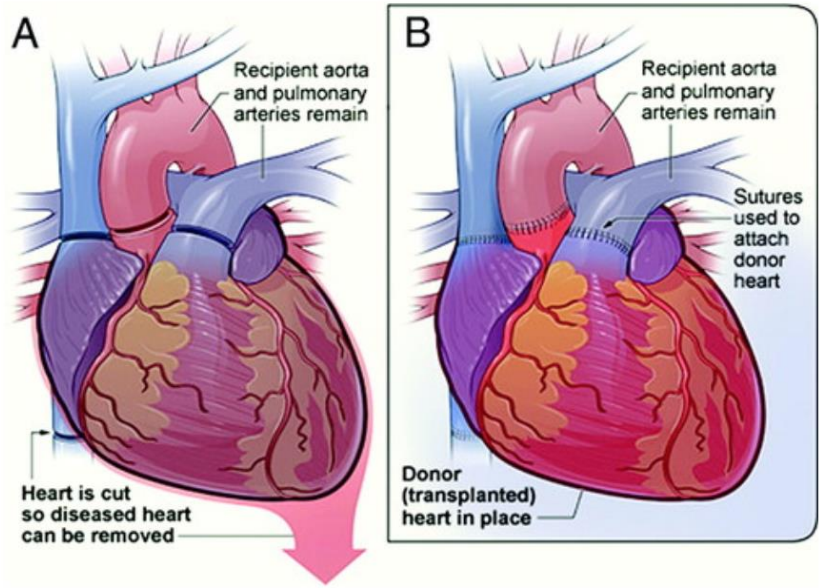
Unmet Need: NYHA 3 and 4





Unmet Need: NYHA 3 and 4

- Unmet



Download figure | Download PowerPoint

Figure. A shows where the diseased heart is cut for removal. **B** shows where the transplanted healthy heart is sutured (stitched) to the recipient's arteries and veins. Figure reproduced from the National Heart, Lung and Blood Institute, National Institutes of Health.[1]

Status 1	• VA ECMO • Non-dischargeable, surgically implanted, non-endovascular biventricular support device • MCSD with life-threatening ventricular arrhythmia
Status 2	• Non-dischargeable, surgically implanted, non-endovascular LVAD • IABP • V-tach / V-fib, mechanical support not required • MCSD with device malfunction/mechanical failure • TAH, BiVAD, RVAD, or VAD for single ventricle patients • Percutaneous endovascular MCSD
Status 3	• Dischargeable LVAD for discretionary 30 days • Multiple inotropes or single high-dose inotrope with continuous hemodynamic monitoring • VA ECMO after 7 days; percutaneous endovascular circulatory support device or IABP after 14 days • Non-dischargeable, surgically implanted, non-endovascular LVAD after 14 days • MCSD with one of the following: device infection, hemolysis, pump thrombosis, right heart failure, mucosal bleeding, aortic insufficiency
Status 4	• Dischargeable LVAD without discretionary 30 days • Inotropes without hemodynamic monitoring • Retransplant • Diagnosis of one of the following: congenital heart disease (CHD), ischemic heart disease with intractable angina, hypertrophic cardiomyopathy, restrictive cardiomyopathy, amyloidosis
Status 5	• On the waitlist for at least one other organ at the same hospital
Status 6	• All remaining active candidates

Source: U.S. Department of Health and Human Services. Organ Procurement and Transplantation Network. Adult Heart Allocation. https://optn.transplant.hrsa.gov/learn/professional-education/adult-heart-allocation. Accessed May 7, 2018.

Quality of Life in ATTR Amyloidosis with Cardiomyopathy

- Shortness of breath, leg swelling, fatigue and eventually cachexia
- Intracardiac conduction disorders and arrhythmias, particularly atrial fibrillation.
- In patients with ATTR-PN, sensory, motor and autonomic fibers are involved
  - paresthesia, hypoesthesia, numbness and pain progressing from hands and feet to arms and legs.
- In more advanced stages, large-fiber neuropathy can develop, eventually leading to wheelchair or bed confinement.
- Autonomic dysfunction can manifest at different disease stages:
  - arrhythmias
  - orthostatic hypotension
  - gastrointestinal, genital and urinary disturbances
  - Typical symptoms are palpitations, fatigue, postural dizziness, blurred vision, syncope, slow digestion, post-prandial nausea, vomit, dysuria, urinary retention, pollakiuria, stress incontinence and erectile dysfunction.

Passini et al. Eur J Clin Invest. 2021 Nov; 51(11): e13598.

Back to the Patient

- Unable to get tafamidis
- Progression of symptoms and had trouble making it through his daughter's wedding
- Has been on diflunisal for 6 months
- Sends me messages frequently asking about the availability of the new drugs that could help him feel better
- We continue to need more options to help improve the quality of life of our patients

Patisiran APOLLO-B Phase 3 Study

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

N = 360
Patient Population

- ATTR amyloidosis; wild-type or any TTR mutation
  - With or without background TTR stabilizer
- Confirmed cardiomyopathy and medical history of symptomatic heart failure
- NYHA ≤III; minimum walk and NT-proBNP limits at baseline

1:1 RANDOMIZATION

Patisiran
IV q3w†
0.3 mg/kg

or

Placebo
IV q3w†

Primary Endpoint

- Change in 6-MWT at 12 months

Secondary Endpoints

- Cardiomyopathy symptoms and health status (KCCQ)
- Death and hospitalization outcomes*

Selected Exploratory Endpoints

- Cardiac biomarkers

Open-Label Extension

ClinicalTrials.gov Identifier: NCT03997383

APOLLO-B

Results presented at ISA and HFSA – Sep ‘22

sNDA submitted 8 Dec 2022

Concomitant use of local standard of care allowed during study, including TTR stabilizer

† To reduce likelihood of infusion-related reactions, patients receive following premedication or equivalent at least 60 min. before each study drug infusion: 10 mg (low dose) dexamethasone; oral acetaminophen; H1 and H2 blockers

NYHA: New York Heart Association; NT-proBNP: N-terminal pro b-type natriuretic peptide; 6-MWT: 6-Minute Walk Test

* Composite all-cause mortality, frequency of CV events, and change from baseline in 6-MWT; Composite all-cause mortality, frequency of all-cause hospitalizations and urgent HF visits in patients not on tafamidis at baseline; Composite all-cause mortality, frequency of all-cause hospitalizations and urgent HF visits in overall population

sNDA Submission for ONPATTRO (patisiran) Announced December 8, 2022

Alnylam Submits Supplemental New Drug Application (sNDA) to U.S. Food and Drug Administration (FDA) for ONPATTRO® (patisiran) for the Treatment of the Cardiomyopathy of ATTR Amyloidosis

– sNDA Submission is Based on Findings from the APOLLO-B Phase 3 Study That Showed Patisiran Demonstrated Significant Improvement on Functional Capacity, Health Status and Quality of Life Compared to Placebo at Month 12 –

– Study Also Demonstrated Encouraging Safety Profile in Patients with Cardiomyopathy of ATTR Amyloidosis –

December 08, 2022 04:00 PM Eastern Standard Time

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), the leading RNAi therapeutics company, today announced the submission of its supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) for patisiran, an investigational RNAi therapeutic in development for the treatment of transthyretin-mediated (ATTR) amyloidosis with cardiomyopathy. Patisiran is the established name for ONPATTRO®, which is currently approved by the U.S. FDA for the treatment of the polyneuropathy of hereditary ATTR amyloidosis in adults.

Patient Demographics and Characteristics

Baseline Characteristics Were Comparable Between Placebo and Patisiran Arms

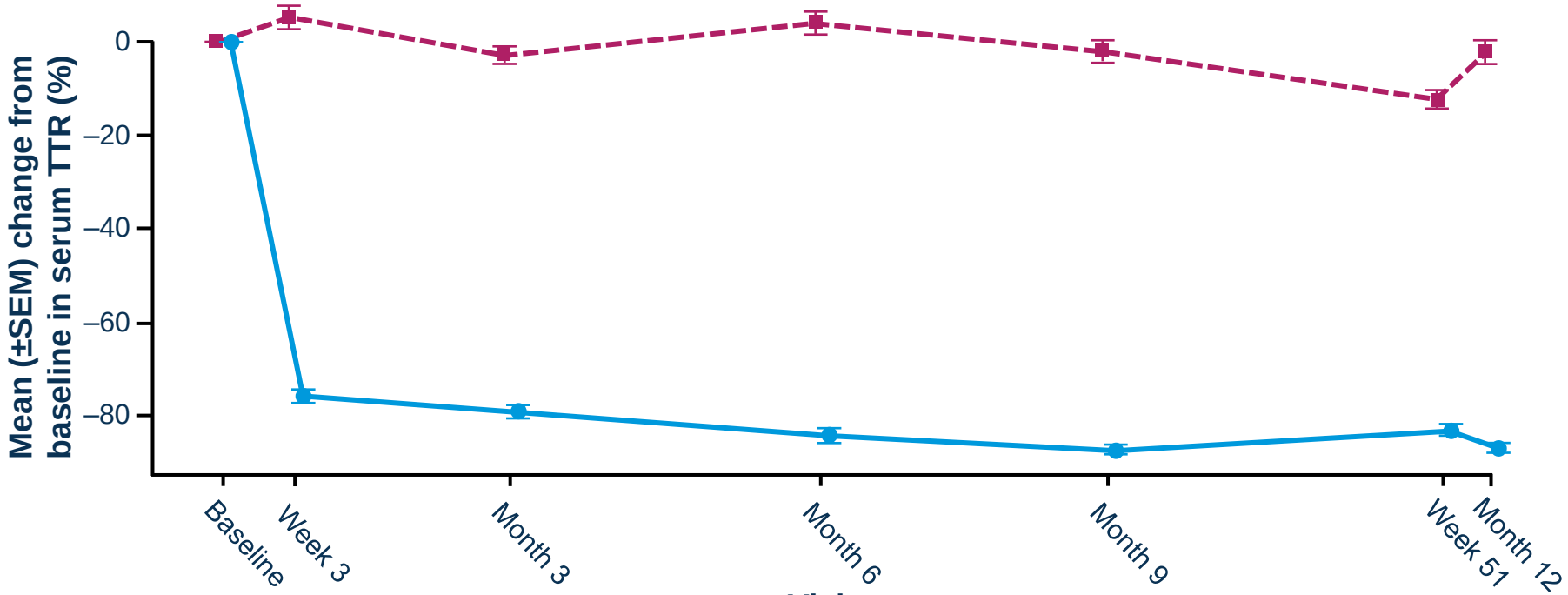
Characteristic	Patisiran (n=181)	Placebo (n=178)
Age (years), median (range)	76.0 (47–85)	76.0 (41–85)
Male sex, n (%)	161 (89.0)	160 (89.9)
wtATTR amyloidosis, n (%)	144 (79.6)	144 (80.9)
Gillmore et al ATTR Amyloidosis Stage[a], n (%)		
Stage 1	124 (68.5)	120 (67.4)
Stage 2	46 (25.4)	45 (25.3)
Stage 3	11 (6.1)	13 (7.3)
Baseline tafamidis use, n (%)	46 (25.4)	45 (25.3)
NYHA Class, n (%)		
Class I	10 (5.5)	15 (8.4)
Class II	156 (86.2)	150 (84.3)
Class III	15 (8.3)	13 (7.3)
6-MWT, m, mean (SD)	360.5 (102.3)	374.6 (102.4)
KCCQ-OS, points, mean (SD)	69.8 (21.2)	70.3 (20.7)
NT-proBNP level, ng/L, median (IQR)	2008 (1135–2921)	1813 (952–3079)

[a]The ATTR amyloidosis disease staging used for this study stratifies patients with ATTR amyloidosis with cardiomyopathy (both hATTR and wtATTR) into prognostic categories using the serum biomarkers NT-proBNP and eGFR. Patients are categorized as follows: Stage 1 (lower risk): NT-proBNP ≤3000 ng/L and eGFR ≥45 ml/min/1.73 m^2; Stage 2 (intermediate risk): all other patients not meeting criteria for Stages 1 or 3; Stage 3 (higher risk): NT-proBNP >3000 ng/L and eGFR <45 ml/min/1.73 m^2 (Gillmore et al. *Eur Heart J*. 2018; 7:2799-806). **Abbreviations:** 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; eGFR, estimated glomerular filtration rate; hATTR, hereditary transthyretin-mediated; IQR, interquartile range; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; m, meter; NT-proBNP, *N*-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation; wtATTR, wild-type transthyretin-mediated.

Rapid and Sustained Serum TTR Reduction with Patisiran

- Patisiran achieved a mean (SD) percent reduction in serum TTR of 86.8% (13.6) at Month 12

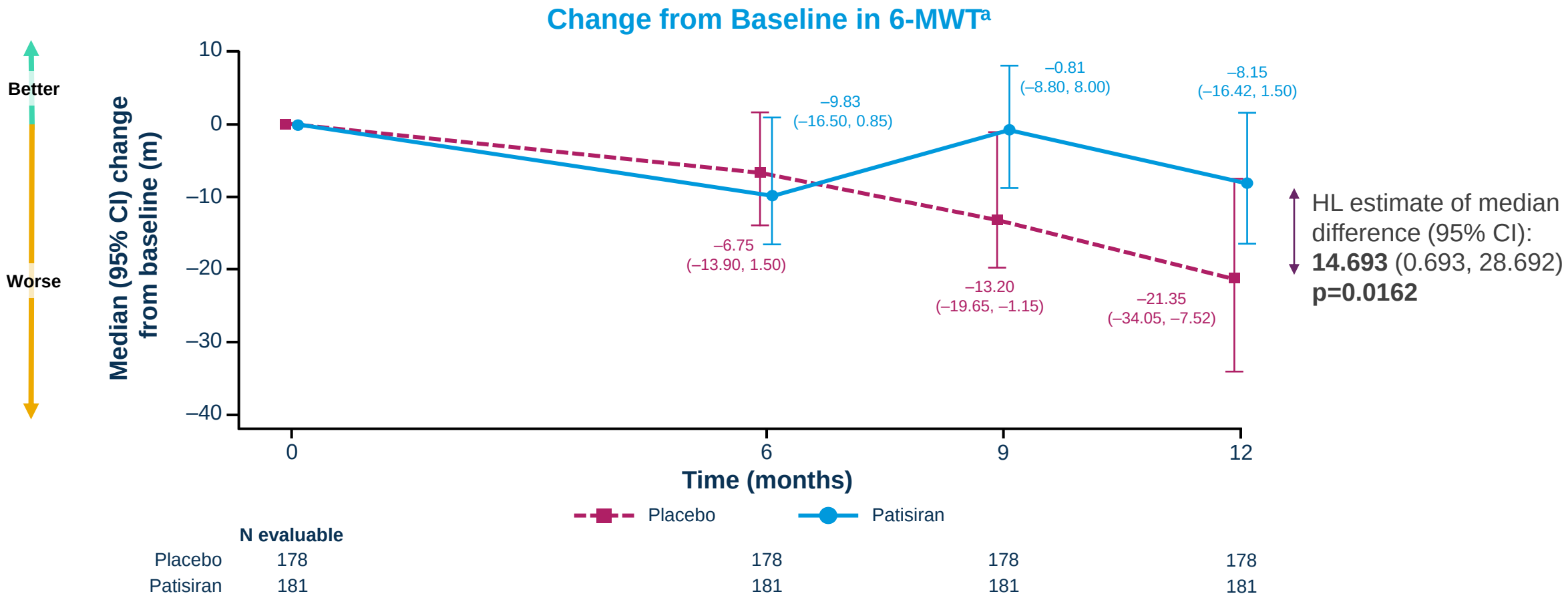
Change from Baseline in TTR Levels[a]



N evaluable							
Placebo	178	170	153	162	162	151	164
Patisiran	181	169	152	164	167	144	158

[a]At baseline mean (SD) serum TTR was 235.32 (68.05) mg/L in the patisiran group and 244.77 (73.17) mg/L in the placebo group. At Month 12 mean (SD) serum TTR was 30.93 (33.60) mg/L in the patisiran group and 229.40 (77.15) mg/L in the placebo group. **Abbreviations:** SD, standard deviation; SEM, standard error of mean; TTR, transthyretin.

Primary Endpoint: Patisiran Demonstrated Statistically Significant Improvement in Functional Capacity (6-MWT) Compared to Placebo at Month 12

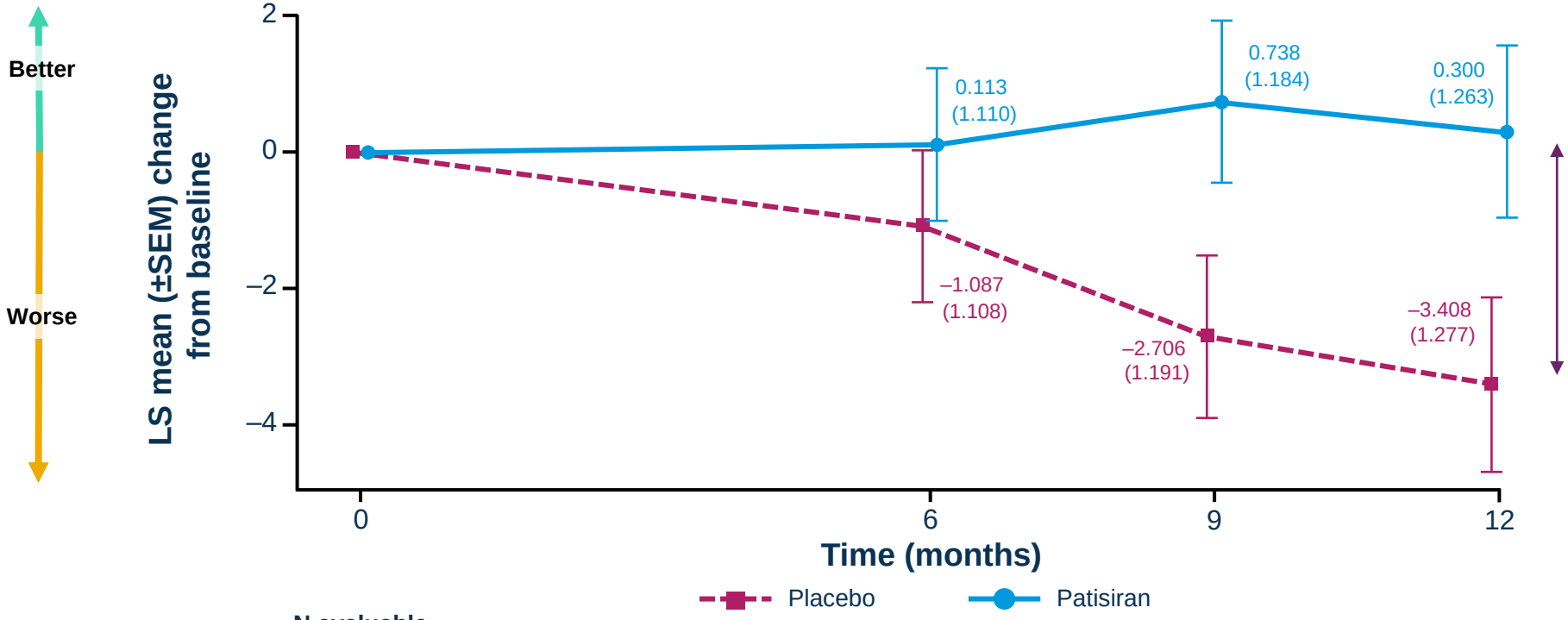


N evaluable				
Placebo	178	178	178	178
Patisiran	181	181	181	181

[a]Primary endpoint analysis based on the stratified Wilcoxon Rank Sum test. Median (95% CI) change from baseline values were based on the observed 6-MWT data and the imputed values; for each patient, the change from baseline was averaged across 100 complete datasets. Missing Month 12 values due to non-COVID-19 death or inability to walk due to progression of ATTR amyloidosis were imputed as the worst 10th percentile change observed across all patients in the double-blind period, capped by the worst possible change for the patient (i.e., 0 minus the patient's baseline 6-MWT). Missing Month 12 data due to other reasons were multiply imputed (assuming data were missing at random) to create 100 complete datasets. At baseline, the median (range) 6-MWT was 358.000 (155.70, 808.00) in the patisiran group and 367.740 (130.00, 740.00) in the placebo group. **Abbreviations:** 6-MWT, 6-minute walk test; ATTR, transthyretin-mediated; CI, confidence interval; HL, Hodges–Lehmann; m, meters.

Secondary Endpoint: Patisiran Demonstrated Statistically Significant Improvement in Health Status and Quality of Life (KCCQ-OS) Compared to Placebo at Month 12

Change From Baseline in KCCQ-OS using MMRM[a]

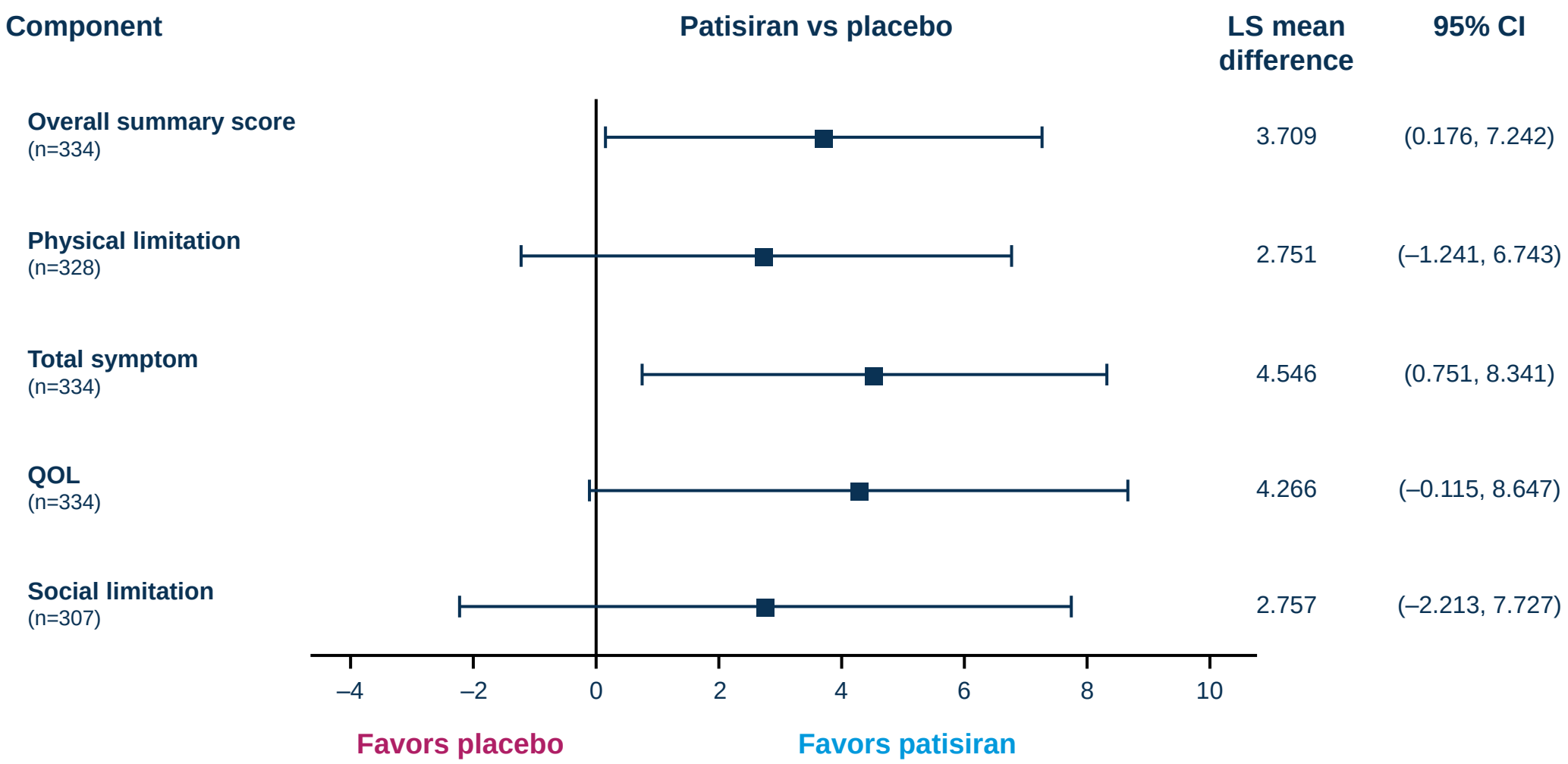


LS mean (SEM) difference:
3.709 (1.796)
p=0.0397

N evaluable				
Placebo	178	170	167	164
Patisiran	181	169	170	170

[a]MMRM model. Missing data not explicitly imputed and assumed to be missing at random. At baseline, the mean (±SD) KCCQ-OS was 69.836 (21.178) in the patisiran group and 70.330 (20.709) in the placebo group. **Abbreviations:** KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary; LS, least squared; MMRM, mixed model repeated measures; SD, standard deviation; SEM, standard error of mean.

Consistent Effects of Patisiran across KCCQ Components of Health Status and QOL



CI, confidence interval; KCCQ, Kansas City Cardiomyopathy Questionnaire; LS, least squares; QOL, quality of life.

Secondary Composite Outcomes Endpoints over 12 Months[a]

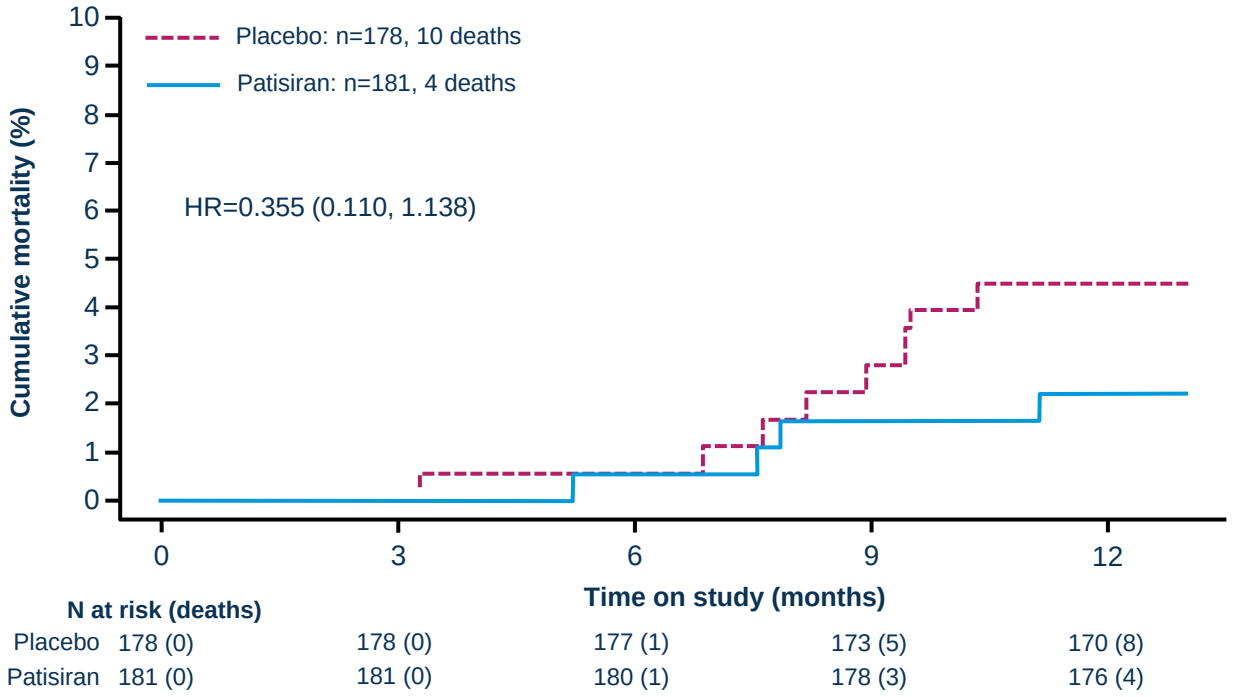
Composite of all-cause mortality, frequency of CV events[b] and change from baseline in 6-MWT over 12 months[a]	
Win ratio (Patisiran vs Placebo)[c]	1.27
95% CI	0.99, 1.61
p-value	0.0574
Composite of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits in patients not on tafamidis at baseline[a,d]	
HR (Patisiran vs Placebo)	0.997
95% CI	0.620, 1.602
Nominal p-value	0.9888
Composite of all-cause mortality and frequency of all-cause hospitalizations and urgent HF visits in the overall study population[a,d]	
HR (Patisiran vs Placebo)	0.883
95% CI	0.582, 1.341
Nominal p-value	0.5609

[a]Deaths, hospitalizations, and urgent HF visits due to COVID-19 excluded from the analysis. Patients who underwent heart transplantation and/or ventricular assist device placement after randomization were handled in the same manner as death in the analysis. [b]CV events were defined as CV hospitalizations and urgent HF visits. [c]The first composite endpoint was analyzed using a generalized rank-based win ratio method stratified by baseline tafamidis use (yes vs. no), which made within-stratum pairwise comparisons for all possible patisiran and placebo patient pairs in a sequential manner (first mortality, then CV events, then 6-MWT). The point estimate, 95% CI and p-value for the stratified win-ratio were based on Dong et al. 2018. [d]The hazard ratio, 95% CI and p-value were derived using an Andersen-Gill model, including treatment arm, type of ATTR amyloidosis, baseline NYHA class, and age group as covariates. For the analysis in the overall population, the model was also stratified by baseline tafamidis use. A hazard ratio <1 represents a favorable outcome for patisiran. **Abbreviations:** 6-MWT, 6-minute walk test; CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; NYHA, New York Heart Association.

All-Cause Mortality over 12-Month Double-Blind Period

- In the overall population, all-cause deaths[a,b] were observed in 10 (5.6%) placebo vs 4 (2.2%) patisiran patients
  - CV-related deaths: placebo 5 (2.8%); patisiran 2 (1.1%)
    - Heart transplant[a]: placebo 2 (1.1%); patisiran 0 (0.0%)
  - HR estimate (patisiran/placebo): 0.355 (95% CI: 0.110, 1.138)
- For patients on baseline tafamidis, all-cause deaths were observed in 3 (6.7%) placebo vs 1 (2.2%) patisiran patient
  - HR (95% CI): 0.296 (0.031, 2.863)
- For patients not on baseline tafamidis, all-cause deaths were observed in 7 (5.3%) placebo vs 3 (2.2%) patisiran patients
  - HR (95% CI): 0.396 (0.102, 1.538)

All-Cause Mortality over 12-Month Double-Blind Period[a,b]



[a]Patients who underwent heart transplantation and/or ventricular assist device placement after randomization were handled the same as death in analyses. [b]Deaths, hospitalizations, and urgent HF visits due to COVID-19 were excluded from event rate calculations. Per SAP definition, for patients who discontinued the study, deaths up to Day 417 were counted in the double-blind period. The figure is truncated at Day 372 (end of Month 12 visit window). 2 placebo deaths that occurred after Month 12 and prior to Day 417 are included in the estimate of HR but not shown on the figure.

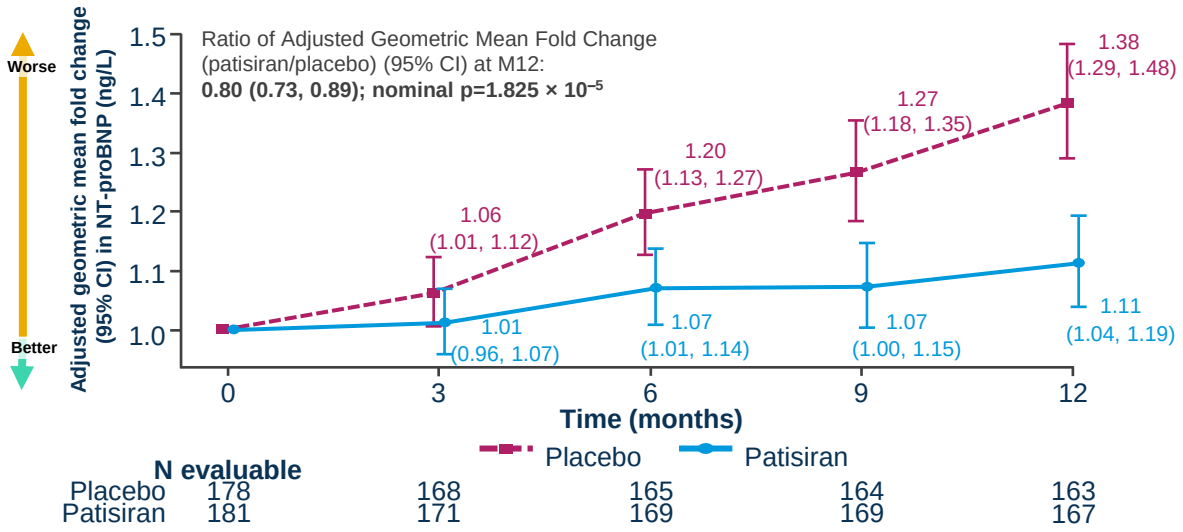
Abbreviations: CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; SAP, statistical analysis plan.

Exploratory Cardiac Biomarkers Support Clinical Relevance of Observed Treatment Effect on Functional Capacity, Health Status and Quality of Life

Patisiran favorably impacted NT-proBNP and troponin I relative to placebo

- Important cardiac biomarkers monitored in clinical practice
- Incorporated in recognized ATTR amyloidosis disease staging systems[1] and expert consensus for defining disease progression[2]

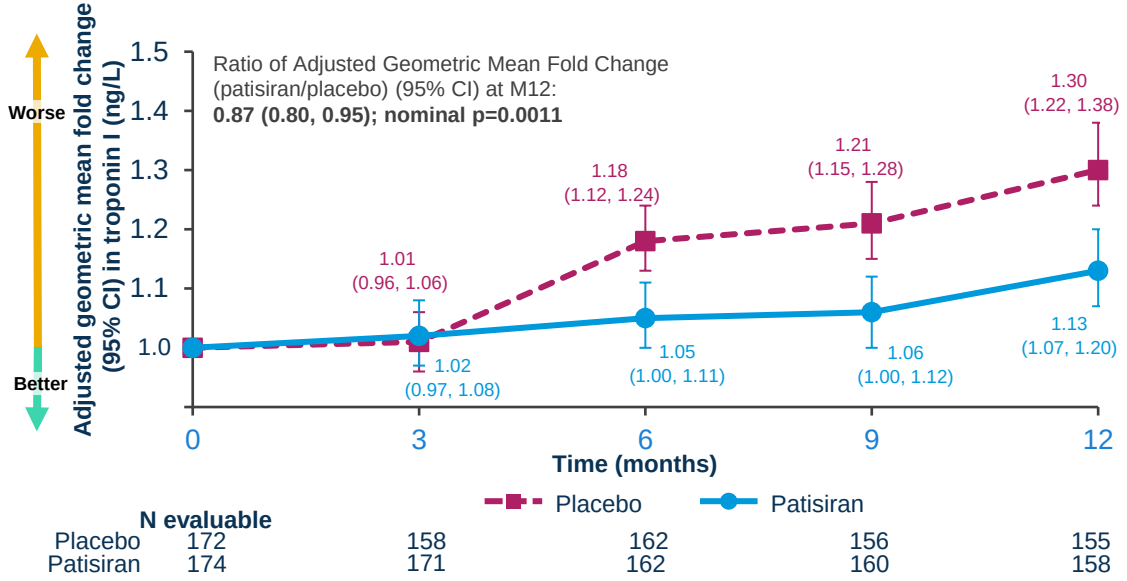
Change from Baseline in NT-proBNP at Month 12[a]



N evaluable

Placebo	178	168	165	164	163
Patisiran	181	171	169	169	167

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



N evaluable

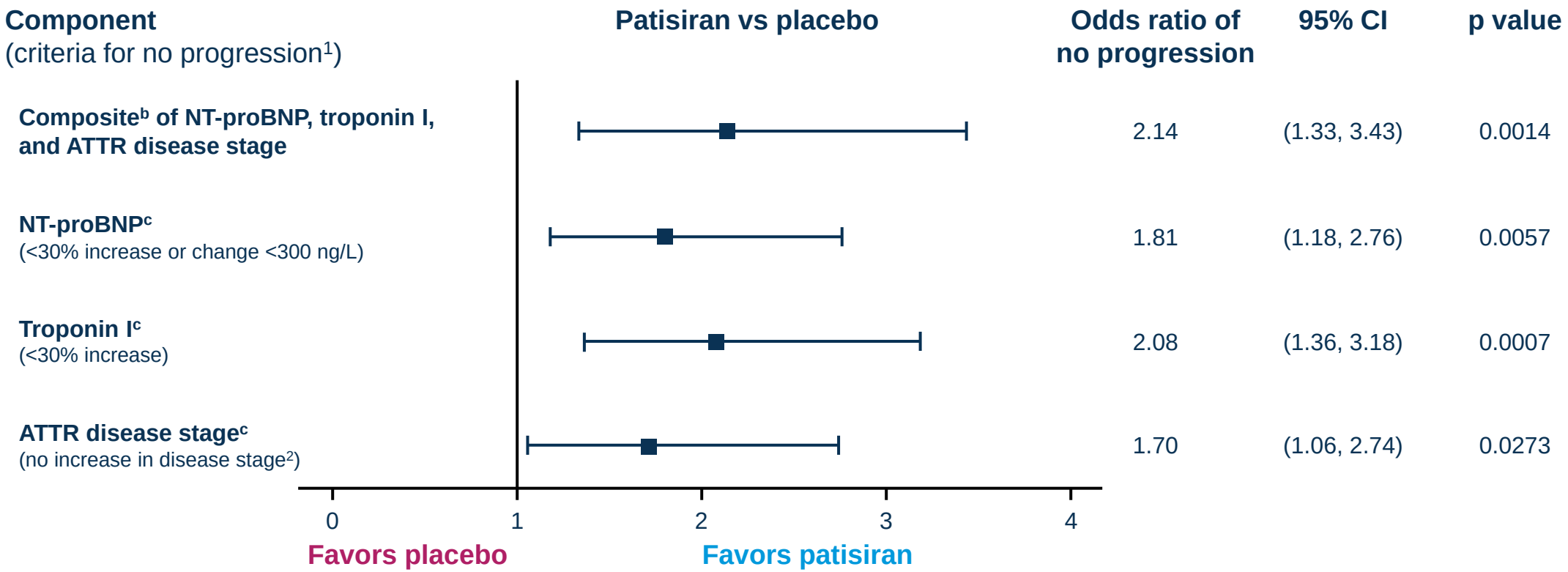
Placebo	172	158	162	156	155
Patisiran	174	171	162	160	158

[a]NT-proBNP is a measure of cardiac stress, with higher values indicating a greater level of cardiac stress. At baseline, median (IQR) NT-proBNP was 2008 (1135–2921) ng/L in the patisiran group and 1813 (952–3079) ng/L in the placebo group. At Month 12, median (IQR) NT-proBNP was 1944 (1158–3726) ng/L in the patisiran group and 2299 (1180–4364) ng/L in the placebo group. Number of evaluable patients at each timepoint are shown. [b]Troponin I is a measure of myocardial injury, with higher values indicating a greater level of myocardial injury. Number of evaluable patients at each timepoint are shown. [c]Progression defined in Garcia-Pavia et al (2021) as ≥30% increase and change ≥300 ng/L for NT-proBNP, as ≥30% increase for troponin I, and as an increase for ATTR disease stage. REFERENCES 1. Pregenzer-Wenzler et al. *JACC Heart Fail* 2020; 8:701-11., 2. Garcia-Pavia et al. *Eur J Heart Fail* 2021; 23:895-905.

Exploratory Analysis Assessing Criteria for Disease Progression in APOLLO-B Patients

- Based on established biomarker thresholds[1], patients in the patisiran group were significantly more likely to show no disease progression compared to patients in the placebo group at Month 12
- In an analysis of NYHA class, worsening occurred more frequently in the placebo group (24.1%) versus the patisiran group (13.6%) at Month 12

Component Analyses of Laboratory Biomarkers of Progression at Month 12[a]

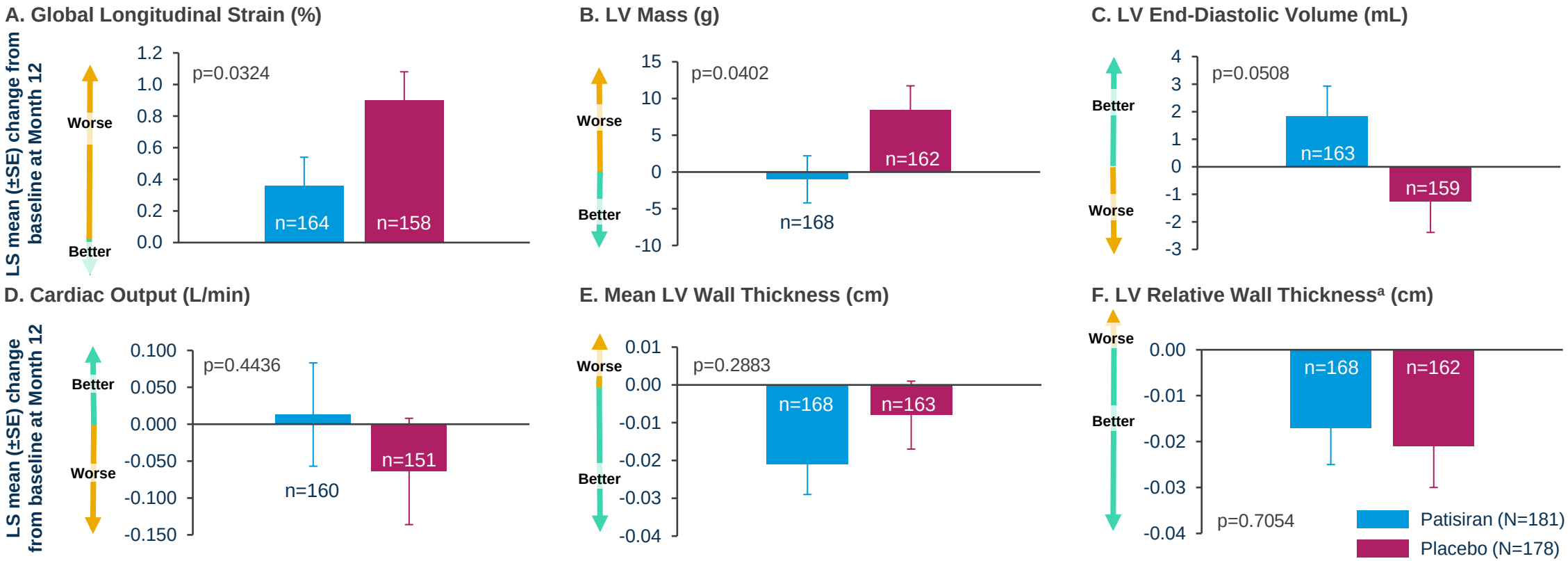


[a]Patients who are missing Month 12 due to COVID-19 are excluded from analysis. Odds ratio and 95% CI from Cochran–Mantel–Haenszel test stratified by baseline tafamidis use. [b]For the composite parameter, the summary presents the odds ratio (95% CI) of no progression on any component (ie, <30% increase or change <300 ng/L in NT-proBNP AND <30% increase in troponin I AND no increase in ATTR disease stage). [c]For each component, the summary presents the odds ratio (95% CI) of no progression on the specified component (ie, <30% increase or change <300 ng/L for NT-proBNP, <30% increase for troponin I, and no increase for ATTR disease stage). **Abbreviations:** ATTR, transthyretin-mediated; CI, confidence interval; NT-proBNP, *N*-terminal pro-brain natriuretic peptide. **References:** 1. Garcia-Pavia P, et al. *Eur J Heart Fail.* 2021 Jun;23(6):895–905. 2. Gillmore JD, et al. *Eur Heart J.* 2018 Aug;39(30):2799–2806.

Exploratory Analysis: Echocardiographic Parameters

- Patisiran demonstrated a benefit or trend toward benefit in change from baseline of most echocardiographic parameters compared with placebo at Month 12

Change from Baseline in Echocardiographic Parameters at Month 12



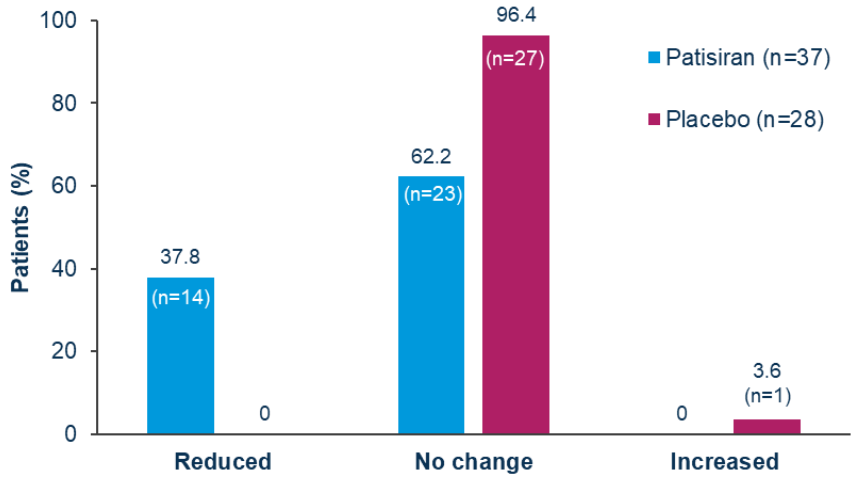
ANCOVA model. Nominal p-value of LS mean difference of patisiran–placebo. [a]Defined as 2 times posterior wall thickness divided by LV diastolic diameter.

Abbreviations: ANCOVA, analysis of covariance; LS, least squared; LV, left ventricular; SE, standard error.

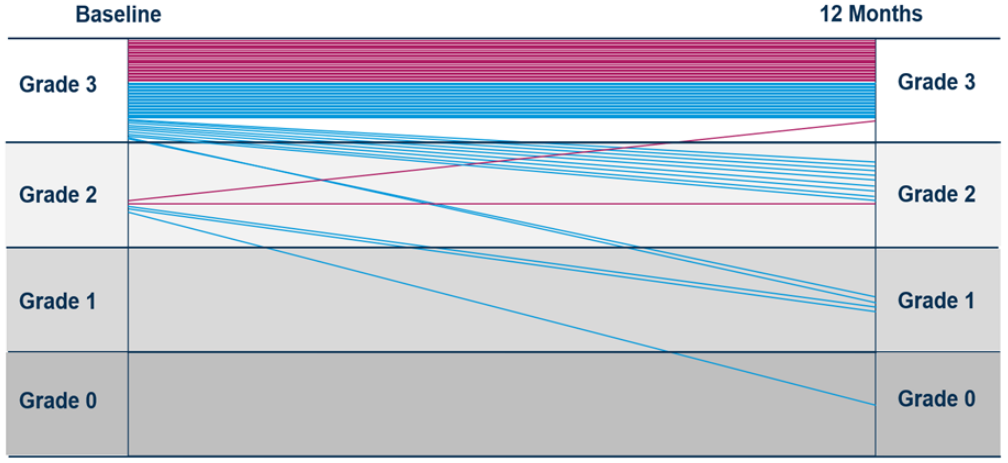
Exploratory Analysis in a Planned Technetium Scintigraphy Cohort

- Tc scintigraphy: non-invasive assessment of cardiac amyloid involvement
  - Perugini grading assesses Tc uptake in myocardium compared to bones; widely used in diagnosis of ATTR amyloidosis
- In 100% of evaluable scintigraphy patients in the patisiran arm (n=37), Perugini grade was reduced or demonstrated no change from baseline at Month 12
  - 14 (37.8%) patients in the patisiran arm demonstrated a reduction from baseline of ≥1 Perugini grade, including 3 (8.1%) patients who reduced by ≥2 Perugini grades at Month 12
  - No patients in the patisiran arm increased from baseline in Perugini grade at Month 12
- Among evaluable patients in the placebo arm (n=28), no patients had a Perugini grade that was reduced from baseline at Month 12

Change from Baseline in Perugini Grade at Month 12 in All Evaluable Patients[a]



Trajectories of All Evaluable Individual Patients in Change from Baseline in Perugini Grade[a]



Analysis includes patients with evaluable data at baseline and Month 12 (n=65)

[a]Analysis includes patients in the patisiran (n=37) and placebo (n=28) arms from the full analysis set with evaluable data at baseline and Month 12. 40 patients in the patisiran group and 37 patients in the placebo group were evaluated at baseline. 37 patients in the patisiran group and 28 patients in the placebo group were evaluated at Month 12.

APOLLO-B Overall Safety Summary[a]

- Majority of AEs were mild or moderate in severity
- AEs ≥5% in patisiran group observed 3% more commonly than in placebo included infusion-related reaction (12.2% vs 9.0%), arthralgia (7.7% vs 4.5%), and muscle spasms (6.6% vs 2.2%)

APOLLO-B Safety Summary

At least one event, n (%)	Patisiran (n=181)	Placebo (n=178)
AEs	165 (91.2)	168 (94.4)
SAEs	61 (33.7)	63 (35.4)
Severe AEs	47 (26.0)	52 (29.2)
AEs leading to treatment discontinuation	5 (2.8)	5 (2.8)
Deaths (safety analysis)[a]	5 (2.8)	8 (4.5)
Deaths (efficacy analysis)[b]	4 (2.2)	10 (5.6)

[a]Safety is reported for the 12-month double-blind treatment period. [b]Deaths in the patisiran arm included sudden cardiac death, undetermined death, death due to HF, and death due to pancreatitis. [c]Efficacy analysis of deaths presented in accordance with pre-defined statistical analysis plan, which excluded deaths due to COVID-19 (1 patisiran patient) and treated cardiac transplant as death (2 placebo patients). **Abbreviations:** AE, adverse event; HF, heart failure; SAE, serious adverse event.

APOLLO-B Cardiac Safety Summary

Cardiac Events over 12-Month Double-Blind Treatment Period

- Compared with placebo, patisiran demonstrated fewer events within Standardized MedDRA Queries (SMQs) exploring potential cardiac safety issues

APOLLO-B Cardiac Safety Summary

At least one event, n (%)	Patisiran (n=181)	Placebo (n=178)
Cardiac disorders (system organ class)[a]	82 (45.3)	100 (56.2)
Cardiac arrhythmia high-level group term	35 (19.3)	48 (27.0)
Supraventricular arrhythmias (including atrial fibrillation)	24 (13.3)	36 (20.2)
Ventricular arrhythmias and cardiac arrest	5 (2.8)	8 (4.5)
Cardiac conduction disorders	8 (4.4)	10 (5.6)
Rate and rhythm disorders not elsewhere classified	5 (2.8)	4 (2.2)
Cardiac failure SMQ (broad)	69 (38.1)	84 (47.2)
QT Prolongation /Torsade de pointes SMQ[b]	12 (6.6)	18 (10.1)

[a]Based on MedDRA "Cardiac Disorders" System Organ Class. [b]There were no identified cases of Torsade de pointes. **Abbreviations:** QT, QT interval; SMQ, Standardized MedDRA (Medical Dictionary for Regulatory Activities) Query.

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 and recurrent all-cause hospitalizations and HF events
- All-cause mortality
- Recurrent CV events
- NT-proBNP

ClinicalTrials.gov Identifier: NCT04153149

HELIOS·B

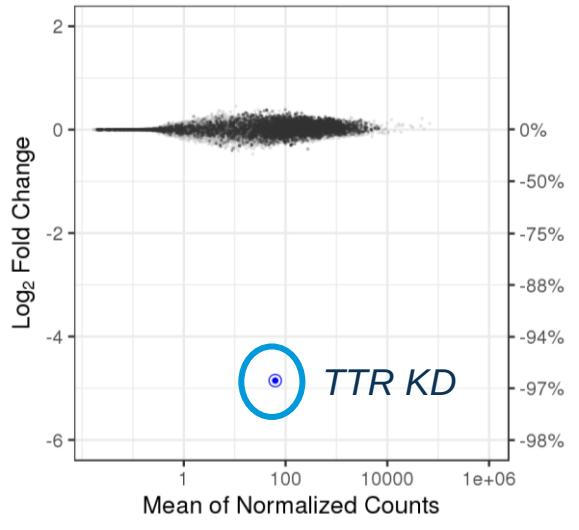
Enrollment complete

Topline results on 30-month endpoint expected **early 2024**

IKARIA™ Platform: Proprietary siRNA Design with Novel Chemistry

Super-specific siRNAs May Enable Higher Doses to Achieve Annual Dosing

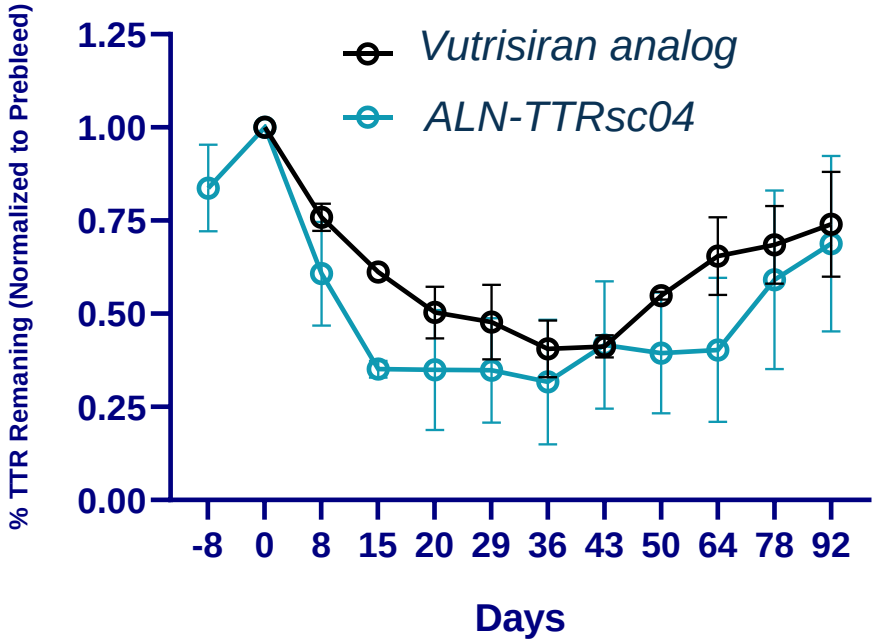
Exquisite specificity



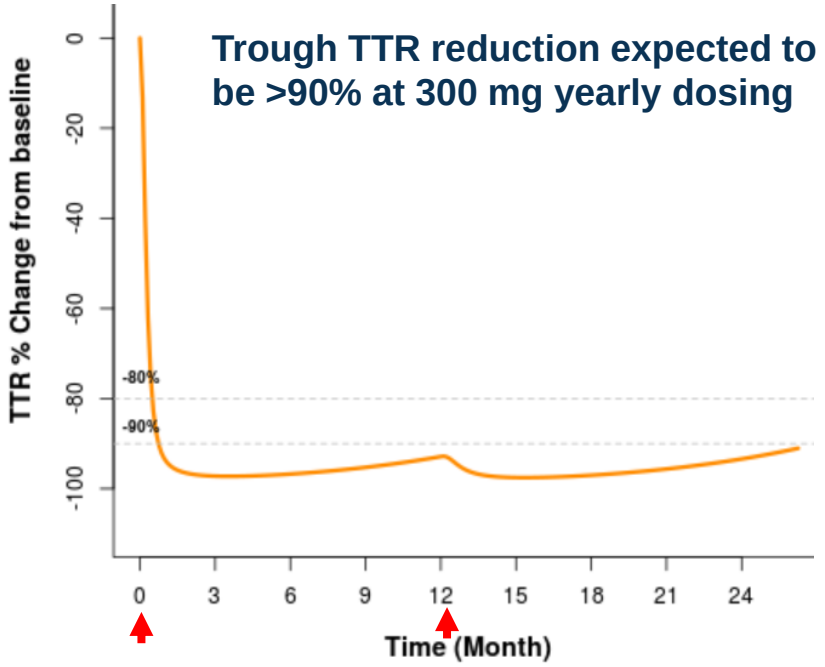
RNAseq analysis

High potency in NHP

0.5 mg/kg single sc dose



Human dose projection



Trough TTR reduction expected to be >90% at 300 mg yearly dosing

Modeling predicts potential for once-a-year dosing in humans with greater than 90% TTR reduction

ALN-TTRsc04 Program Update

ALN-TTRsc04

An Investigational RNAi Therapeutic for Potential Treatment of ATTR Amyloidosis

Initiate Phase 1 healthy volunteer study at or around year-end 2022

Report topline Phase 1 data in late 2023

About ALN-TTRsc04

- Potential for annual subcutaneous dosing regimen with potent and reversible effects
  - >90% serum TTR reduction
- No third-party royalty obligations
- Exclusivity expected to extend beyond 2040
- Alnylam demonstrated track record for rapidly advancing innovation in ATTR amyloidosis
  - E.g., ~3 years from vutrisiran first-in-human readout to positive Phase 3 data in HELIOS-A

Upcoming Milestones Building a Robust TTR Franchise

- Initiate Phase 1 study of ALN-TTRsc04 at or around year-end ’22
- Report data from the evaluation of a vutrisiran biannual dosing regimen in early ‘23
- Submit supplemental New Drug Application (sNDA) for a vutrisiran biannual dosing regimen in early ’23
- Achieve patisiran approval from the U.S. Food and Drug Administration (FDA) in late ’23 for the treatment of the cardiomyopathy of ATTR amyloidosis
- Continue global launches of AMVUTTRA® (vutrisiran) in hATTR amyloidosis with polyneuropathy
- Report topline ALN-TTRsc04 Phase 1 study data in late ’23
- Execute HELIOS-B Phase 3 study, with topline data in early ’24

Reimagining Hypertension Care to Impact Cardiovascular Morbidity and Mortality

Dion Zappe, Ph.D.

Executive Director, Clinical Development

Alnylam@20

Uncontrolled Hypertension is a Global Health Crisis

Hypertension is Highly Prevalent and Carries Substantial Risk of CV Morbidity and Mortality

Primary Hypertension[1] in 7 Major Markets, 2020

~219MM

High CV Risk with Hypertension[2] in 7 Major Markets, 2020[a]

~77MM

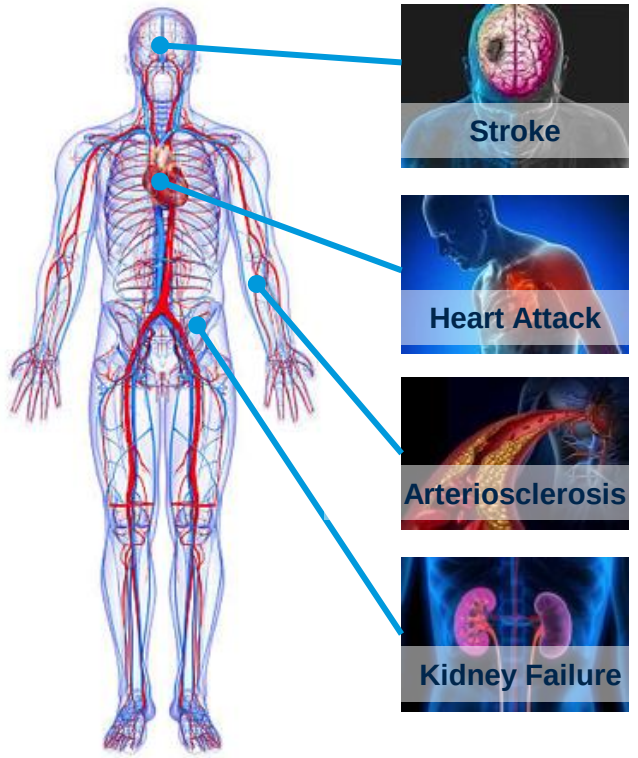
~70%

UNCONTROLLED HYPERTENSION
(>130/80 mmHg despite treatment)[3]

Hypertension risk further exacerbated by **variability in BP control**, **lack of nighttime dipping**, and **poor medication adherence**

Together, contribute to substantial risk of CV morbidity and mortality

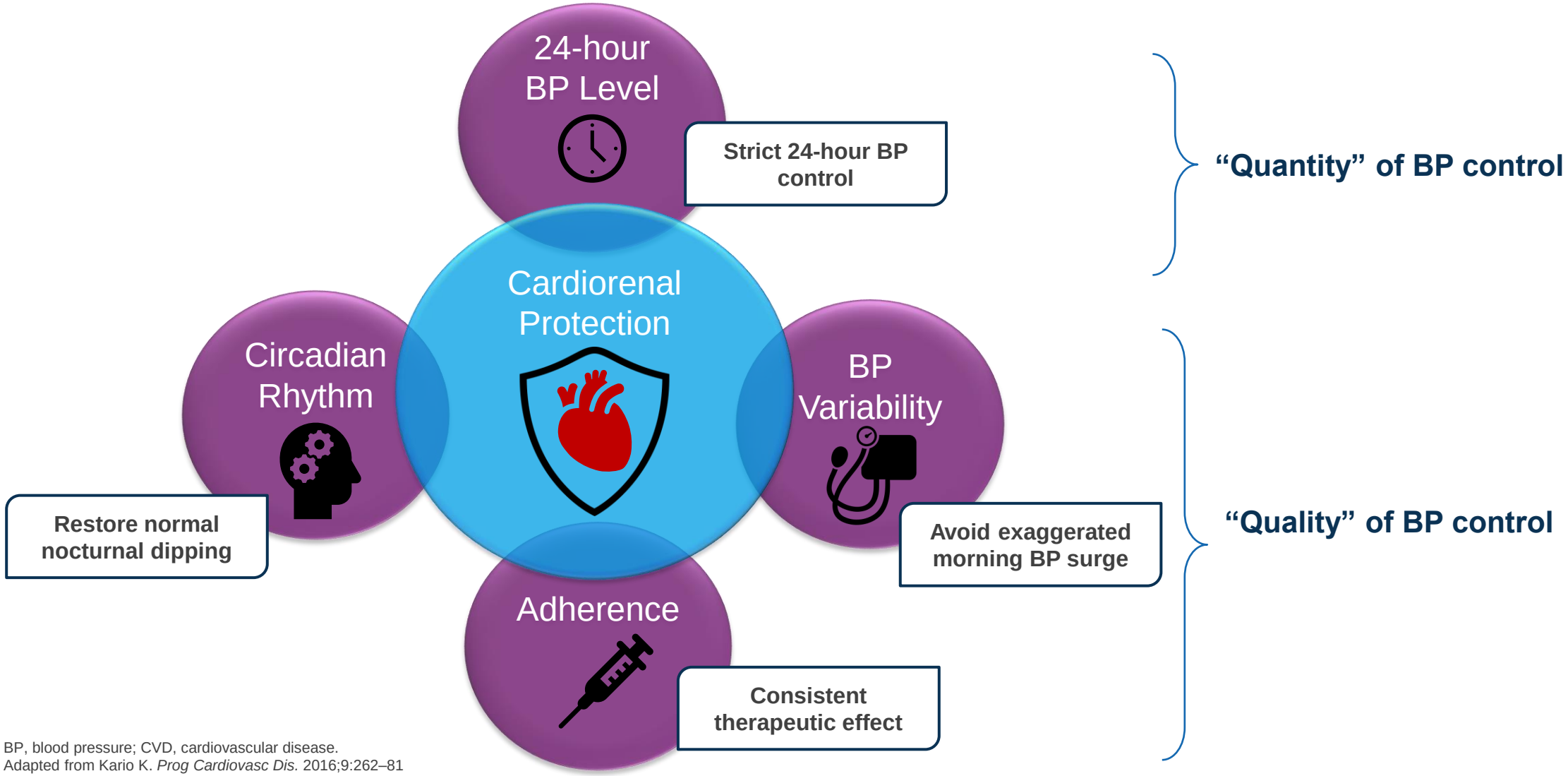
Potential complications of uncontrolled hypertension



[a]Excluding stroke and WOCBP.
BP, blood pressure; CV, cardiovascular; MM, million; mmHg, millimeters of mercury
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. Estimated from multiple sources and internal estimates: Dorans et al. *J Am Heart Assoc* 2018;7:e008888; Al Kibria et al. *Hypertens Res*. 2019;42:1631–43; CDC Hypertension Cascade. 2019; High CV risk: ASCVD risk score ≥20% and/or history of CVD; 3. U.S. Department of Health and Human Services. The Surgeon General's Call to Action to Control Hypertension. Washington, DC: U.S. Department of Health and Human Services, Office of the Surgeon General, 2020.

Targeting "Tonic" BP Control to Potentially Reduce Cardiorenal Risks

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

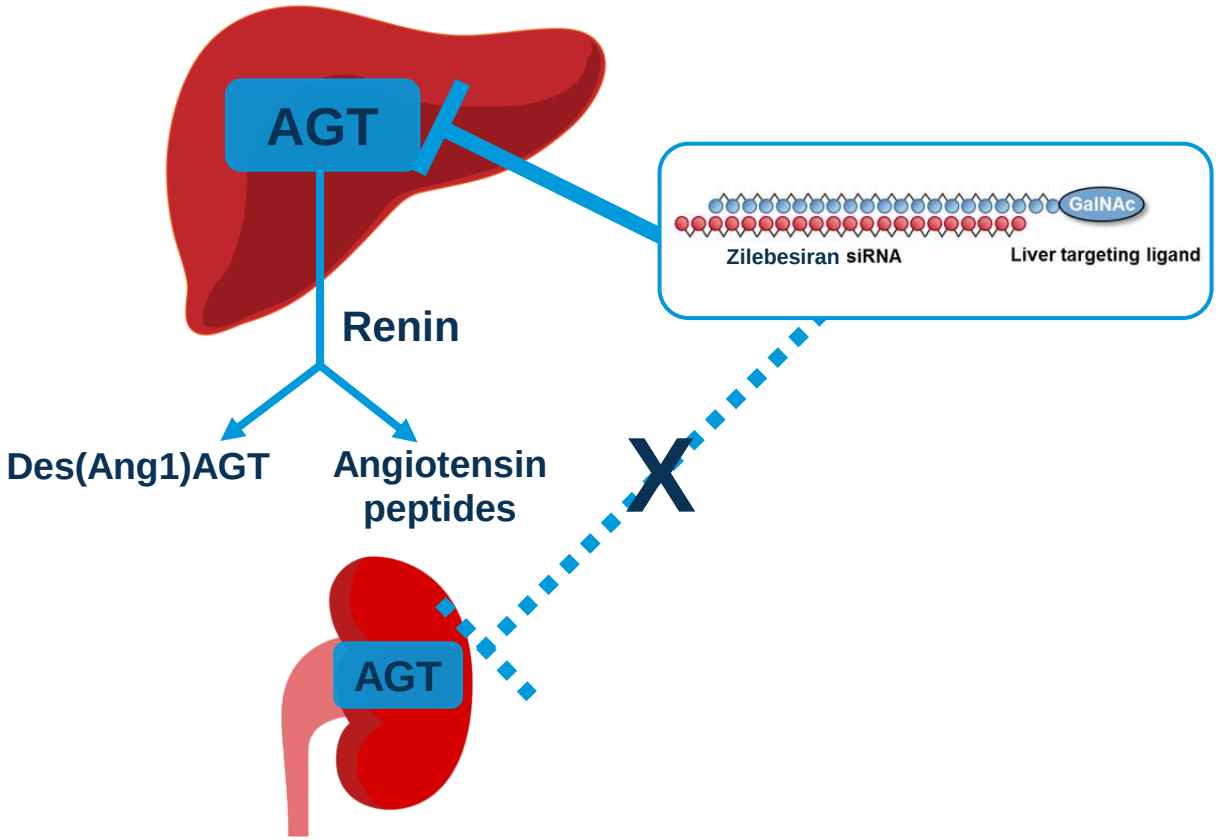


BP, blood pressure; CVD, cardiovascular disease.
Adapted from Kario K. *Prog Cardiovasc Dis.* 2016;9:262–81

Therapeutic Hypothesis for Zilebesiran

Investigational Therapeutic in Development for the Treatment of Hypertension

Liver-specific AGT Knockdown



Potential Mechanistic Advantages

- **Liver-specific silencing of AGT**
- **Prolonged duration of action**
  - Consistent and durable BP response
  - Infrequent dose administration, with potential for improved adherence
- **Facilitates Improved RAAS Inhibition**
  - Potentially avoiding RAAS escape phenomena

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.

Zilebesiran Phase 1 Study

Multicenter Phase 1 Study designed to evaluate safety, tolerability, PK/PD effects of subcutaneous administration of zilebesiran in patients with mild-to-moderate hypertension

Study was conducted in 4 parts	*1. Single Dose Proof-of-Concept*
	2. Multiple Dose Proof-of-Concept
	3. Safety/tolerability of Volume Depletion
	4. Safety/tolerability in Combination with Potent ARB

ARB, angiotensin receptor blocker; PD, pharmacodynamics; PK, pharmacokinetics.

Zilebesiran Single Ascending Dose Phase 1 Study

Part 1

- Patients received either zilebesiran (n=8 per cohort) or placebo (n=4 per cohort)
- Study conducted in outpatient setting with usual activity and dietary sodium intake

Patient Population
(n=12 per dose cohort)

- Adults 18 to 65 years of age
- AOBP SBP >130 and ≤165 mmHg without antihypertensive meds
- 24h ABPM SBP ≥130 mmHg
- BMI ≥18 and ≤35 kg/m^2
- Exclude secondary hypertension
- Treatment naïve or had prior antihypertensives washed out before enrollment[a]

2:1 RANDOMIZATION

- Zilebesiran 10 mg SC x 1
- Zilebesiran 25 mg SC x 1
- Zilebesiran 50 mg SC x 1
- Zilebesiran 100 mg SC x 1
- Zilebesiran 200 mg SC x 1
- Zilebesiran 400 mg SC x 1
- Zilebesiran 800 mg SC x 1

OR

- Placebo SC x 1

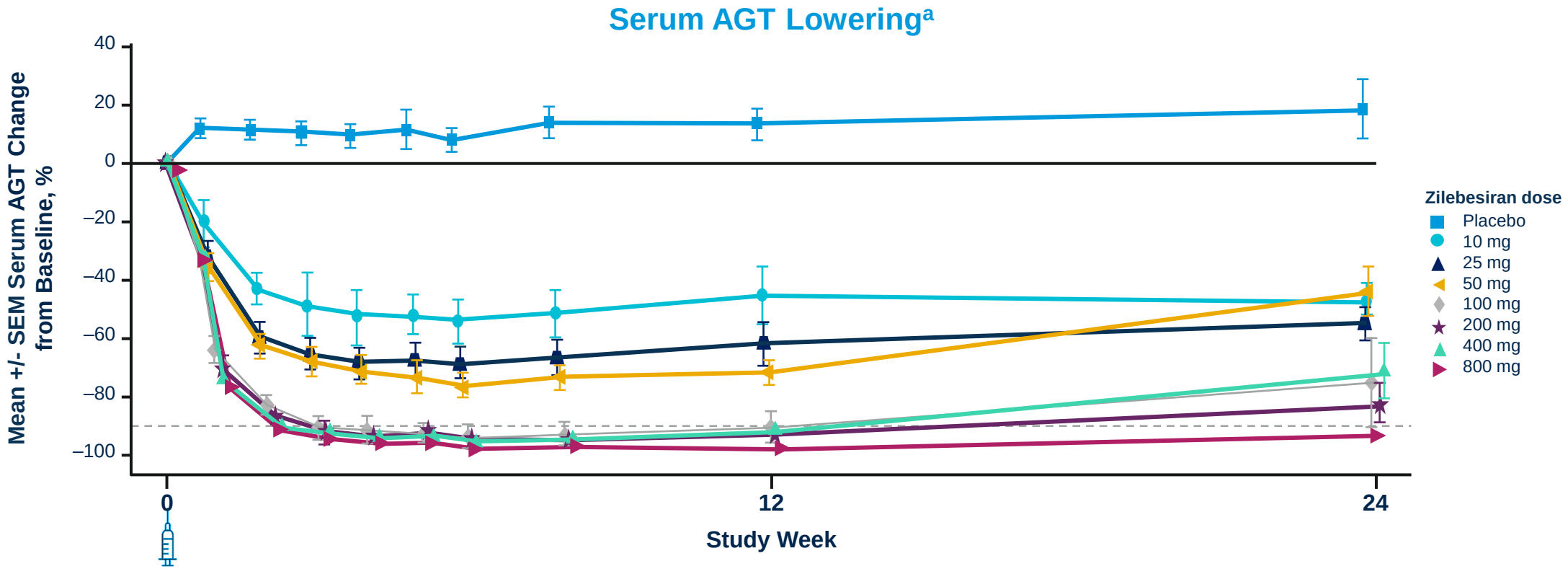
Primary Endpoint
- Safety and tolerability

Secondary Endpoints
- Change from baseline in serum AGT
- Plasma & Urine PK

Exploratory Endpoint
- Change from baseline in SBP/DBP by 24-hour ABPM

[a]Patients previously taking medication for hypertension must be without antihypertensives for ≥2 weeks prior to screening.
ClinicalTrials.gov Identifier: NCT03934307.
ABPM, ambulatory blood pressure monitoring; AGT, angiotensinogen; AOBP, automated office blood pressure; BMI, body mass index; DBP, diastolic blood pressure; PK, pharmacokinetics; SBP, systolic blood pressure; SC, subcutaneous.

Durable Dose-Dependent Lowering of Serum AGT

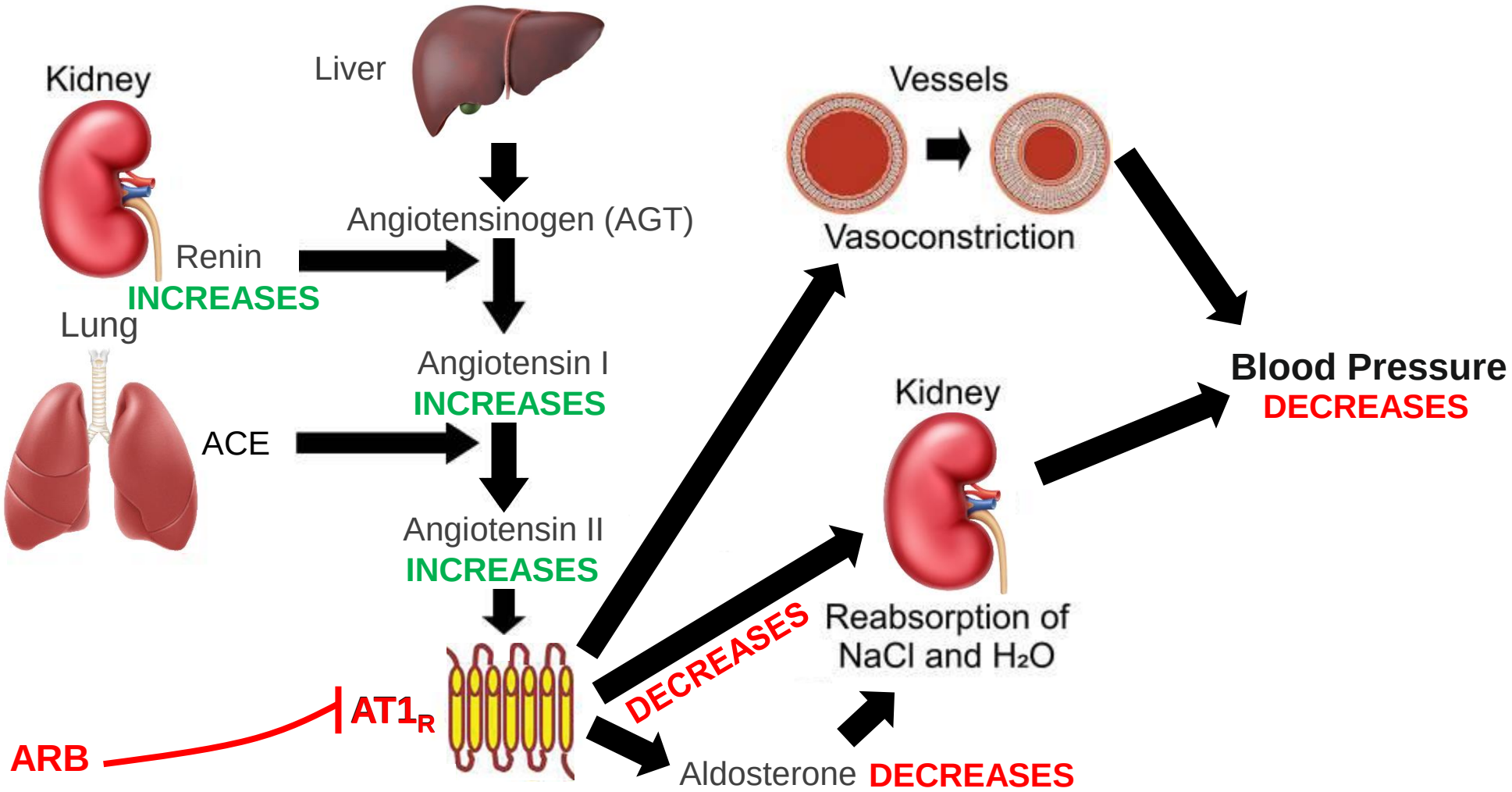


- ≥90% mean reduction in serum AGT from baseline was observed with single doses of zilebesiran ≥100 mg from Week 3 and sustained to Week 12
- All patients who received a single dose of zilebesiran 800 mg maintained >90% mean reduction in serum AGT through Week 24

AGT, angiotensinogen; SEM, standard error of the mean.
[a]Patient numbers at each assessment point: Placebo n=28 baseline and week 12, n=12 week 12; 10mg n=8 baseline and week 12, n=5 week 24; 50mg n=8 baseline, n=7 weeks 12 and 24; 100mg n=8 baseline, n=7 weeks 12 and 24; 25, 200, 400mg n=8 all assessments.
Huang et al. AHA Scientific Sessions 2021.

Renin Angiotensin Aldosterone System (RAAS)

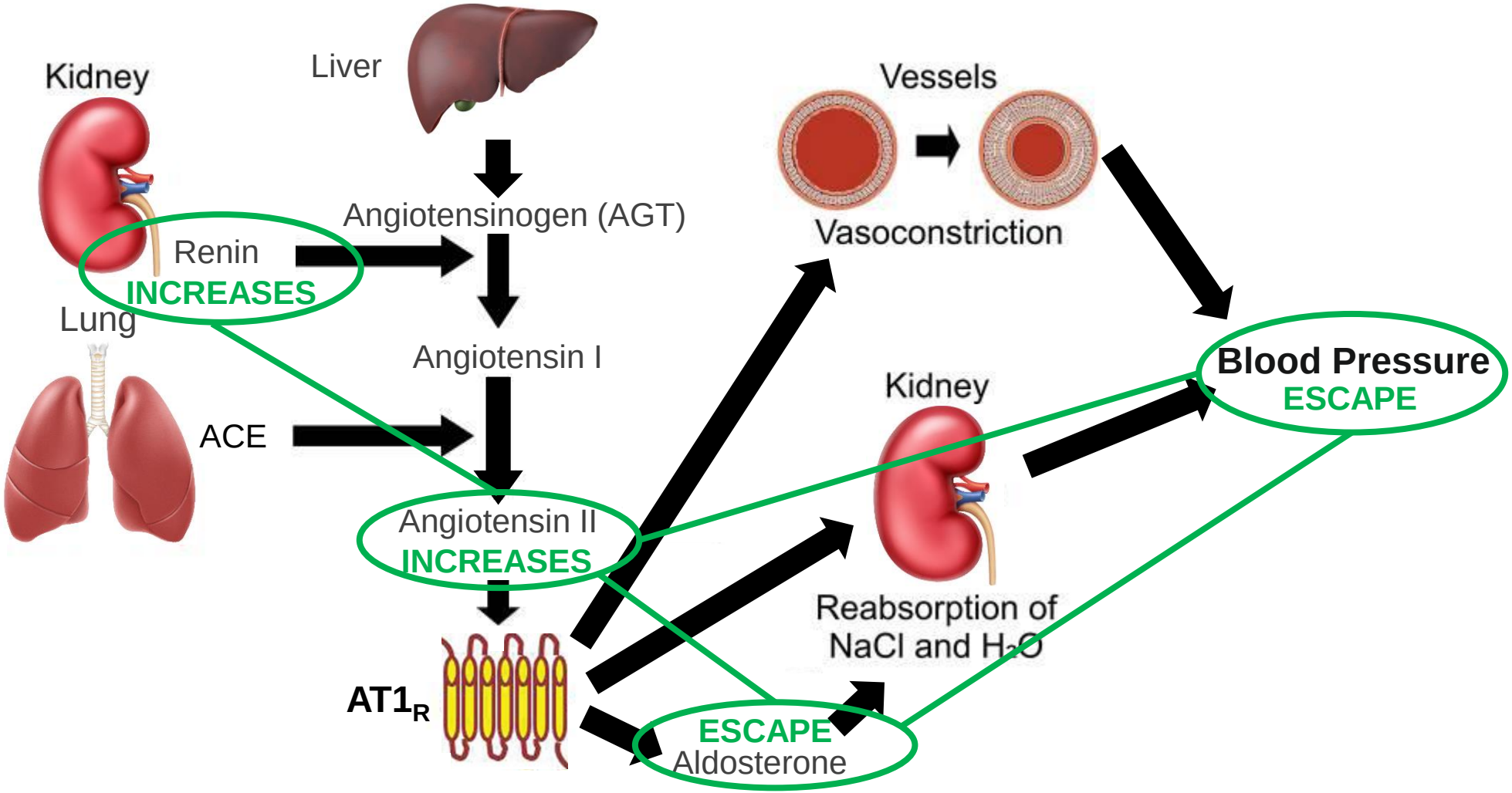
Angiotensin II Receptor Blockers (ARBs)



ACE, angiotensin-converting enzyme; AGT, angiotensinogen; ARB, angiotensin receptor blocker; $AT1_R$, angiotensin II receptor type 1; H_20, water; NaCl, sodium chloride; RAAS, renin angiotensin aldosterone system.
Adapted from Vargas-Rodriguez et al. *Front Med (Lausanne)* 2022;8:758414

Renin Angiotensin Aldosterone System (RAAS)

RAAS Escape with Oral RAAS Blockade



ACE, angiotensin-converting enzyme; AGT, angiotensinogen; ARB, angiotensin receptor blocker; $AT1_R$, angiotensin II receptor type 1; H_20, water; NaCl, sodium chloride; RAAS, renin angiotensin aldosterone system.
Adapted from Vargas-Rodriguez et al. *Front Med (Lausanne)* 2022;8:758414

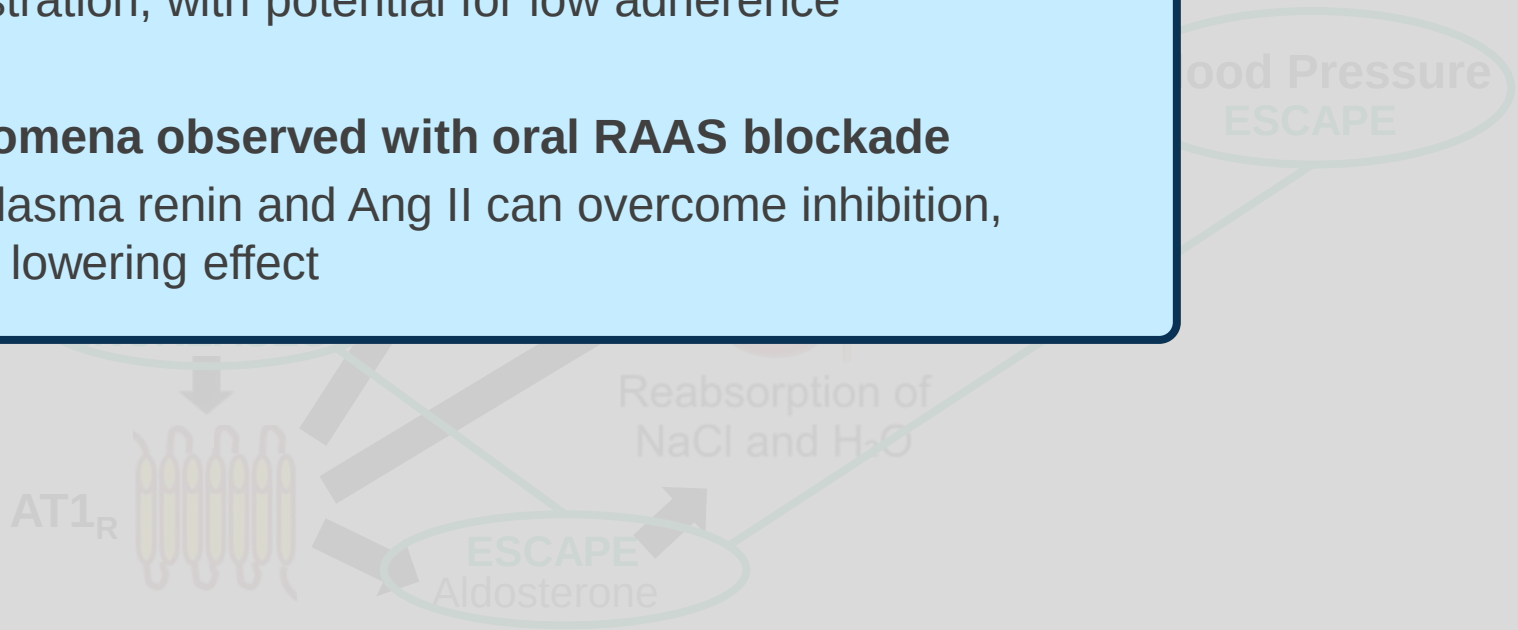
Renin Angiotensin Aldosterone System (RAAS)

RAAS Escape with Oral RAAS Blockade

Potential Mechanistic Disadvantages – Oral RAAS Blockade

- **Short duration of action**
  - Variable BP reduction
  - Potential for incomplete RAAS inhibition
  - Daily dose administration, with potential for low adherence

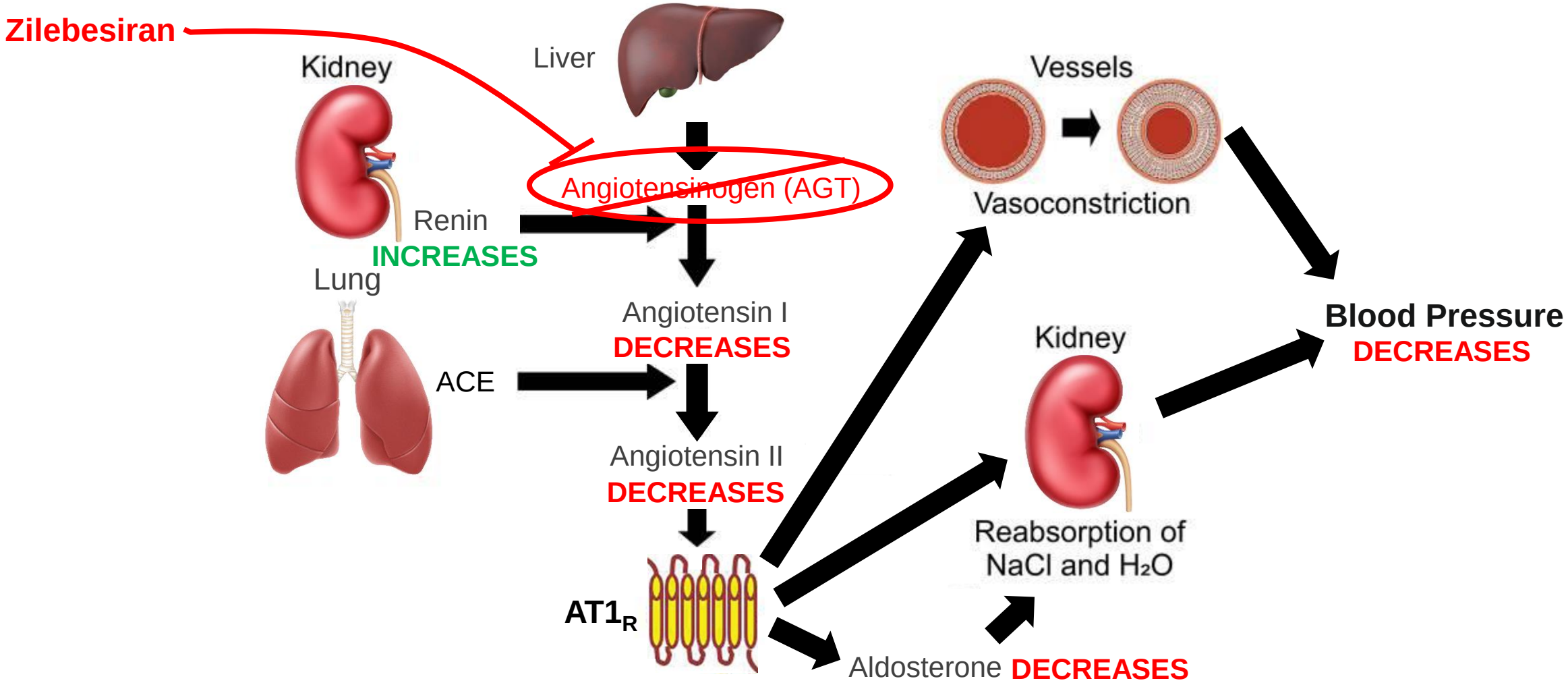
- **RAAS escape phenomena observed with oral RAAS blockade**
  - Reactive rises in plasma renin and Ang II can overcome inhibition, causing loss of BP lowering effect



ACE, angiotensin-converting enzyme; AGT, angiotensinogen; ARB, angiotensin receptor blocker; $AT1_R$, angiotensin II receptor type 1; H_2O, water; NaCl, sodium chloride; RAAS, renin angiotensin aldosterone system.
Adapted from Vargas-Rodriguez et al. *Front Med (Lausanne)* 2022;8:758414

Renin Angiotensin Aldosterone System (RAAS)

RNA Interference (RNAi) Targeting Angiotensinogen



ACE, angiotensin-converting enzyme; AGT, angiotensinogen; ARB, angiotensin receptor blocker; $AT1_R$, angiotensin II receptor type 1; H_20, water; NaCl, sodium chloride; RAAS, renin angiotensin aldosterone system.
Adapted from Vargas-Rodriguez et al. *Front Med (Lausanne)* 2022;8:758414

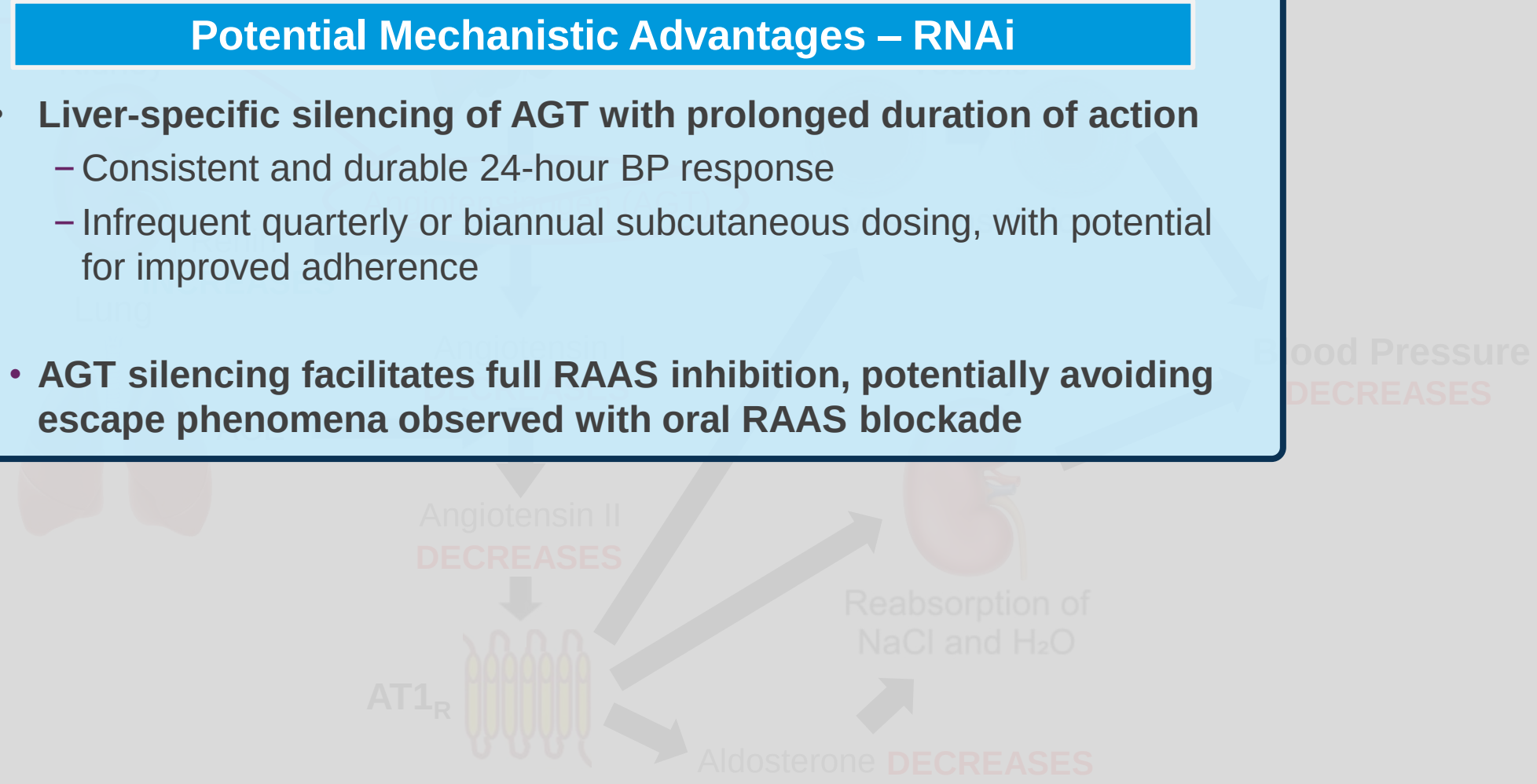
Renin Angiotensin Aldosterone System (RAAS)

RNA Interference (RNAi) Targeting Angiotensinogen

Zilebesiran

Potential Mechanistic Advantages – RNAi

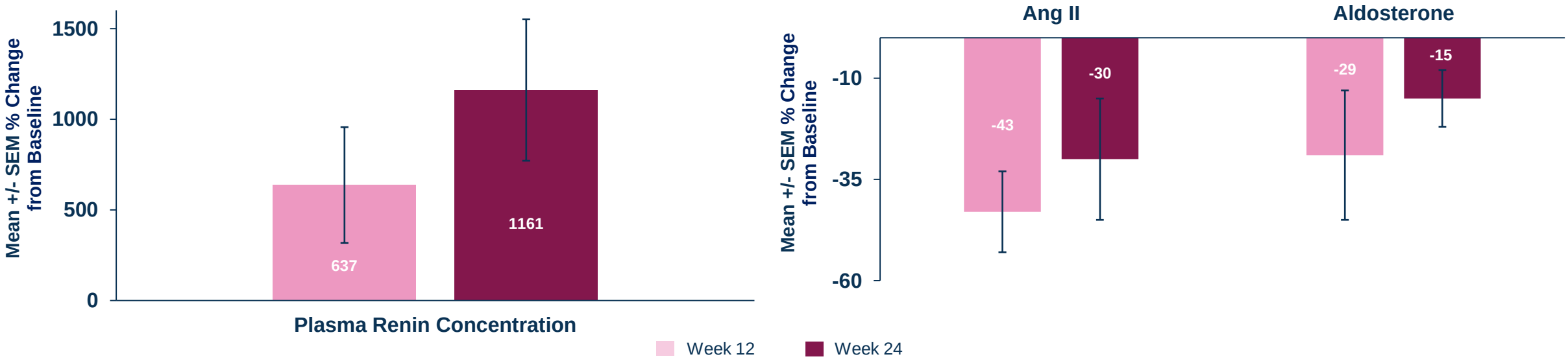
- **Liver-specific silencing of AGT with prolonged duration of action**
  - Consistent and durable 24-hour BP response
  - Infrequent quarterly or biannual subcutaneous dosing, with potential for improved adherence
- **AGT silencing facilitates full RAAS inhibition, potentially avoiding escape phenomena observed with oral RAAS blockade**



ACE, angiotensin-converting enzyme; AGT, angiotensinogen; ARB, angiotensin receptor blocker; $AT1_R$, angiotensin II receptor type 1; H_2O, water; NaCl, sodium chloride; RAAS, renin angiotensin aldosterone system.
Adapted from Vargas-Rodriguez et al. *Front Med (Lausanne)* 2022;8:758414

Durable Effect on Plasma Renin and Ang II

Change in RAAS Biomarkers with Zilebesiran 800mg



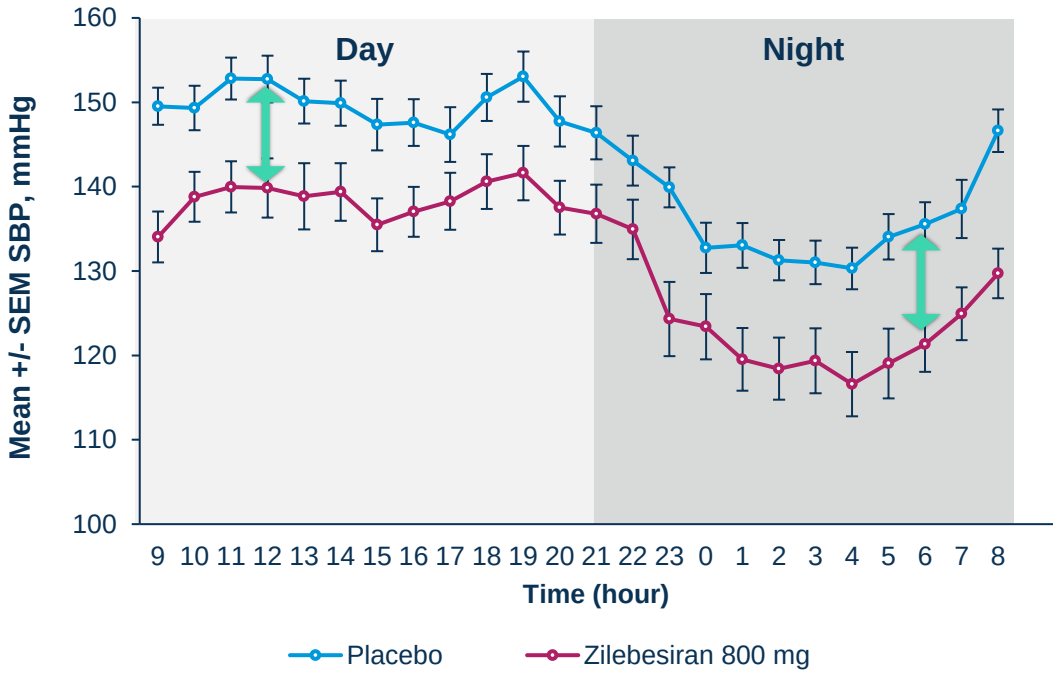
- Consistent rise in plasma renin at Weeks 12 and 24 after single dose of zilebesiran
  - Reduction in AGT removes renin substrate, leading to elevated plasma renin concentration with low activity
- Decreases in downstream vasoactive peptide Ang II and plasma aldosterone

AGT, angiotensinogen; Ang II, angiotensin II; RAAS, renin-angiotensin-aldosterone system; SEM, standard error of the mean.
Alnylam data on file.

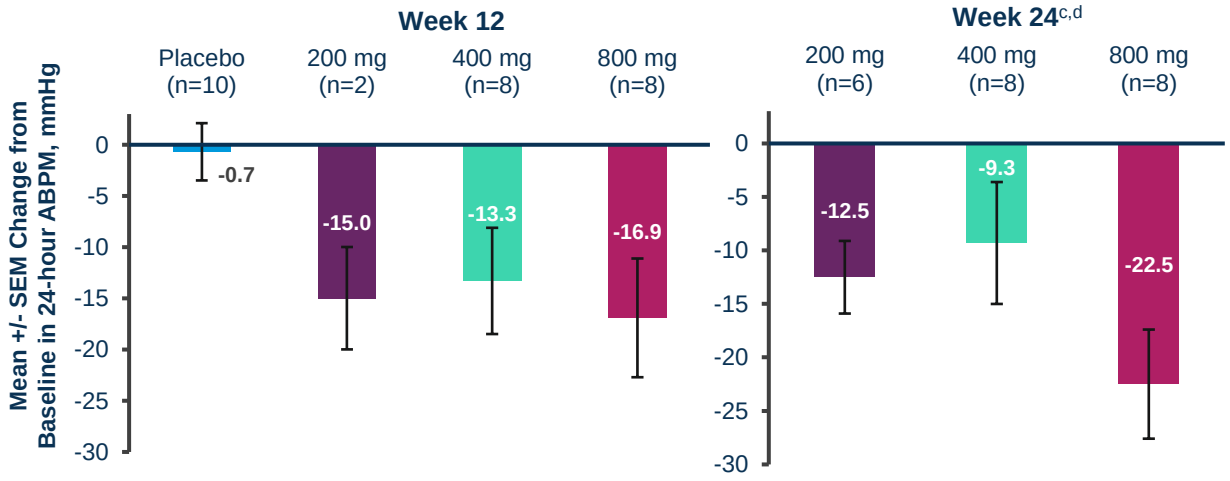
BP Reduction was Observed with Single Dose of Zilebesiran

Durable Antihypertensive Effect was Observed, with Consistent BP Reduction Over 24 Hours

Zilebesiran: 24-Hour SBP at Week 6[a]



Mean Change From Baseline in 24-Hour Ambulatory SBP[b]



[a]All patients at Week 6 were receiving zilebesiran only (no rescue antihypertensives). [b]Median baseline SBP/DBP: Placebo – 142/88 mmHg; 200 mg – 139/83 mmHg; 400 mg – 138/90 mmHg; 800 mg – 142/88 mmHg. [c]After Week 12, patients on placebo were not required to be followed. [d]2 patients in the 200 mg dose group, 1 patient in 400 mg, and 2 patients in 800 mg received add-on antihypertensive therapy.
ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; SEM, standard error of the mean.
Huang et al. AHA Scientific Sessions 2021.

Zilebesiran Phase 1 Study

Multicenter Phase 1 Study designed to evaluate safety, tolerability, PK/PD effects of subcutaneous administration of zilebesiran in patients with mild-to-moderate hypertension

Study was conducted in 4 parts	*1. Single Dose Proof-of-Concept*
	2. Multiple Dose Proof-of-Concept
	3. Safety/tolerability of Volume Depletion
	4. Safety/tolerability in Combination with Potent ARB

ARB, angiotensin receptor blocker; PD, pharmacodynamics; PK, pharmacokinetics.

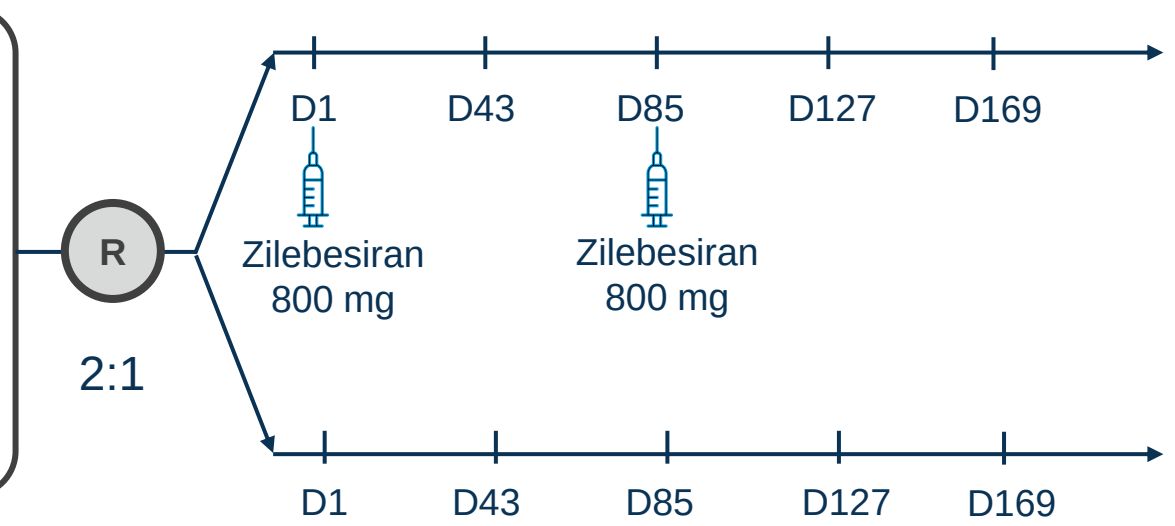
Randomized, Multiple Dose Phase in Obese Patients (Part 2)

Objective: Assess Safety/Tolerability of Multiple Doses of Zilebesiran in Obese Patients

A cohort of 12 patients randomized 2:1 to receive zilebesiran (800 mg) or irbesartan (150 mg PO)

Patient Population (N=12)

- Adults 18–65 years of age
- BMI > 35 kg/m^2 and ≤ 50 kg/m^2
- AOBP SBP > 130 and ≤ 165 mmHg without antihypertensive medications[a]
- Secondary hypertension excluded[b]



Key Baseline Characteristics

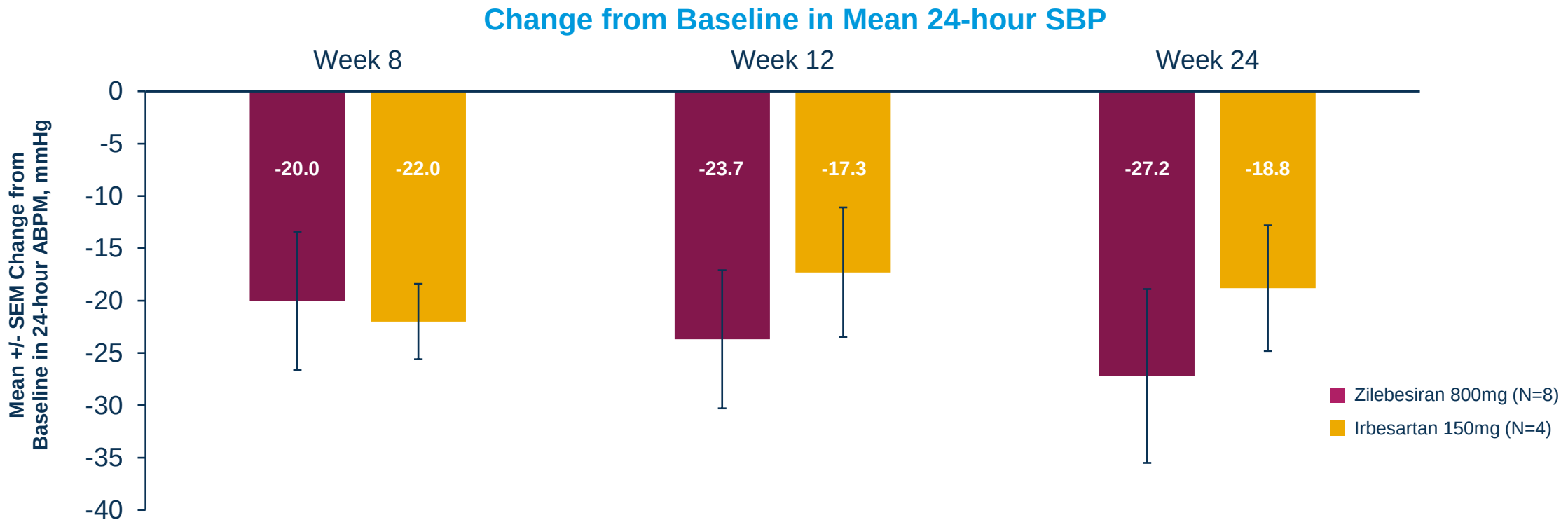
BMI median *39.2 kg/m^2*
AOBP median *150/92 mmHg*
24-h ABPM median *144/87 mmHg*

- BP measured by ambulatory BP monitoring (ABPM) at Day 42 (Week 6), Day 56 (Week 8), Day 84 (Week 12); Day 126 (Month 4.5), Day 140 (Month 5), and Day 168 (Month 6)
- **Evaluated the following:**
  - Multiple dosing of zilebesiran 800 mg q3M
  - Head-to-head comparison with irbesartan 150 mg qD
  - Impact of increased adiposity/BMI on zilebesiran PK and PD parameters
  - Effect of zilebesiran on body weight/composition and metabolic parameters

[a]Following washout of ≥2 weeks or 4 weeks for long-acting anti-hypertensive medications such as chlorthalidone and long-acting calcium channel blockers; [b]Hypertension arising from an identifiable underlying primary cause.

ABPM, ambulatory blood pressure measurement; AOBP, automated office blood pressure; BMI, body mass index, BP, blood pressure; PD, pharmacodynamics; PK, pharmacokinetics; PO, oral; qD, once daily; q3M, every 3 months (quarterly); qD, once daily; R, randomization; SBP, systolic blood pressure. Alnylam data on file.

Antihypertensive Effect of Multiple Doses of Zilebesiran



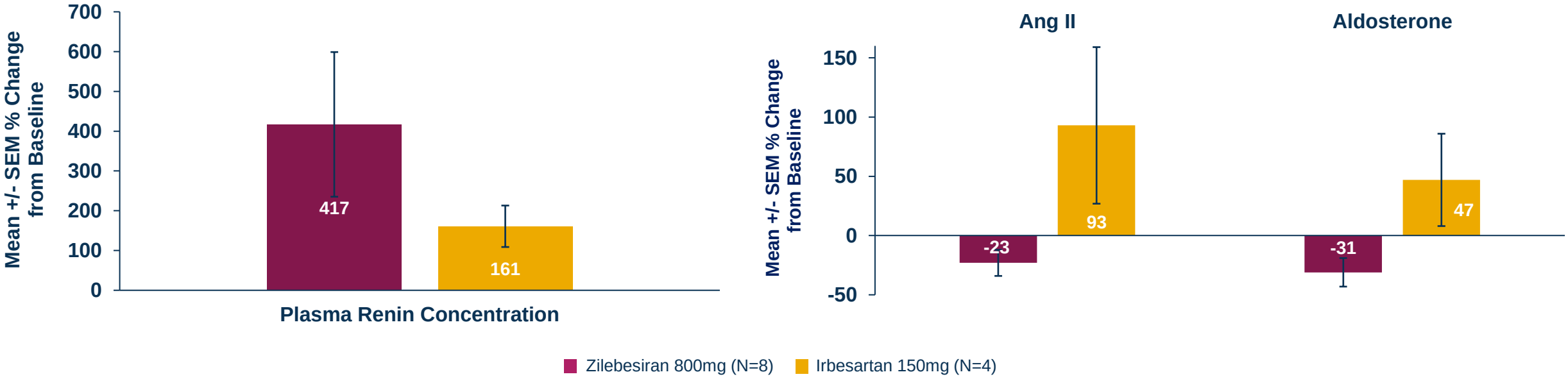
- Sustained reductions in mean 24-hour SBP for zilebesiran 800 mg out to 24 weeks
- The antihypertensive response to zilebesiran was associated with >99% inhibition of AGT from Week 8 to 24 (data not shown)

ABPM, ambulatory blood pressure monitoring; BP, blood pressure.; SBP, systolic blood pressure; SEM, standard error of the mean.

Alnylam data on file. Mean baseline SBP was 143.1 mmHg for zilebesiran and 144.3 mmHg for irbesartan. No add-on oral medications were required for both zilebesiran and irbesartan arms over 24 weeks.

Durable Rise in Plasma Renin and Reduced Ang II with Zilebesiran

Change in RAAS Biomarkers with Zilebesiran 800mg and Irbesartan 150 mg at Week 24



- Increases in plasma renin with zilebesiran and irbesartan after 24 weeks
- Zilebesiran was associated with reductions in ang II and aldosterone in contrast to irbesartan

AGT, angiotensinogen; PRC, plasma renin concentration; Ang II, angiotensin II; RAAS, renin-angiotensin-aldosterone system; SEM, standard error of the mean.
Alnylam data on file.

Zilebesiran Phase 1 Study

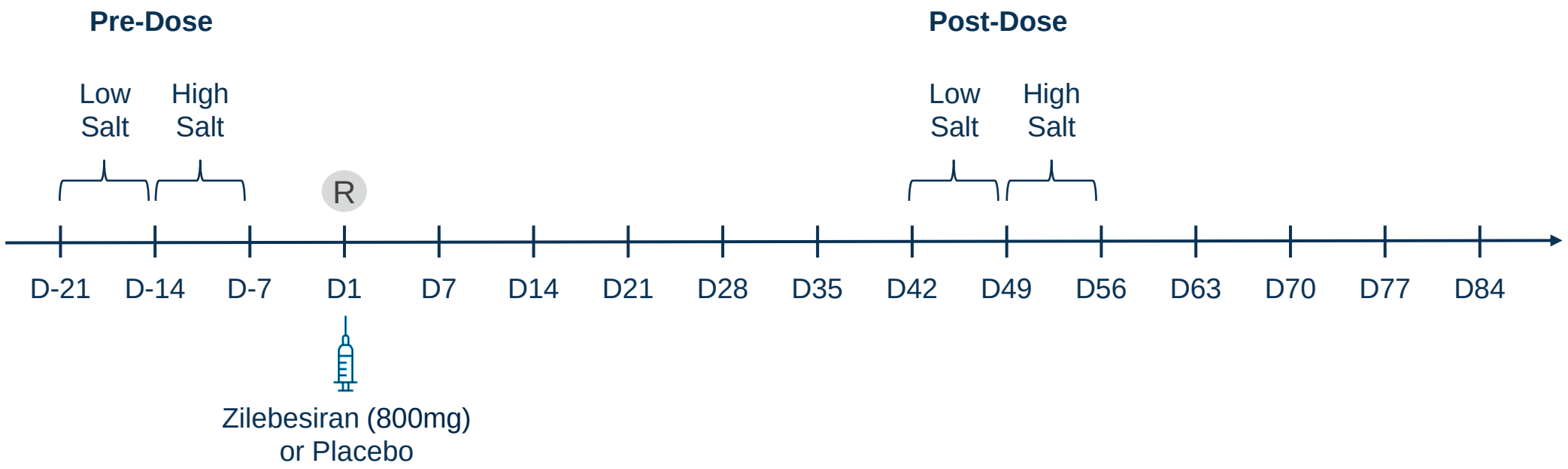
Multicenter Phase 1 Study designed to evaluate safety, tolerability, PK/PD effects of subcutaneous administration of zilebesiran in patients with mild-to-moderate hypertension

Study was conducted in 4 parts	*1. Single Dose Proof-of-Concept*
	2. Multiple Dose Proof-of-Concept
	3. Safety/tolerability of Volume Depletion
	4. Safety/tolerability in Combination with Potent ARB

ARB, angiotensin receptor blocker; PD, pharmacodynamics; PK, pharmacokinetics.

Randomized, Placebo-Controlled, Single Dose Study with Controlled Salt Intake (Part 3)

Objective: Assess Safety/Tolerability of Zilebesiran During Salt Deprivation

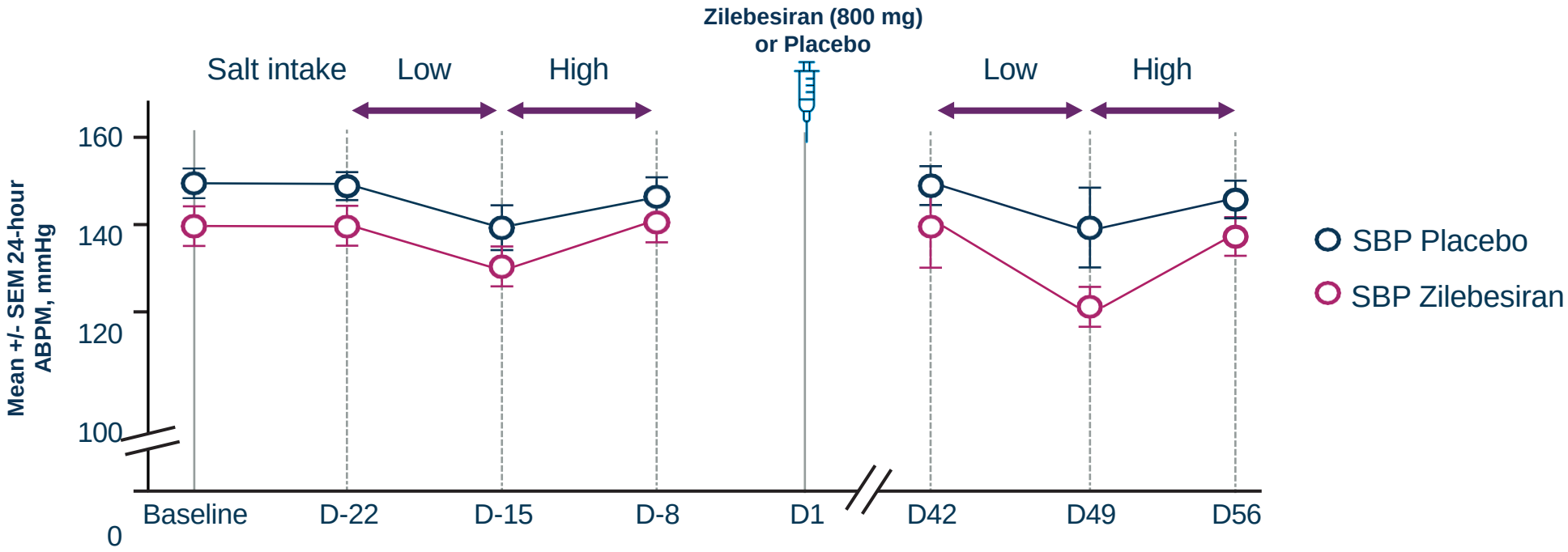


- A cohort of 12 patients randomized 2:1 to receive zilebesiran 800 mg or placebo subcutaneous on Day 1
- Two-week controlled salt intake of low-salt diet (0.23 g sodium per day) followed by high-salt diet (5.75 g sodium per day) during the pre-defined pre-dose and post-dose periods

D, day; PBO, placebo; R, randomization.

Changes in 24-Hour SBP in Low/High Salt Diet

Δ Mean 24-Hour SBP during Controlled Salt Intake



- **Pre-dose:** A reduction in 24-hour SBP was observed for all patients at day –15 following a low-salt diet; BP increased at day –8 upon switching to a high-salt diet
- **Post-dose:** Changes in 24-hour SBP were more profound following a low-salt diet for patients receiving zilebesiran (–19.8 mmHg) vs placebo (–10.0 mmHg); a high-salt diet attenuated the BP lowering effect of zilebesiran
- Zilebesiran 800 mg resulted in a reduction in serum AGT levels of >90%, sustained between Weeks 2 and 12 (data not shown)

ABPM, ambulatory blood pressure monitoring; AGT, angiotensinogen; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; SEM, standard error of the mean.
Huang et al. AHA Scientific Sessions 2021.

Zilebesiran Phase 1 Study

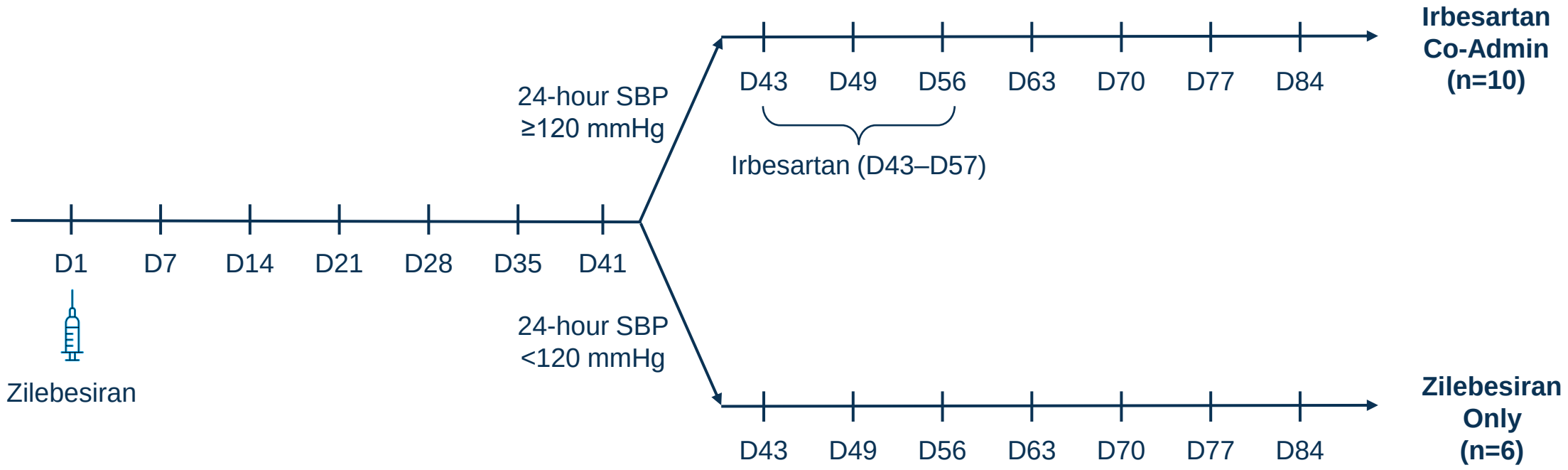
Multicenter Phase 1 Study designed to evaluate safety, tolerability, PK/PD effects of subcutaneous administration of zilebesiran in patients with mild-to-moderate hypertension

Study was conducted in 4 parts	*1. Single Dose Proof-of-Concept*
	2. Multiple Dose Proof-of-Concept
	3. Safety/tolerability of Volume Depletion
	4. Safety/tolerability in Combination with Potent ARB

ARB, angiotensin receptor blocker; PD, pharmacodynamics; PK, pharmacokinetics.

Open-Label, Single Dose Study with Co-Administration of Irbesartan (Part 4)

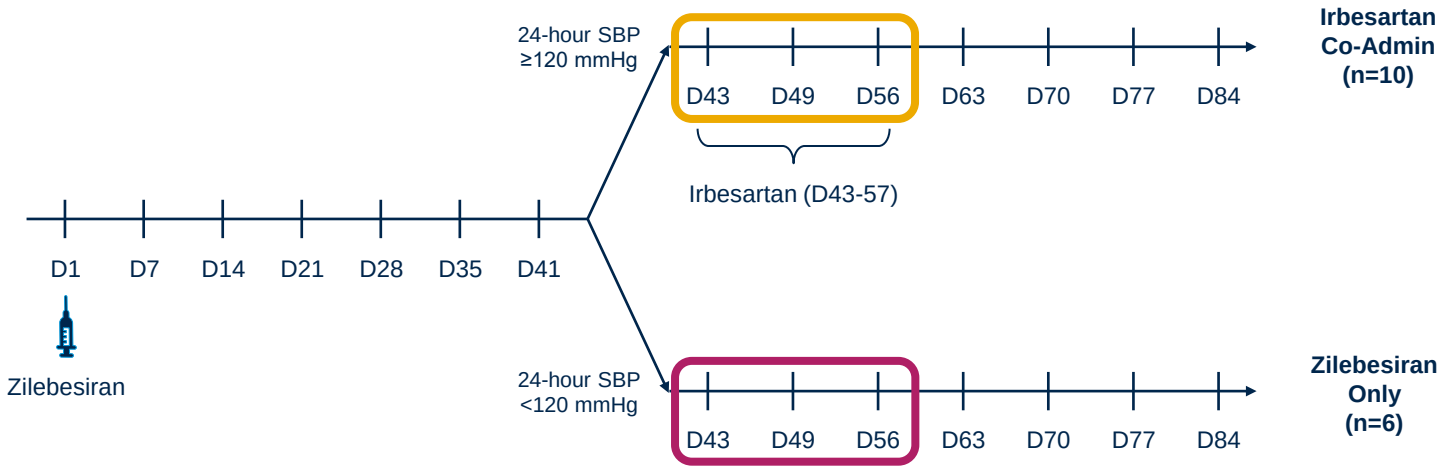
Objective: Assess Safety/Tolerability of Zilebesiran during ARB (Irbesartan) Co-Administration



- All patients (n=16) received open-label treatment with zilebesiran 800 mg SC on Day 1
- On Day 41, patients with 24-hour mean SBP ≥120 mmHg (n=10) proceeded to receive irbesartan 300 mg PO qD for 14 days (Day 43 to Day 57)

ARB, angiotensin receptor blocker; PO, oral; qD, once daily; SBP, systolic blood pressure; SC, subcutaneous.

Irbesartan Further Reduced BP without Clinically Significant Changes in Creatinine or Potassium



Time Period	Δ 24-hour SBP mmHg; mean (SEM)	
	Zilebesiran Only (n=6)	Irbesartan Co-Admin (n=10)
Day 41 vs Day 1	**–22.0** (2.9)	**–7.7** (2.5)
Day 57 vs Day 41	**0.4** (2.9)	**–6.3** (3.1)

BP, blood pressure; SBP, systolic blood pressure; SEM, standard error of the mean.

Huang et al. AHA Scientific Sessions 2021.

Zilebesiran Phase 1: Safety

Part 1 – Single Dose Proof-of-Concept

- Zilebesiran generally well tolerated; no treatment-related SAEs
  - All AEs were mild or moderate in severity and resolved without intervention
  - No patient required intervention for low blood pressure, and there were no elevations in liver enzymes, serum creatinine or potassium during the study

Part 2 – Multiple Dose Proof-of-Concept

- Multiple doses of zilebesiran 800mg generally well tolerated; no treatment-related SAEs
  - All AEs were mild or moderate in severity and resolved without intervention
  - No patient required intervention for low blood pressure, and there were no elevations in liver enzymes, serum creatinine or potassium during the study

Part 3 – Safety/Tolerability of Volume Depletion

- Zilebesiran 800mg generally well tolerated; no treatment-related SAEs
  - All AEs were mild in severity and resolved without intervention
  - No patient required intervention for low blood pressure, including during the sodium deprivation period and no significant elevations in liver enzymes, serum creatinine or potassium during the study

Part 4 – Safety/Tolerability in Combination with Potent ARB

- Zilebesiran 800mg generally well tolerated; no treatment-related SAEs
  - All AEs were mild in severity and resolved without intervention
  - There were no AEs of concern for hypotensive events during irbesartan coadministration, and no patient required intervention for low blood pressure
  - No clinically significant elevations in liver enzymes, serum creatinine or potassium during zilebesiran treatment or co-administration with irbesartan

ARB, angiotensin receptor blocker; SAEs, Serious Adverse Events; AEs, Adverse Events

Huang et al. AHA Scientific Sessions 2021.
Alnylam Data on file.

Phase 2 Clinical Development Plan

KARDIA$_1$

Monotherapy Phase 2 Study (N ~ 375)

- Evaluate efficacy and safety of zilebesiran as a monotherapy in patients with mild-to-moderate hypertension
- Exploring both quarterly and biannual dosing regimens
- Enrollment completion expected at or around year-end 2022; topline results expected mid-2023

KARDIA$_2$

Combination Phase 2 Study (N ~ 630)

- Evaluate efficacy and safety of zilebesiran as concomitant therapy
- Background treatment standardized with ARB, calcium channel blocker or diuretic
- Enrollment completion expected early 2023; topline results expected at or around year-end 2023

ARB, angiotensin receptor blocker.

Zilebesiran KARDIA-1 Phase 2 Monotherapy Study

Randomized, Double-Blind, Placebo-Controlled Study in Patients with Mild-to-Moderate Hypertension

N ~ 375
Patient Population

Key Inclusion Criteria:
- 18–75 years of age
- Daytime SBP ≥135 & ≤160 mmHg
- Treatment naive or prior antihypertensives washed out before enrollment

Key Exclusion Criteria:
- Secondary HTN
- eGFR <30 ml/min/1.73m^2

ClinicalTrials.gov Identifier: NCT04936035

≥2–4 Week Washout

1:1:1:1:1 RANDOMIZATION

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

Primary Endpoint (at Month 3)
- Change from baseline in mean SBP by ABPM

Secondary Endpoints Include
- Change from baseline at Month 3 in office SBP
- Change from baseline at Month 6 in mean SBP by ABPM and office SBP
- Time-adjusted change in SBP and DBP by ABPM

Enrollment completion expected **at or around YE'22**

Topline results expected **Mid'23**

*Placebo randomized across 4 zilebesiran treatment arms after 6 months on study.

ABPM, ambulatory blood pressure measurement; aHTN, arterial hypertension; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HTN, hypertension; q3M, every 3 months (quarterly); SBP, systolic blood pressure; SC, subcutaneous; YE, year end.

Zilebesiran KARDIA-2 Phase 2 Add-On Study

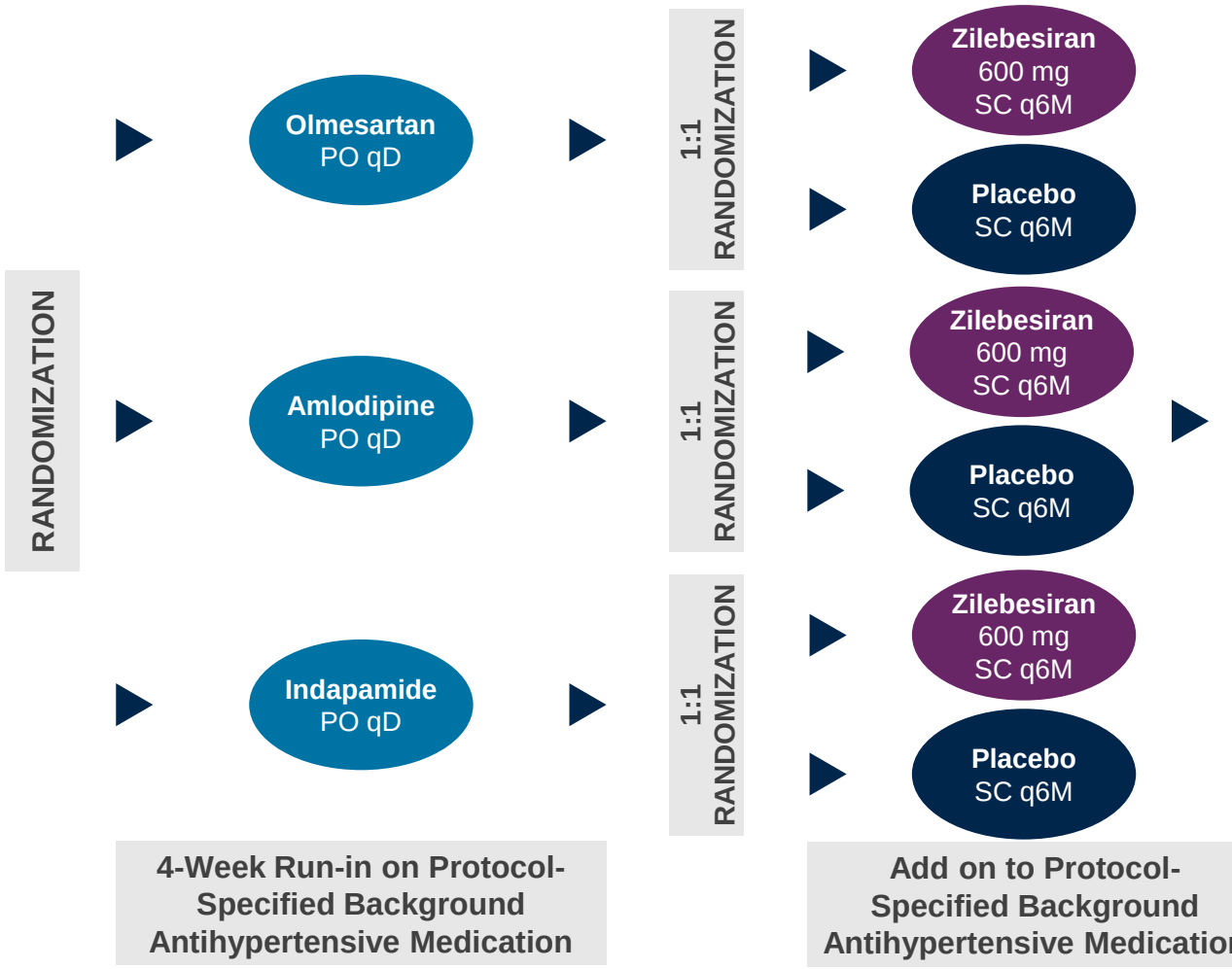
Randomized, Double-Blind, Placebo-Controlled Study in Patients with BP Not Adequately Controlled on SoC Antihypertensive Therapies

N ~ 630
Patient Population

Key Inclusion Criteria:
- 18–75 years of age
- 24-hour mean SBP ≥130 & ≤160 mmHg
- Treatment naive or on stable therapy before enrollment

Key Exclusion Criteria:
- Secondary HTN
- eGFR <30 ml/min/1.73m^2

ClinicalTrials.gov Identifier: NCT05103332



Primary Endpoint (at Month 3)
- Change from baseline in mean SBP by ABPM

Secondary Endpoints Include
- Change from baseline at Month 3 in SBP by office BP
- Time-adjusted change from baseline through Month 6 in SBP by ABPM and office BP

Enrollment completion expected **Early 2023**

Topline results expected **at or around YE'23**

ABPM, ambulatory blood pressure measurement; aHTN, arterial hypertension; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HTN, hypertension; q6M, every 6 months (semiannual); PO, oral; qD, once daily; SBP, systolic blood pressure; SC, subcutaneous; SoC, standard-of-care; YE, year end.

Summary and Next Steps

Significant unmet need for treatment of hypertension in patients with uncontrolled blood pressure could potentially be addressed by zilebesiran

- Goal of achieving tonic BP control with infrequent dosing could benefit patients with uncontrolled hypertension and high CV risk
- Potential to become new antihypertensive treatment for patients with primary hypertension
- Potential for substantially differentiated profile from oral RAAS inhibitors

Data from Phase 1 study in patients with mild-to-moderate hypertension support continued development

- Part 1: Zilebesiran demonstrated reductions in angiotensinogen and increases in plasma renin suggesting effective RAAS inhibition
  - Greater than 20 mmHg reductions in 24-hr mean SBP observed with single 800mg dose through week 24
- Part 2: Multiple doses of zilebesiran demonstrated sustained reduction in BP in obese patients, similar to in non-obese patients
  - Durable increases in renin and decreases in vasoactive RAAS biomarkers were observed, suggesting effective RAAS inhibition
- Part 3: High-salt diet modulated BP lowering effect of zilebesiran, providing early evidence that standard intervention could be effective in treating potential hypotensive adverse events
- Part 4: Addition of irbesartan to zilebesiran further reduced BP without clinically significant changes in creatinine or potassium

KARDIA Phase 2 Program

- KARDIA-1 study expected to complete enrollment at or around YE'22; topline results expected mid'23
- KARDIA-2 study ongoing with enrollment completion expected in early 2023; topline results expected at or around YE'23

BP, blood pressure; CV, cardiovascular; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; YE, year end.

Alnylam Data on file.

Early and Mid-Stage Investigational Programs: Impacting New Areas of High Unmet Need

Weinong Guo, MD, PhD, FACC
SVP, Clinical Research

Alnylam@20

Alnylam Clinical Development Pipeline

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] (OLE/Phase 4/IIS/registries)	COMMERCIAL RIGHTS
onpattro (patisiran)	*hATTR Amyloidosis with PN[2]*			●	Global
GIVLAARI (givosiran)	*Acute Hepatic Porphyria[3]*			●	Global
OXLUMO (lumasiran)	*Primary Hyperoxaluria Type 1[4]*			●	Global
LEQVIO (inclisiran)	*Hypercholesterolemia[5]*			●	Milestones & up to 20% Royalties[6]
amvuttra (vutrisiran)	*hATTR Amyloidosis with PN[7]*			●	Global
Patisiran	*ATTR Amyloidosis with CM*			●	Global
Vutrisiran	*ATTR Amyloidosis with CM*		●		Global
ALN-TTRsc04*	*ATTR Amyloidosis*	●			Global
Fitusiran*	*Hemophilia*		●		15-30% Royalties
Cemdisiran (+/- Pozelimab)[8]*	*Complement-Mediated Diseases*		●		Global; Milestone/Royalty
Belcesiran[9]*	*Alpha-1 Liver Disease*	●			Ex-U.S. option post-Phase 3
ALN-HBV02 (VIR-2218)[10]*	*Hepatitis B Virus Infection*	●			50-50 option post-Phase 2
Zilebesiran*	*Hypertension*	●			Global
ALN-HSD*	*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] Approved in the U.S. and Canada for the PN of hATTR amyloidosis in adults, and in the EU, Japan and other countries for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; [3] Approved in the U.S., Brazil and Canada for the treatment of adults with acute hepatic porphyria (AHP), and in the EU and Japan for the treatment of AHP in adults and adolescents aged 12 years and older; [4] Approved in the U.S. for the treatment of PH1 to lower urinary oxalate and plasma oxalate levels in pediatric and adult patients; [5] Approved in the U.S. for the treatment of heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) and in the EU for the treatment of hypercholesterolemia or mixed dyslipidemia; [6] 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; [7] Approved in the U.S. for the PN of hATTR amyloidosis in adults, and in the EU and Japan for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy; [8] Alnylam and Regeneron are evaluating potential combinations of the investigational therapeutics cemdisiran and pozelimab; [9] Dicerna is leading and funding development of belcesiran; [10] Vir is leading and funding development of ALN-HBV02; * Not approved for any indication and conclusions regarding the safety or efficacy of the drug have not been established.

As of December 2022

Multiple Drivers of Future Growth in Early and Mid-Stage Pipeline

Programs Across Multiple Tissues and Diseases, Efficiently Executed Alone or With Partners

- **Type 2 Diabetes Program**
- **CNS Programs**
- **NASH Programs**
- **Partner-Led Programs**

Multiple Drivers of Future Growth in Early and Mid-Stage Pipeline

Programs Across Multiple Tissues and Diseases, Efficiently Executed Alone or With Partners

- **Type 2 Diabetes Program**

  ALN-KHK

- **CNS Programs**

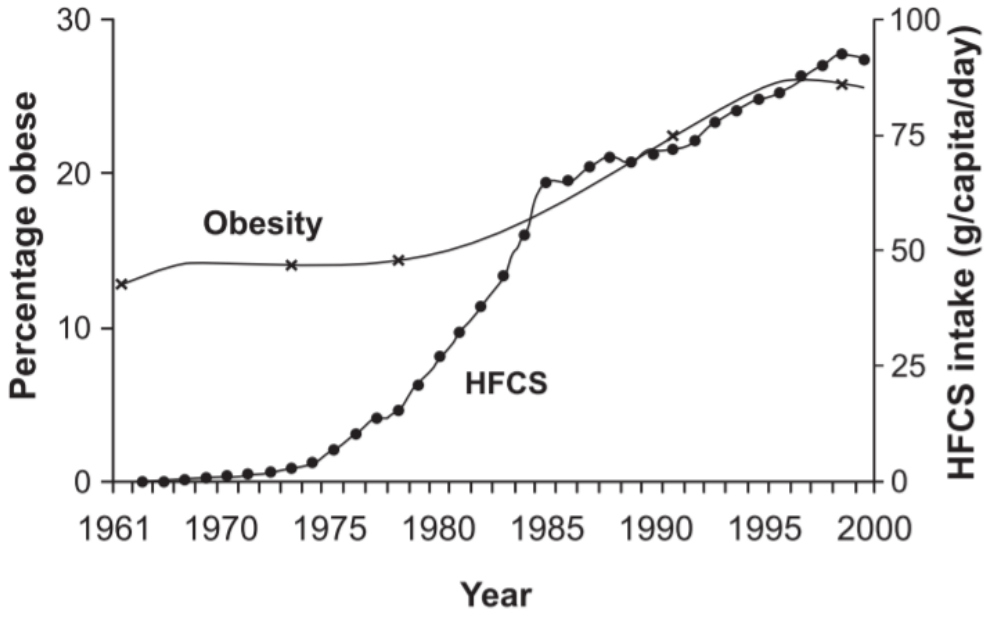
- **NASH Programs**

- **Partner-Led Programs**

Fructose Metabolism Contributes to Metabolic Syndrome

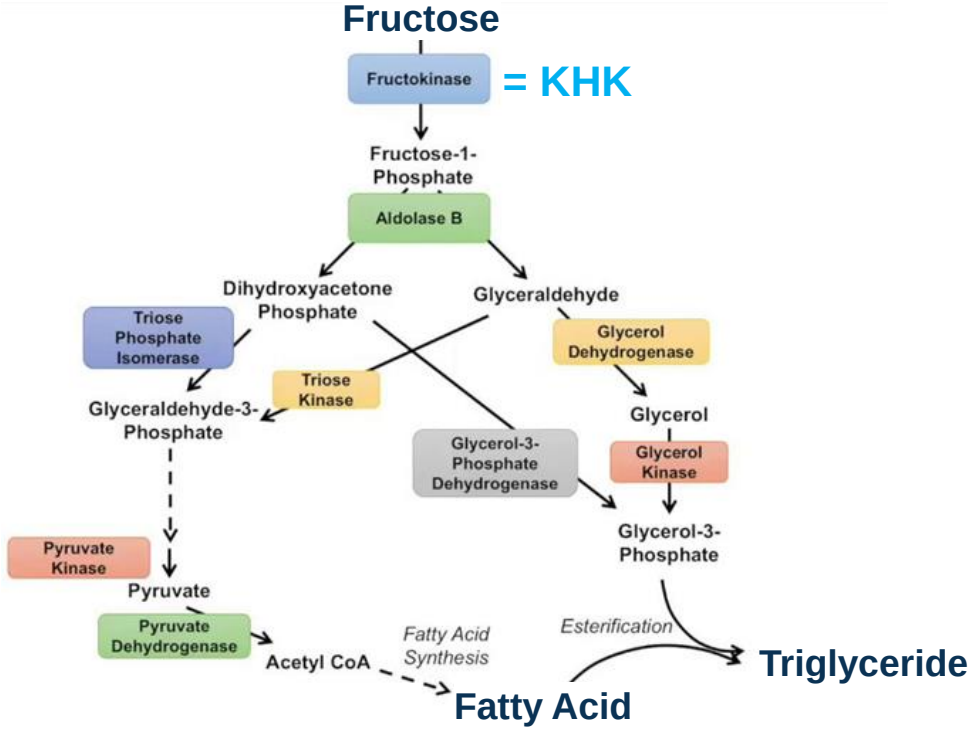
Dietary Fructose Intake Underlies Development of Obesity and T2DM

- Sucrose and high-fructose corn syrup (HFCS) added to numerous manufactured foods and beverages
- Obesity and fatty liver commonly associated with T2DM, with underlying insulin resistance



KHK Regulates Fructose Metabolism

- KHK-mediated fructose metabolism contributes to hepatic lipogenesis and insulin resistance
- LOF mutations in humans cause essential fructosuria
  - Benign, asymptomatic defect
  - Characterized by increased urinary fructose

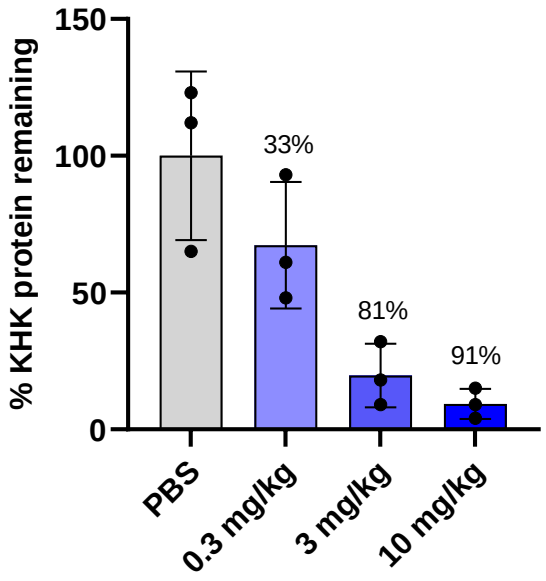


T2DM: Type 2 Diabetes Mellitus KHK: ketohexokinase LOF: loss of function

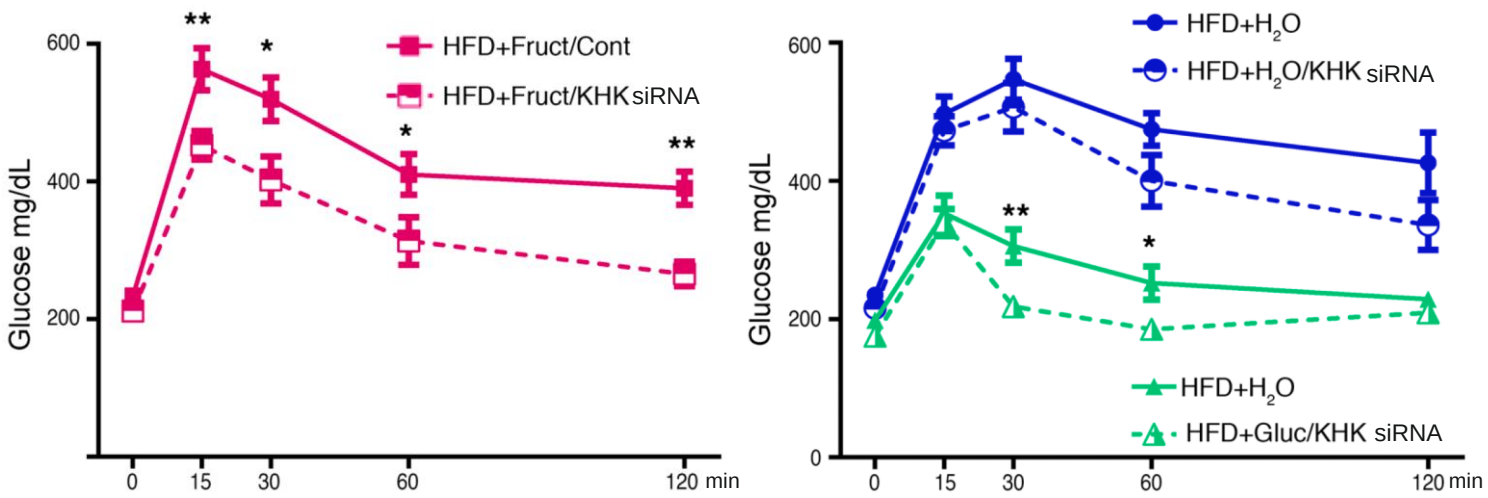
Preclinical Data Support Therapeutic Hypothesis of ALN-KHK

KHK Liver Knockdown Improves Glucose Tolerance and Insulin Sensitivity in Preclinical Species

KHK Protein Remaining 29 Days Post Dose (Non-human primate)



Oral Glucose Tolerance Test (Mice)



HFD: high-fat diet

Softic et al. (2017) *J. Clin. Invest.* 127:4059 [Alnylam collaboration]

ALN-KHK Phase 1 Overview

Randomized, Double-Blind Study in Obese Healthy Subjects and Obese Patients with Type 2 Diabetes

Part A: Single Ascending Dose in obese healthy subjects

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

Primary Objective: Safety and tolerability of ALN-KHK

Secondary Objective: Pharmacology of ALN-KHK

- Potential to expand development opportunities of ALN-KHK in other metabolic disorders, including fatty liver disease

CTA submission expected
by YE 2022

Phase 1 initiation expected
early 2023

Multiple Drivers of Future Growth in Early and Mid-Stage Pipeline

Programs Across Multiple Tissues and Diseases, Efficiently Executed Alone or With Partners

- **Type 2 Diabetes Program**

- **CNS Programs**

Alnylam PHARMACEUTICALS REGENERON

ALN-APP	*Phase 1 ongoing*
ALN-SOD	*IND-enabling*
New targets	*HTT, SNCA, others*

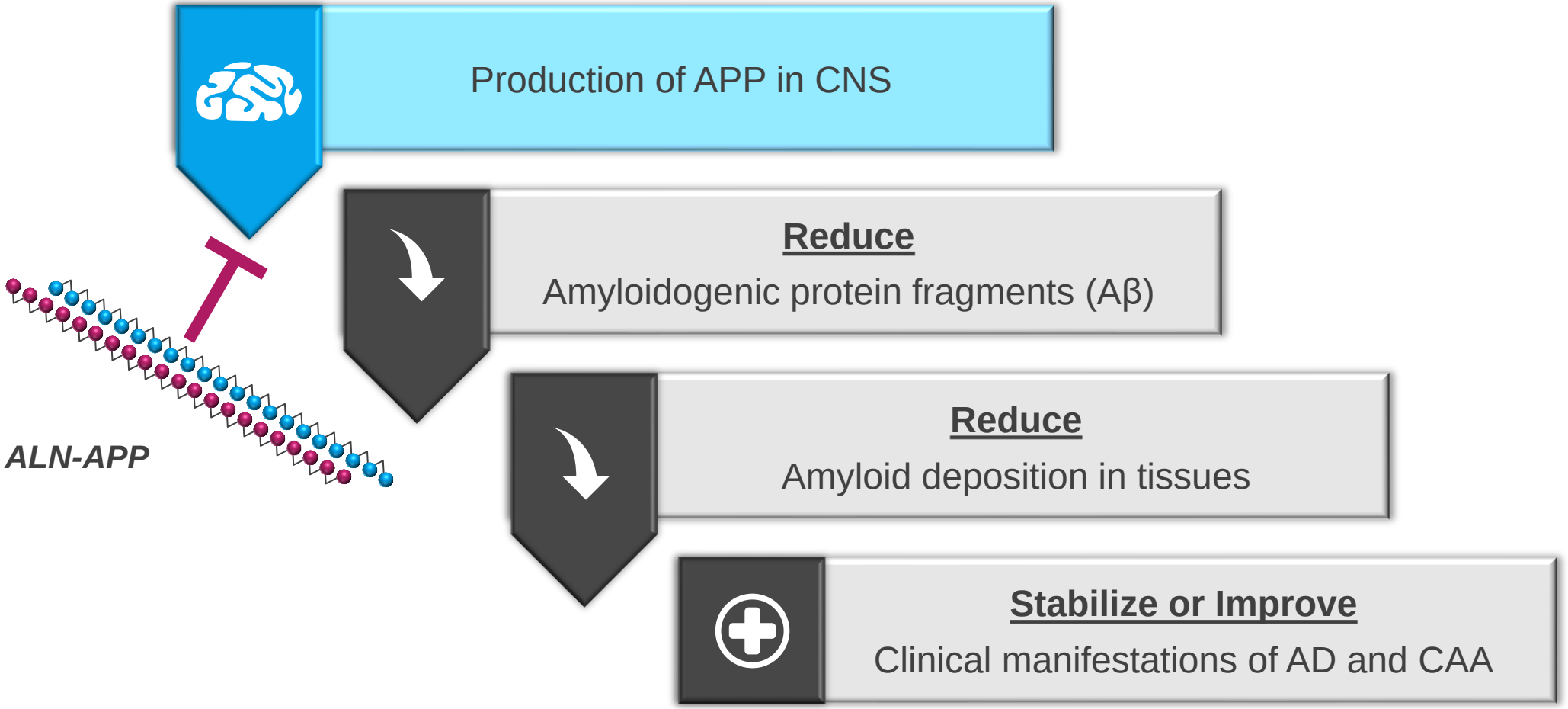
- **NASH Programs**

- **Partner-Led Programs**

Building on Success of RNAi Therapeutics for Other Types of Amyloidosis

ALN-APP Designed to Reduce APP Production Upstream of Amyloidogenic Process

Therapeutic hypothesis

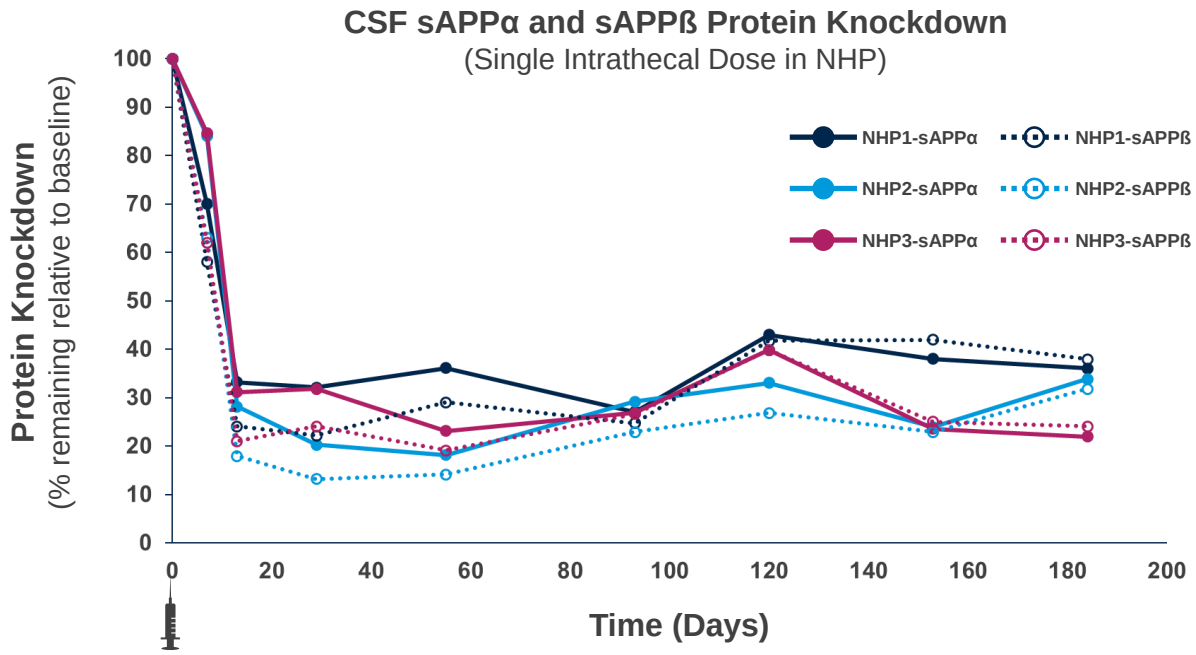


APP: amyloid precursor protein

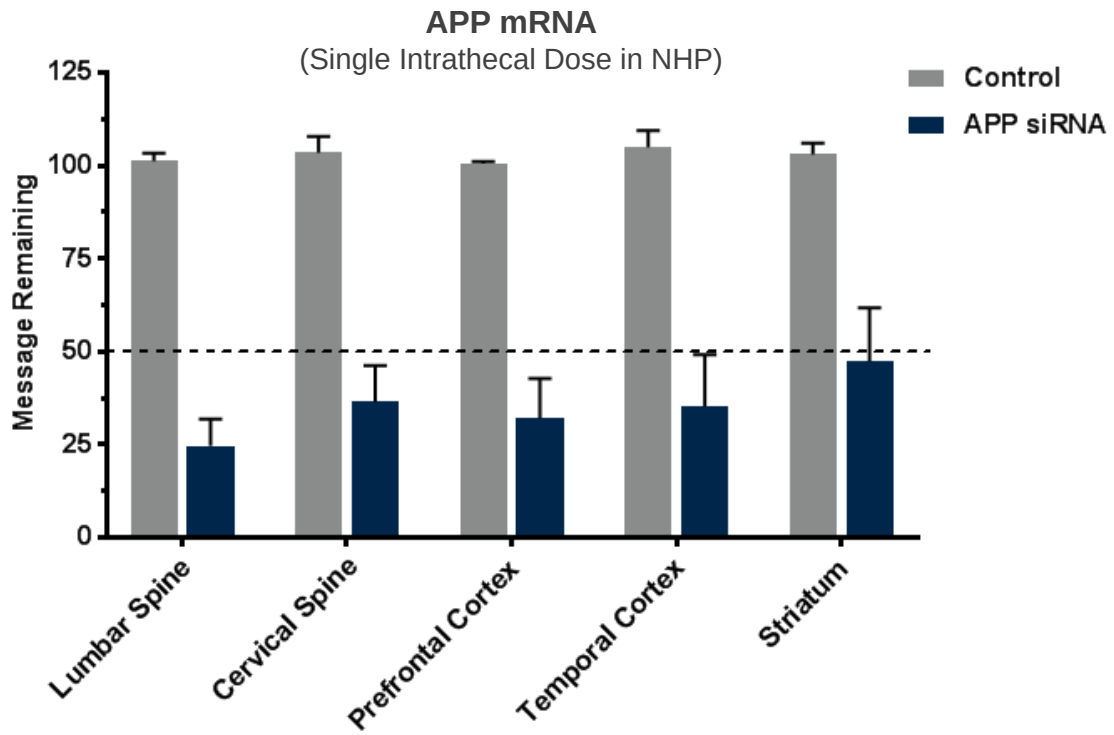
ALN-APP is an investigational RNAi therapeutic in development for the treatment of Alzheimer's Disease (AD) and Cerebral Amyloid Angiopathy (CAA)

Preclinical Data Demonstrate Extensive, Potent, and Durable APP Reduction

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



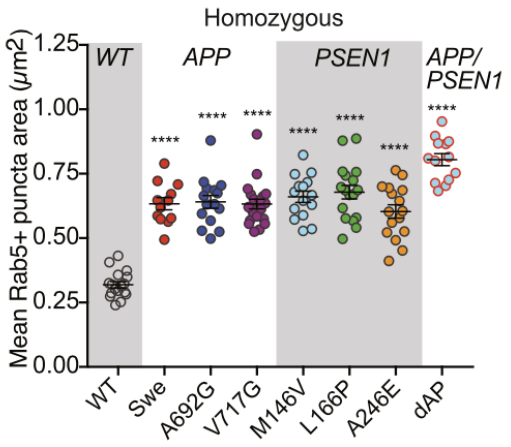
Single Intrathecal Dose of APP siRNA Distributes Throughout Spine and Brain



Data on file

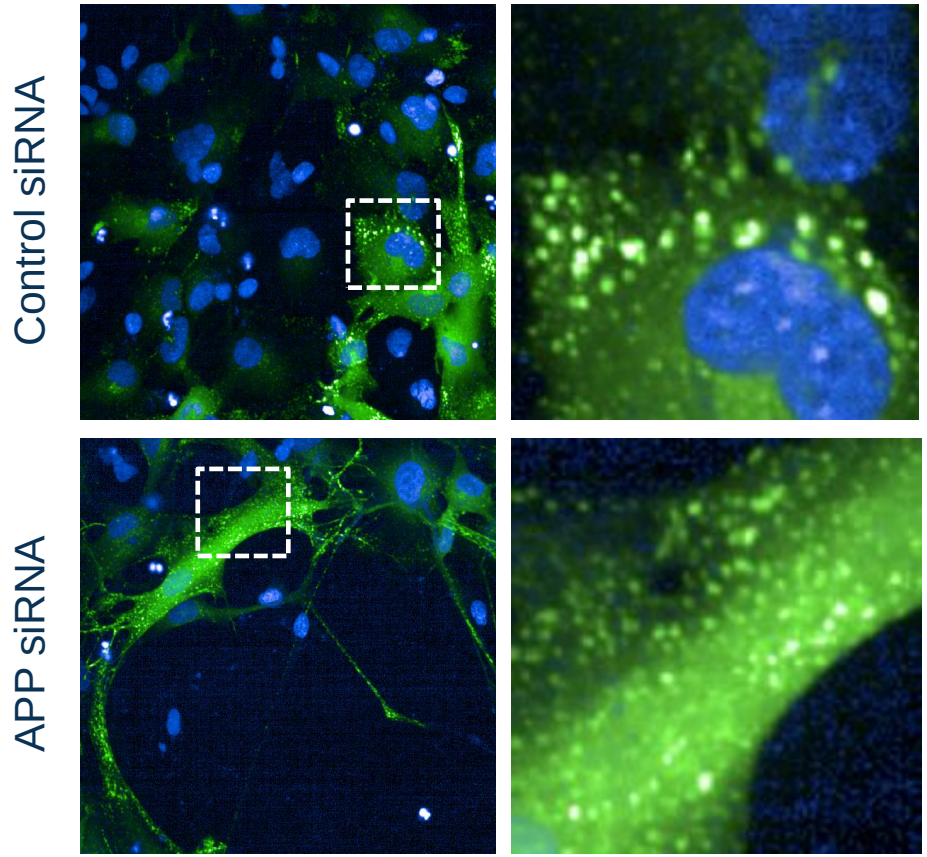
APP siRNA Corrects Intracellular ADAD Endosomal Phenotype

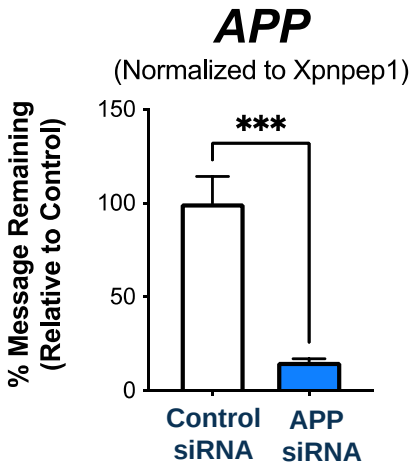
Patient iPSC-Derived Neurons Treated with APP siRNA Show Reduction in Intracellular Aggregates

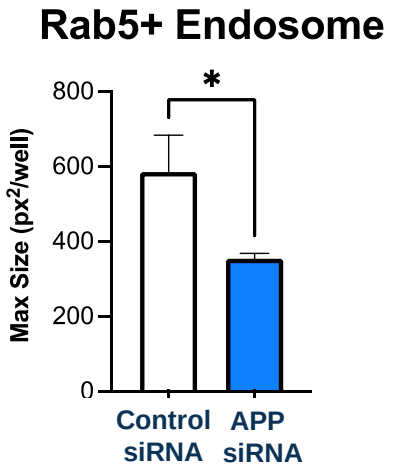


Mutations in APP and PSEN1 cause enlargement of Rab5+ Early Endosomes in human iPSC derived Neurons

Kwart et al., Neuron 2019







- Phenix High Content Imaging, 63X, analysis on Harmony
- Rab5+ endosome Alexa 488 for live imaging

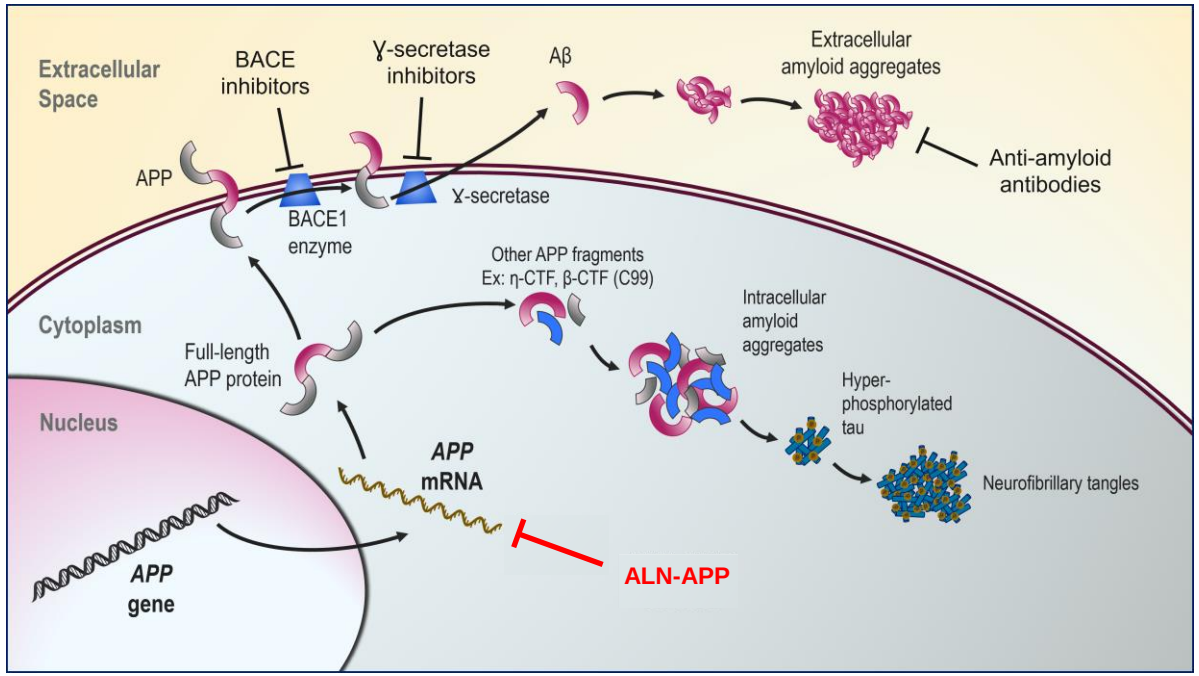
ADAD: autosomal dominant Alzheimer's disease; iPSC: induced pluripotent stem cell

Targeting APP for Alzheimer's Disease (AD)

Most Common Cause of Dementia Worldwide

High prevalence and unmet need for new therapies

- Over 5M people affected by AD in US (over 30M worldwide)
- Significant driver of disability and mortality in older adults
- Current therapies not shown to halt or reverse disease



Therapeutic hypothesis

ALN-APP lowers APP production *at its source*, upstream of pathogenic process

- Reduce ***both intracellular*** and ***extracellular*** drivers of disease pathology
- ***Reduce all APP cleavage products*** including all species of Aβ
- Remove substrate for amyloid deposit formation and ***enable natural clearance***

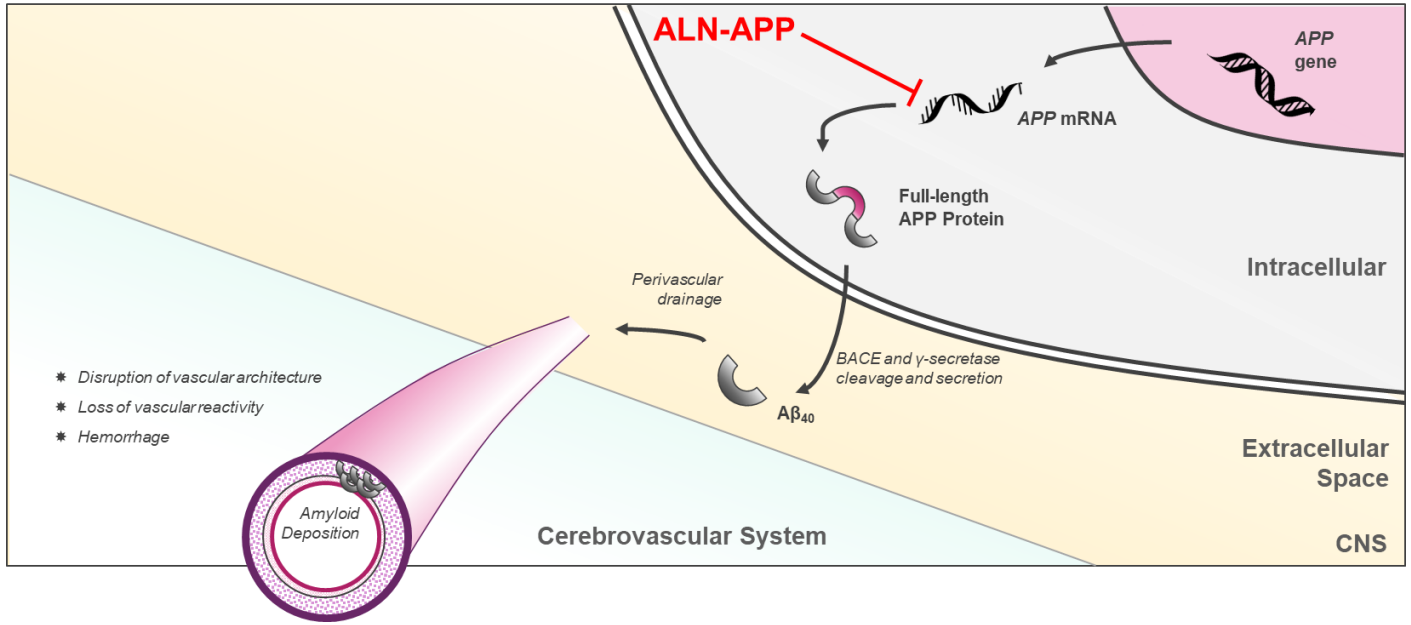
2020 AD Facts and Figures, Alzheimer's Dementia (2020); WHO Dementia Fact Sheet (2021); Tom SE, et al., Am J Public Health (2015)

Targeting APP for Cerebral Amyloid Angiopathy (CAA)

Currently No Targeted Therapies Available and Little Ongoing Development

High unmet need for new treatments to address CAA

- Second-leading cause of ICH after hypertension
- APP metabolism results in Aβ protein fragments that aggregate into amyloid deposits in vessels of brain
- No specific treatments available for CAA
- Targeting vascular amyloid with antibodies has been unsuccessful



Therapeutic hypothesis

ALN-APP targets pathogenic protein production *at its source,* upstream of amyloid production and deposition

- Lower ***all Aβ isoforms*** including AB_{40}, primary component of vascular amyloid deposits
- Enable **natural clearance mechanisms** and reversal of vascular damage

ICH: intracerebral hemorrhage

Jäkel L, et al., Alzheimer's Dement (2021); Aguilar MI, et al., Neurohospitalist (2012); Kozberg MG et al., Int J Stroke (2020).

Figure republished with permission of the American College of Cardiology from DeSimone CV, et al., J Am Coll Cardiol (2017)

ALN-APP Phase 1 Overview

Randomized, Double-Blind Study in Patients with Early-Onset Alzheimer's Disease (EOAD)

Part A: Single Ascending Dose
(Ongoing)

Part B: Multiple Dose
(expected to begin 2023)

- **Population**: Patients with Early Onset Alzheimer's Disease
- **Primary Objective**: Safety and tolerability of ALN-APP
- **Secondary Objective**: Pharmacology of ALN-APP
- **Exploratory Objective**: Impact of ALN-APP on disease
  - Fluid biomarkers for amyloid, tau, and neurodegeneration
  - Measures of synaptic health
  - Neuroimaging
  - Exploratory cognitive and functional clinical measures

Dose escalation in Part A
Ongoing

Topline Phase 1 data expected
Early 2023

NCT05231785

Multiple Disease Populations with High Unmet Need

Phase 1 Data will Potentially Unlock Development Opportunities in Both AD and CAA

Phase 1 Study
Early Onset Alzheimer's Disease

Alzheimer's Disease Opportunities

- **Early Onset AD (<65 yo) (EOAD)**
  - Autosomal Dominant AD(ADAD)
  - Non-familial early onset AD (nf-EoAD)
  - Down Syndrome AD
- **Late Onset AD (>65 yo) (LOAD)**

Cerebral Amyloid Angiopathy Opportunities

Hereditary CAA: Ultra-orphan, genetically-defined population found primarily in Netherlands and Australia; onset in 40s/50s

Sporadic CAA: More common cause of ICH that increases with age; onset typically >60 yo

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

Multiple Drivers of Future Growth in Early and Mid-Stage Pipeline

Programs Across Multiple Tissues and Diseases, Efficiently Executed Alone or With Partners

- **Type 2 Diabetes Program**

- **CNS Programs**

- **NASH Programs**

REGENERON Alnylam PHARMACEUTICALS

ALN-HSD	*Phase 1 data*
ALN-PNP	*Phase 1 initiating*
New targets	*CIDEB, others*

- **Partner-Led Programs**

Therapeutic Strategies for Nonalcoholic Fatty Liver Disease (NAFLD)

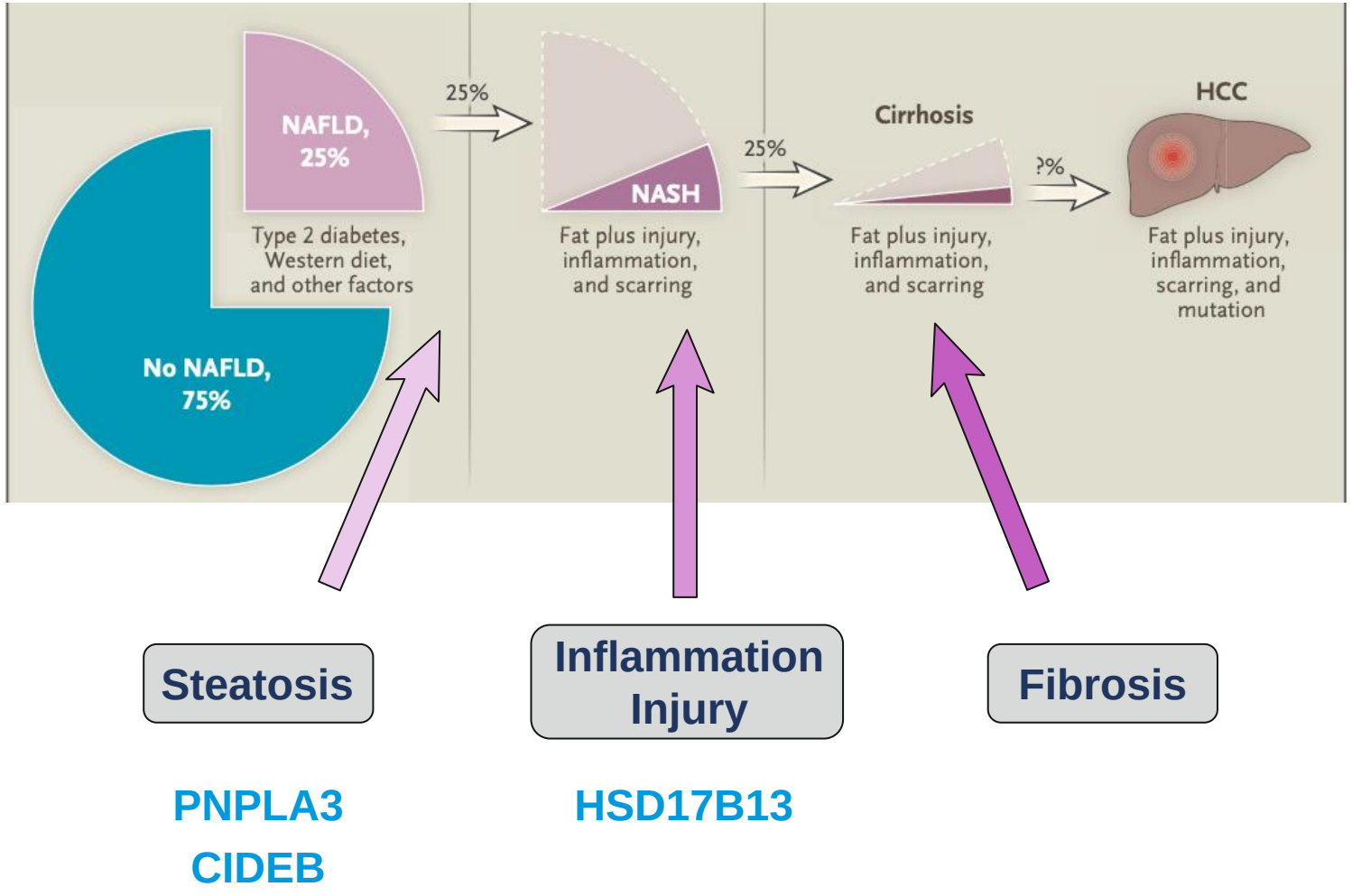
Each Stage of NASH Pathogenesis Presents Opportunity for Intervention

Nonalcoholic steatohepatitis (NASH)

- Subset of NAFLD defined by presence of liver cell injury and inflammation
- Associated with progressive fibrosis leading to cirrhosis and hepatocellular carcinoma
- Comorbidities include obesity, metabolic syndrome and T2DM

NASH treatment

- No approved medical therapies
- Weight loss is effective but difficult to achieve and generally not durable



Adapted from *Diehl, A., Day, C.* (2017). NEJM 377(21), 2063-2072.

ALN-HSD Phase 1 Study Design

Primary Endpoint: Safety and tolerability of ALN-HSD

Key Secondary Endpoints: ALN-HSD PK/PD

Exploratory Endpoints: Assess effects of ALN-HSD on histologic and circulating biomarkers of NASH

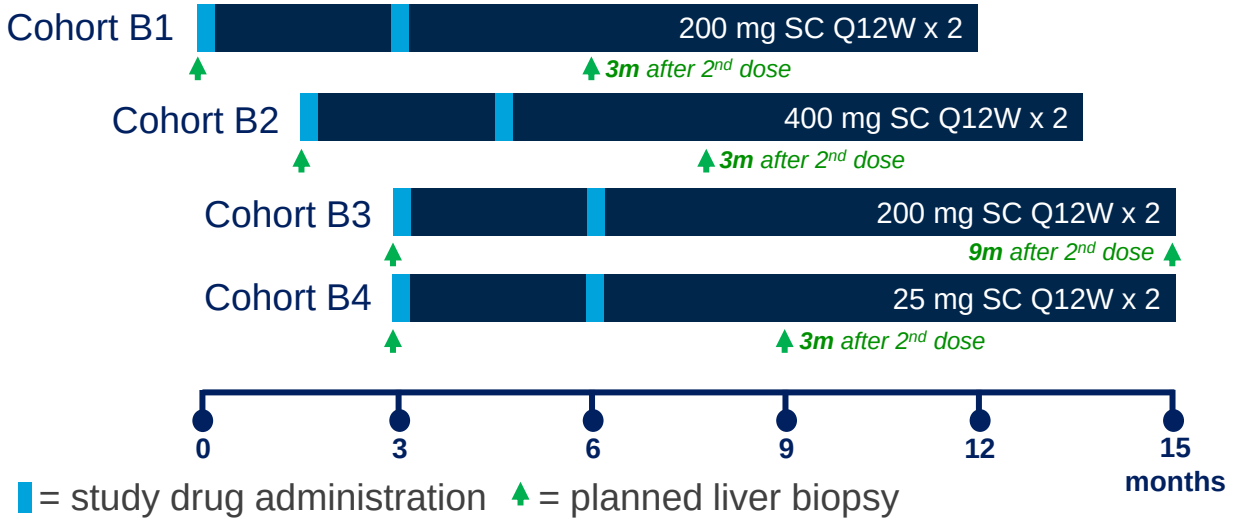
Part A: Healthy volunteers

Well Tolerated in Healthy Volunteers

- Most common treatment-emergent adverse event in healthy volunteers treated with ALN-HSD was injection site reaction (ISR) in 5 patients; all ISRs mild in severity
- No treatment-related SAEs occurred; no deaths or AEs leading to study withdrawal
- No clinically significant elevations in serum ALT or other laboratory abnormalities

Part B: NASH patients

MAD Cohorts



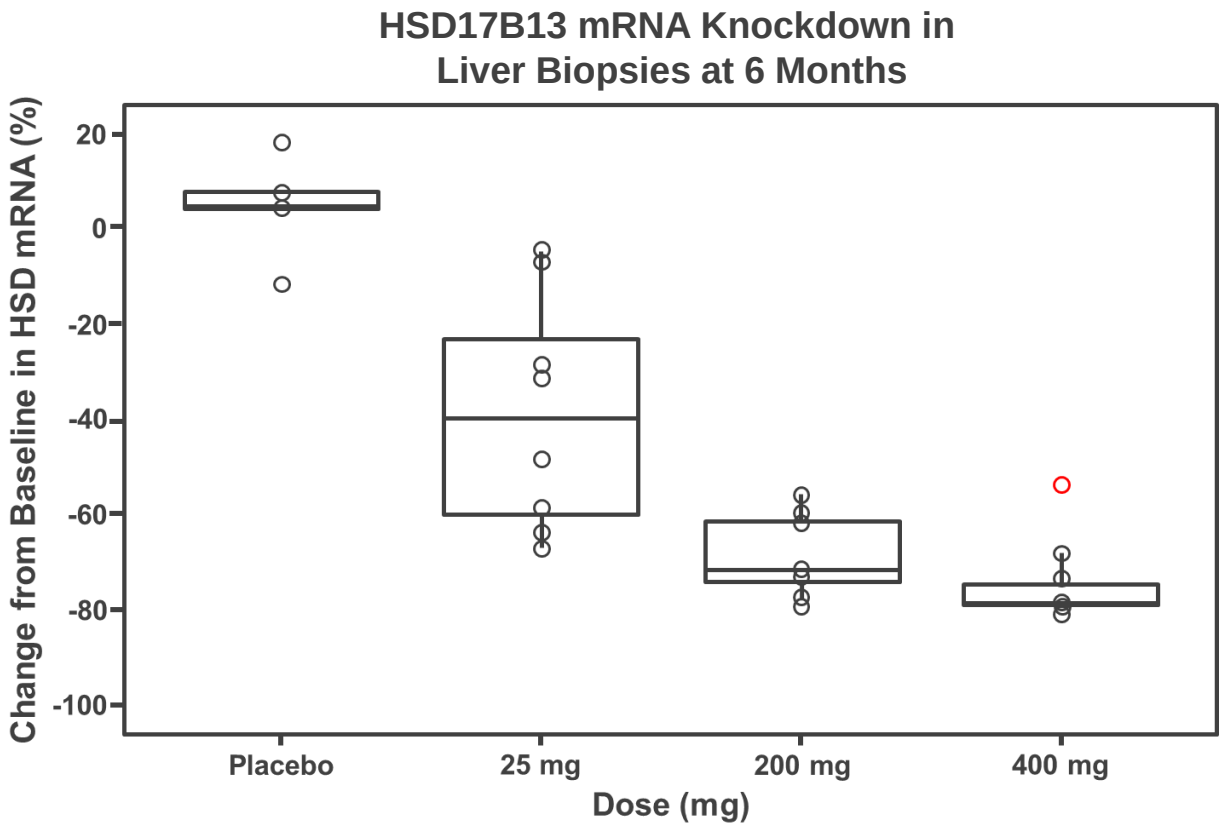
Well Tolerated in NASH Patients

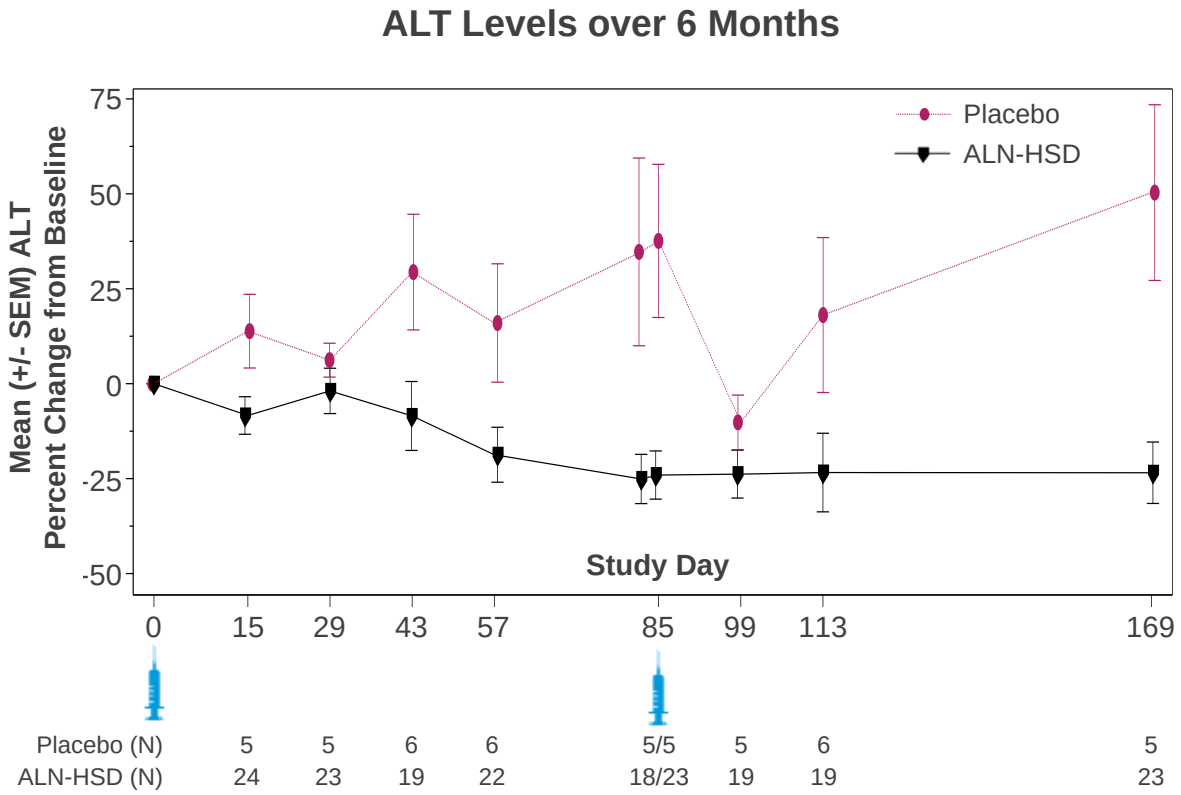
- No discontinuations or interruptions related to study drug
- No treatment-related SAEs
- 2 SAEs, both graded severe and deemed unrelated to study drug
  - Skin laceration
  - Appendicitis

NCT04565717

ALN-HSD is an investigational RNAi therapeutic in development for the treatment of NASH

Positive Results with Quarterly Dosing in NASH Patients





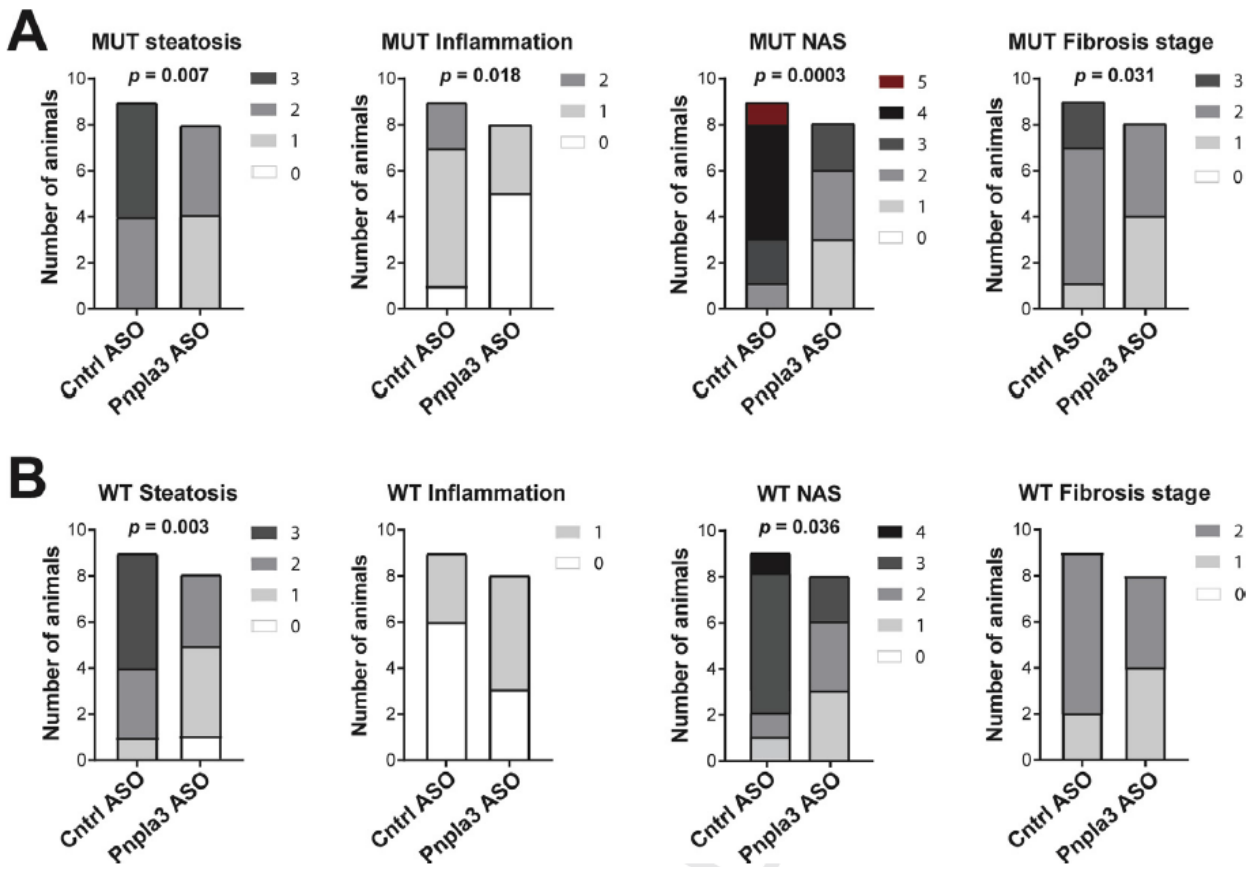
- ALN-HSD demonstrated dose-dependent reduction of liver HSD17B13 mRNA at 6 months
- Mean HSD mRNA reduction of 40%, 71%, and 78% at 25, 200, and 400 mg, respectively

- ALN-HSD associated with improvement in biopsy-derived NAFLD Activity Score (NAS) over six months in patients receiving ALN-HSD vs. placebo

Red dot in 400 mg group represents subject who received only single dose of ALN-HSD (6 months prior to biopsy)

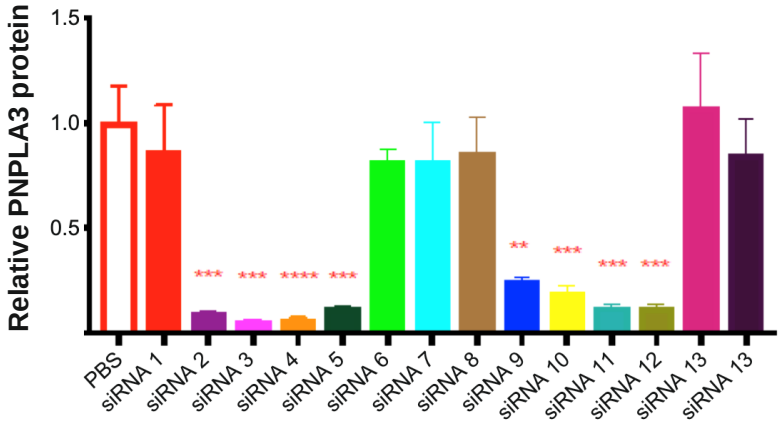
Silencing Hepatic PNPLA3 as Potential Mechanism to Treat NASH

ASO-mediated lowering of PNPLA3 reduces steatosis and NASH activity in mouse model



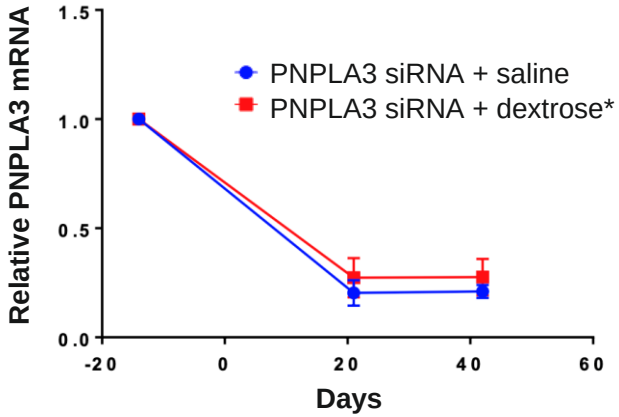
Efficient KD of PNPLA3 protein by candidate siRNAs

Human PNPLA3 I148M knock-in mice



Durable RNAi-mediated silencing of PNPLA3 in NHPs

Following single SC injection

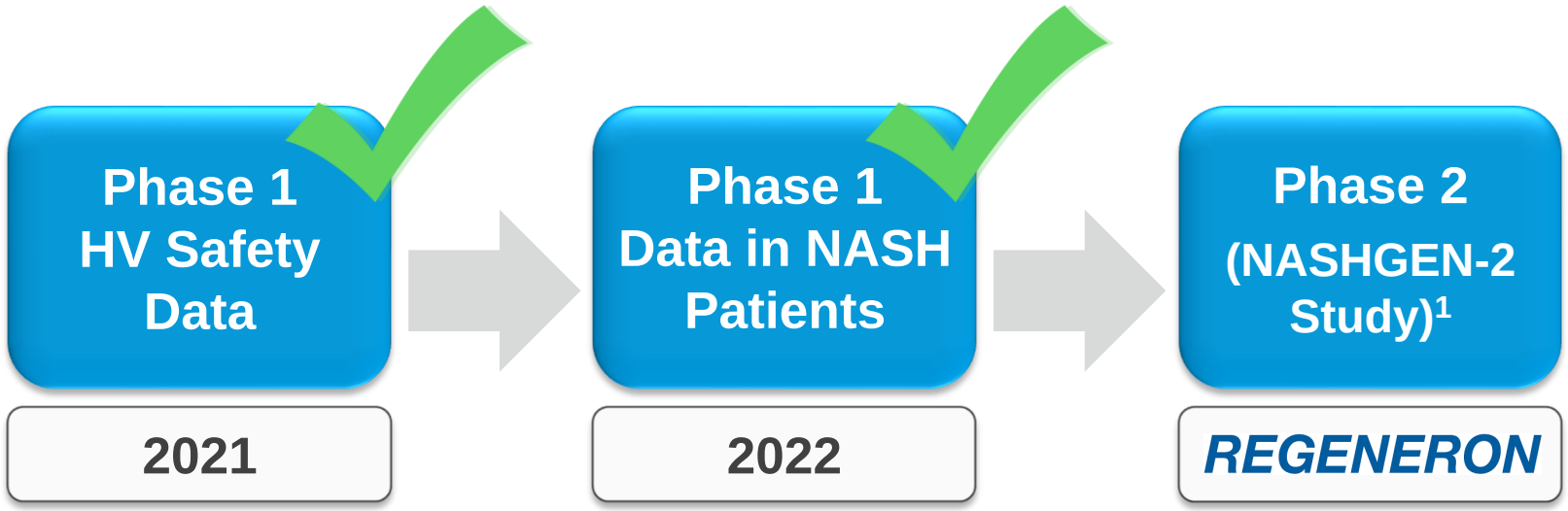


*PNPLA3 is induced by elevated blood glucose

Lindén, D., et al. (2019). Molecular Metabolism 22(), 49-61. https://dx.doi.org/10.1016/j.molmet.2019.01.013

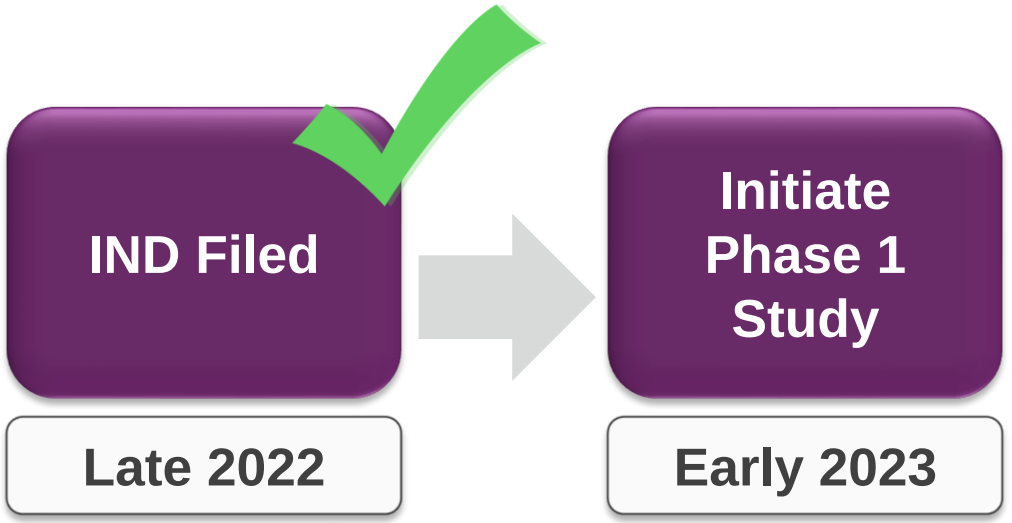
Planned Next Steps for NASH Programs

ALN-HSD



ALN-PNP

REGENERON



[1]NCT05519475

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Programs Across Multiple Tissues and Diseases, Efficiently Executed Alone or With Partners

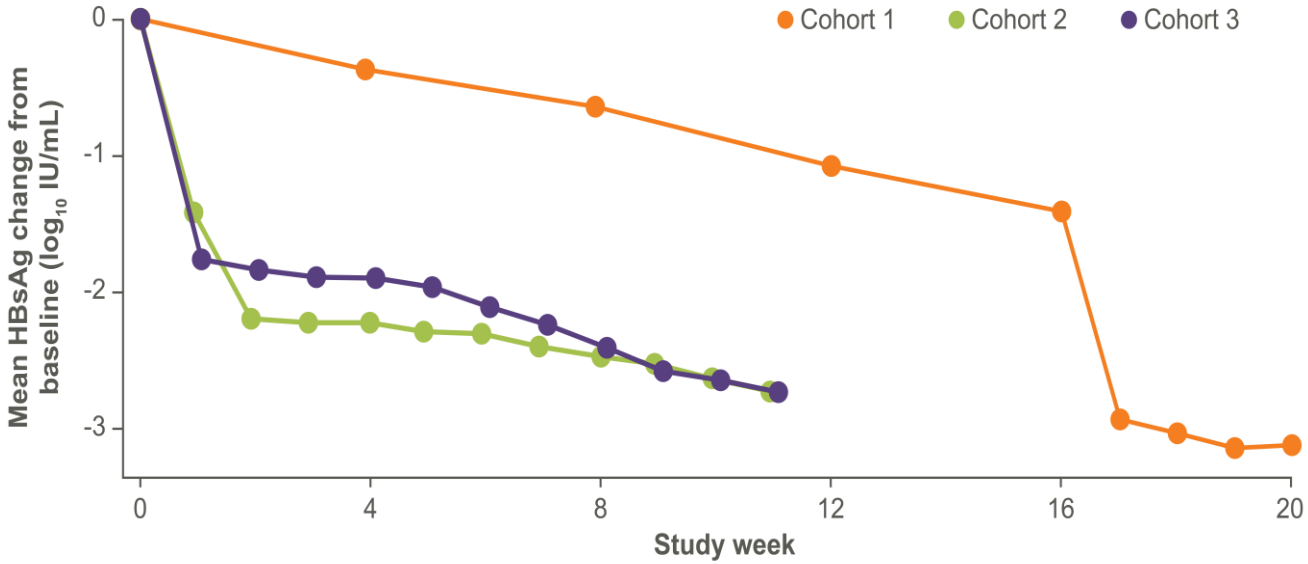
- **Type 2 Diabetes Program**
- **CNS Programs**
- **NASH Programs**
- **Partner-Led Programs**

ALN-HBV02 (VIR-2218)	*Phase 2 studies ongoing*	VIR
Fitusiran	*Phase 3 data*	sanofi
Cemdisiran/pozelimab	*Phase 3 studies ongoing: PNH, MG*	REGENERON

HBV: Global Health Problem Impacting Developed and Developing Countries

Estimated ~290M Diagnosed and Undiagnosed WW; ~24M Diagnosed in Top High-/Middle-Income Countries

VIR-2218 (ALN-HBV02) in combination w/ VIR-3434 (anti-HBV Mab)*



Mean (SD) HBsAg Change from Baseline at end of treatment (log_{10} IU/mL)

Cohort 1	-3.1 (0.4)
Cohort 2	-2.7 (0.3)
Cohort 3	-2.7 (0.6)

- Potential for functional cure of chronic HBV infection with VIR-2218 / VIR-3434 combo regimen
- Achieved mean HBsAg reductions >2.5 log10 IU/mL in all cohorts
- Absolute HBsAg levels <10 IU/mL achieved in most participants (65-100%) at end of treatment
- HBsAg kinetics suggest additive HBsAg reduction from complementary mode of action of VIR-2218 and VIR-3434

Additional Phase 2 HBV readouts expected in **2023**

Phase 2 HDV study ongoing; data expected in **2023**

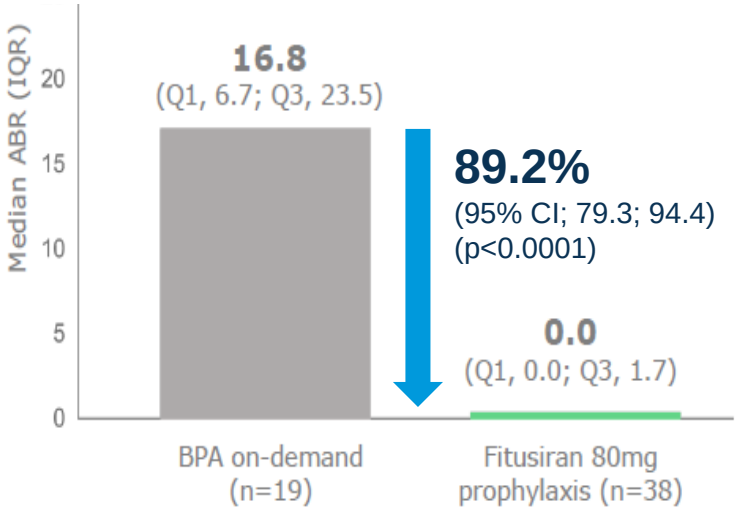
Alnylam opt-in right to VIR-2218 prior to Phase 3

Gane et al., AASLD 2022.

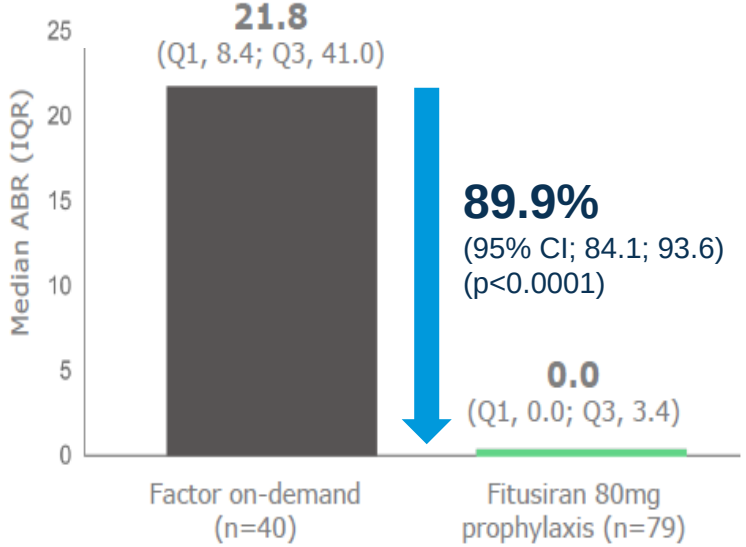
* Investigational therapies in development by VIR

Fitusiran* Demonstrated Profound Reduction in ABR in Hemophilia Patients

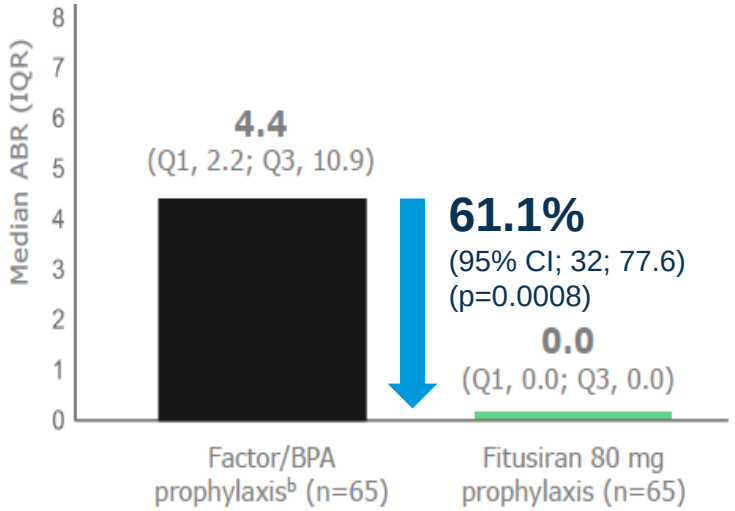
ATLAS-INH: fitusiran vs on-demand bypassing agents: hem A or B **with** inhibitors[1]



ATLAS-A/B: fitusiran vs on demand factor: hem A or B **without** inhibitors[2]



ATLAS-PPX: fitusiran vs prior factor/BPA prophylaxis: hem A or B, **with or without** inhibitors[3]



Safety summary

- Most common Treatment Emergent Adverse Events of Special Interest (TEAESI) in fitusiran patients were liver enzyme elevations >3x ULN (~23%)
- Vast majority of liver enzyme elevations returned to normal and did not result in study discontinuation
- Four suspected or confirmed thromboembolic events in fitusiran arm

Additional Phase 3 data with lower doses expected **Late 2023**

NDA submission expected **2024**

ABR: Annualized Bleeding Rate; BPA: bypassing agent

* Fitusiran is an investigational RNAi therapeutic in Phase 3 development by Sanofi

[1] Young G, et al. Blood 2021;138(Supplement 1):4; [2] Srivastava A, et al. Blood 2021;138(Supplement 2):LBA-3; [3] Kenet G, et al. presented at ISTH 2022

sanofi

Evaluating Role for Combination Therapy in Complement-Mediated Diseases

Multiple Ongoing Clinical Studies with Cemdisiran + Pozelimab*

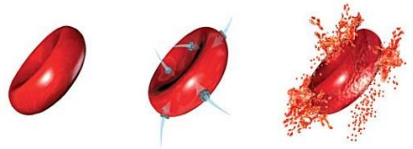
- Pursuing novel approach for diseases where potent inhibition of C5 required

Myasthenia Gravis
Prevalence ~175K
Improve Motor Function & Activities of Daily Living

Phase 3 Study (ongoing)

- **NIMBLE** Study: Adult patients with myasthenia gravis[1]

Paroxysmal Nocturnal Hemoglobinuria
Prevalence ~25K
Reduce RBC hemolysis



Phase 2 Studies (ongoing)

- Evaluating safety and tolerability of two dosing regimens of combination therapy[2]
- Patients who switch from eculizumab therapy[3]

Phase 3 Studies (ongoing)

- **ACCESS-1**: Treatment-naïve adult patients[4]
- **ACCESS-2**: Combo vs eculizumab or ravulizumab[5]

* Pozelimab is an investigational anti-C5 monoclonal antibody in development by Regeneron; cemdisiran is an investigational RNAi therapeutic in development by Alnylam
[1]NCT05070858; [2]NCT04811716; [3]NCT04888507; [4]NCT05133531; [5]NCT05131204

Significant Opportunities from Investigational RNAi Therapeutics

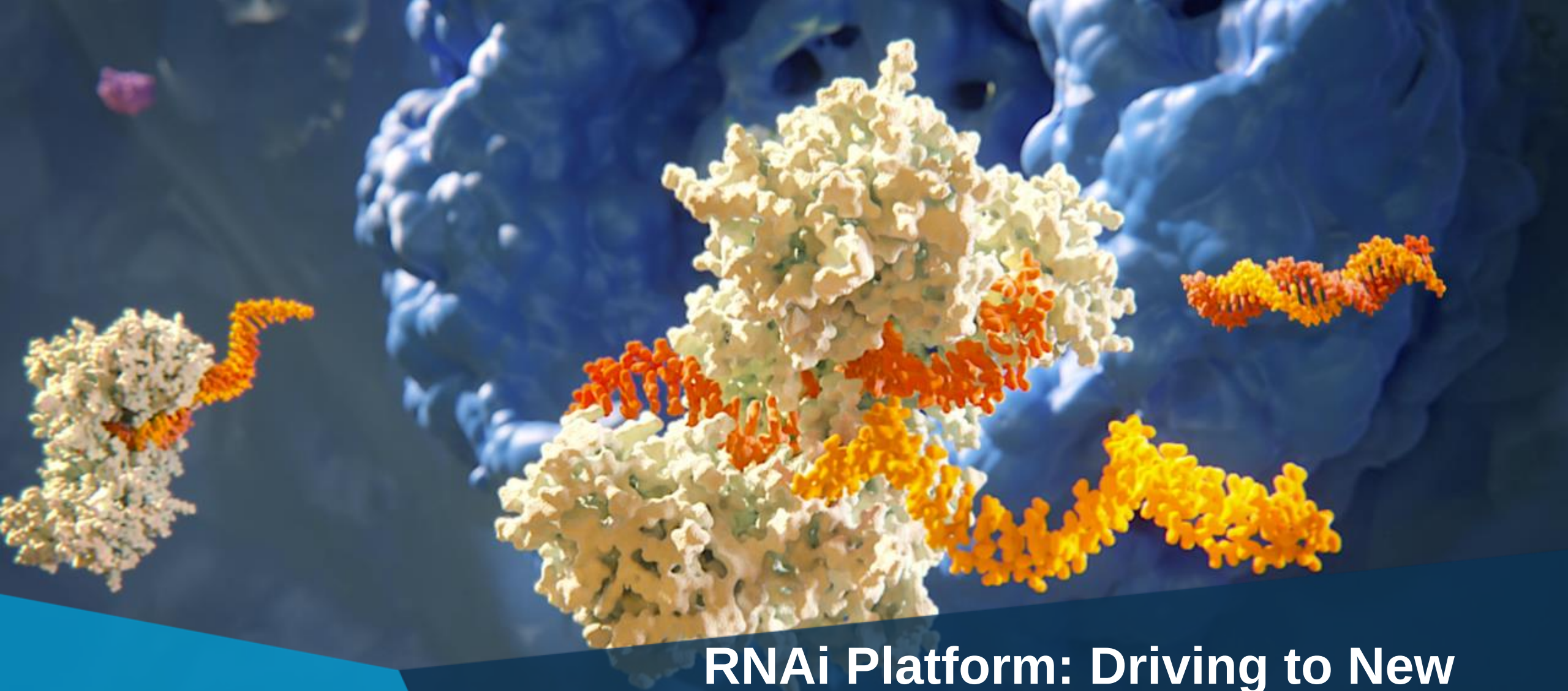
Highly Differentiated Medicines Against Multiple Genetically Validated Targets

- Multiple attractive early-to-mid stage programs addressing areas of high unmet need
  - *ALN-KHK for Type 2 Diabetes*
  - *ALN-APP for Alzheimer's Disease and Cerebral Amyloid Angiopathy*
  - *ALN-HSD and ALN-PNP for NASH*

- Partner programs serve as additional potential source of growth and value creation
  - *ALN-HBV02 (VIR-2218) for chronic HBV infection*
  - *Fitusiran for hemophilia A or B, with or without inhibitors*
  - *Cemdisiran/pozelimab combination for complement-mediated diseases*

- Reliance on genetically validated targets expected to increase probability of success

- Diversity of programs across rare, specialty, and prevalent market opportunities, supported by platform safety profile and potential for tonic control of target gene expression with infrequent dosing



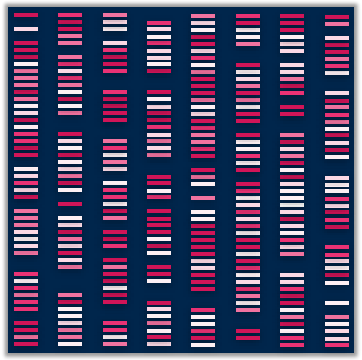
RNAi Platform: Driving to New Targets and Tissues

Aimee Deaton, Ph.D. – Associate Director, Human Genetics
Vasant Jadhav, Ph.D. – SVP, Research

Alnylam®@20

Sources of Sustainable Innovation

Human Genetics



+ Our Future Health

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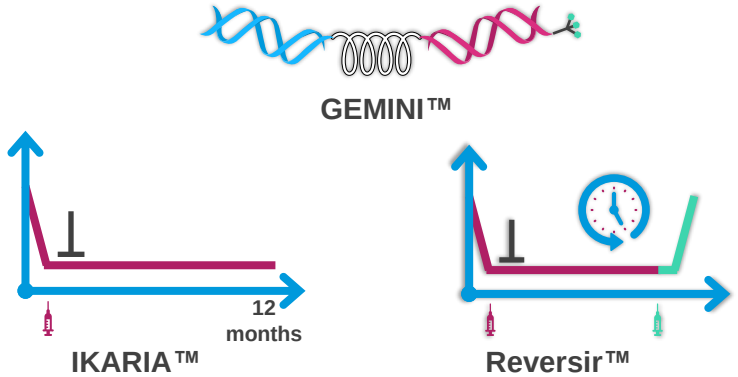
- Sourcing novel, genetically validated targets
- Secured access to large PheWAS databases
- Proven ability to uncover novel gene targets (e.g., *HSD17B13*, *INHBE*, and more)

Platform Designs



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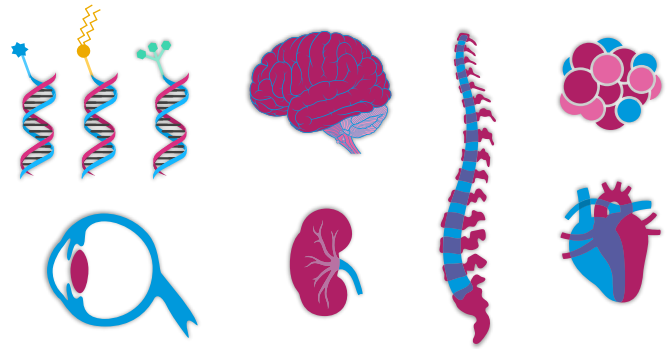
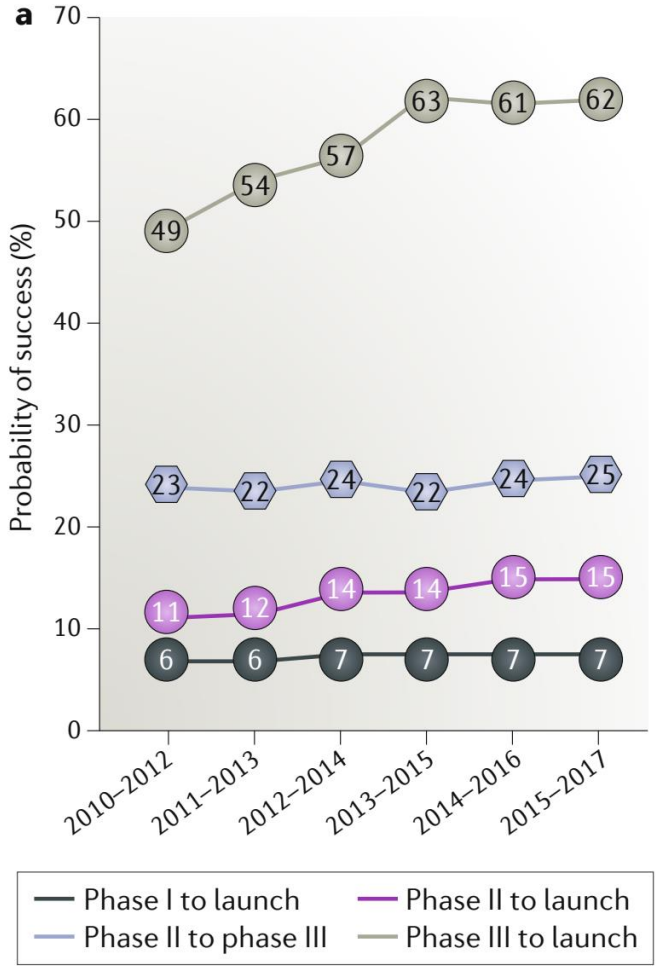
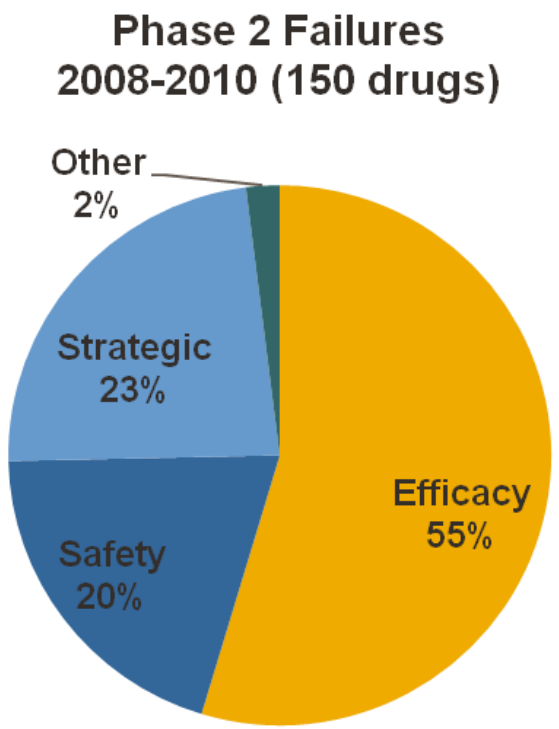
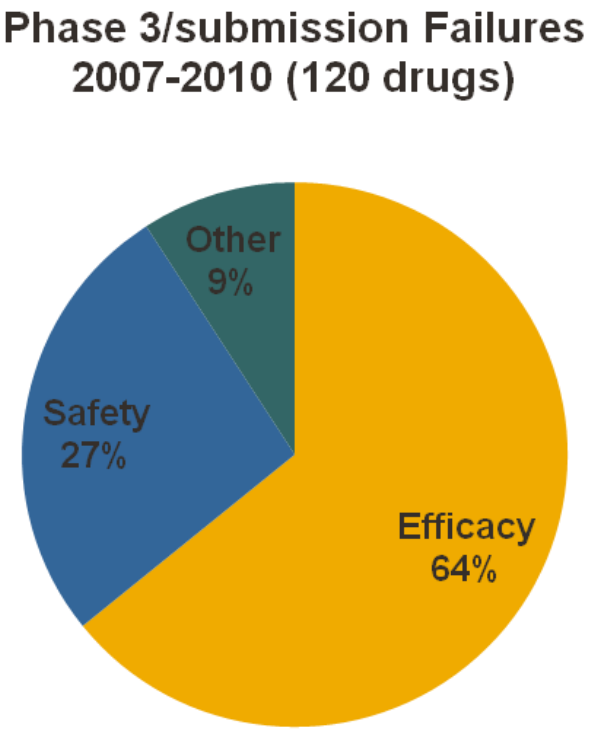


- Novel conjugates with variety of ligands for delivery beyond liver
- C16 conjugate provides robust CNS knockdown with wide biodistribution and long duration of action
- Peptide and antibody-based approaches being explored for targeted siRNA delivery to new tissues

Drug Development Has a High Rate of Failure







Sources: Dowden and Munro (2019) Nat. Rev. Drug Disc. 18, 495-496, Hay et al. (2014) Nat. Biotech. 32:40-51, Arrowsmith & Miller (2013) Nat. Rev. Drug. Disc. 12:569

Traditional Target Discovery Has Had Challenges

Lack of Understanding of Disease Mechanisms in Humans

≠

Human Genetically Validated Targets More Likely to Lead to Approved Drugs

Mutation in gene encoding drug target → **Phenotype that matches desired outcome**

Medicines are 2x more likely to be approved if target is genetically validated

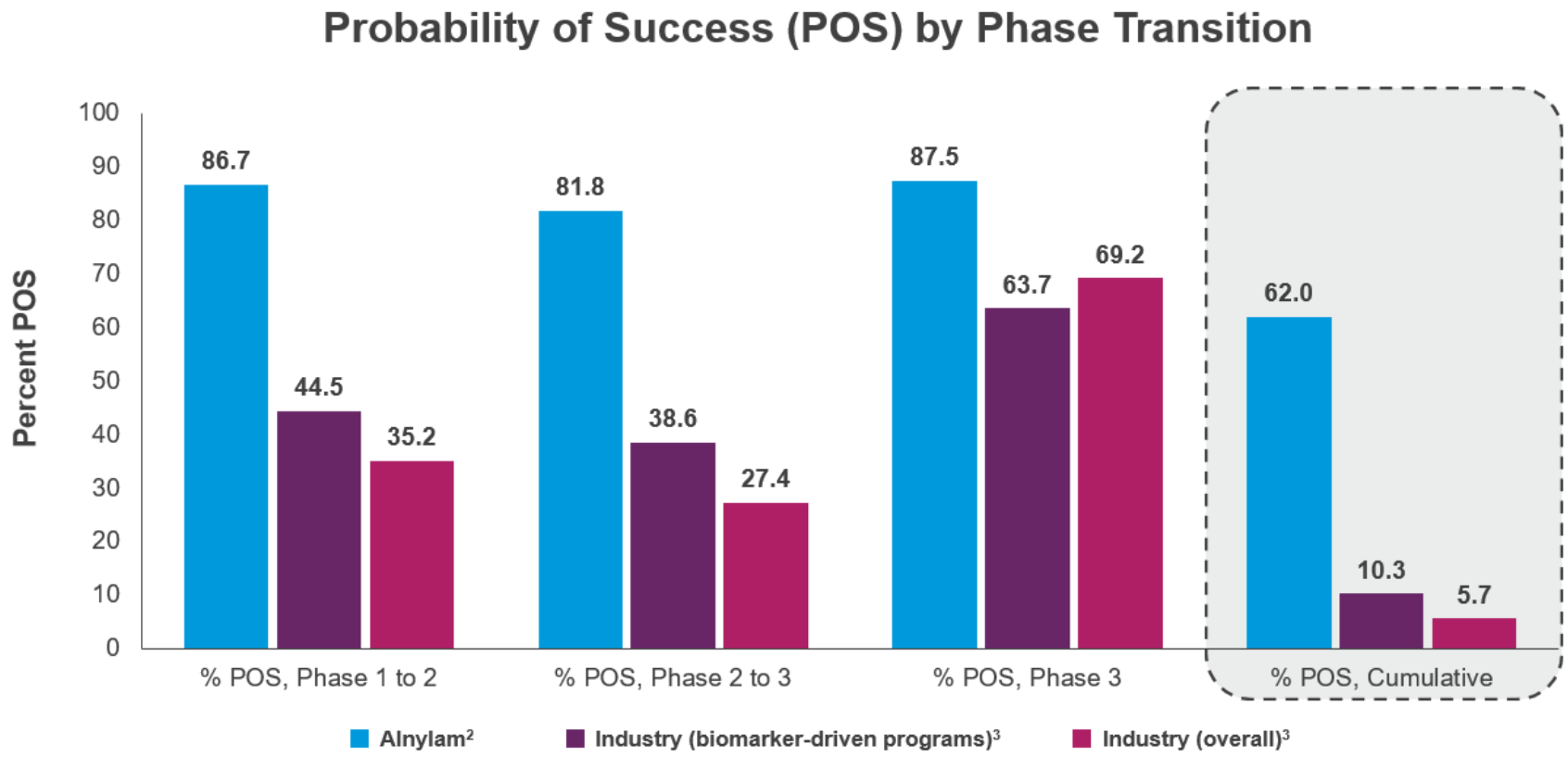
Progression	*p*(progress|genetics) / *p*(progress|no genetics)
Phase I to Phase II	1.2 (1.1-1.3)
Phase II to Phase III	1.5 (1.3-1.7)
Phase III to Approval	1.1 (1.0-1.2)
Phase I to Phase III	1.8 (1.5-2.1)
Phase I to Approval	2.0 (1.6-2.4)

Nelson et al., Nat Gen. 2015,47:856-60.

King et al, 2019 https://doi.org/10.1371/journal.pgen.1008489
Nelson et al, 2015 https://doi.org/10.1038/ng.3314

Alnylam's Rate of Success is Higher Than Industry Standards

- Historic probability of clinical success multiples higher than industry standards[1]
- In part, due to our focus on genetically validated targets and genetic disease



[1] Analysis as of December 2022; Past rates of Alnylam and industry respectively may not be predictive of the future
[2] Alnylam programs biomarker-driven at all stages of development (100%); figures include Alnylam-originated molecules now being developed by partners
[3] Wong et al., Biostatistics (2019) 20, 2, pp. 273–286

Investing to Discover New Genetically Validated Targets

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- 500,000 participants
- Genotyping
- Exome sequencing
- Biomarkers
- Diseases
- Proteomics

- ***TTR* V122I & polyneuropathy**
- ***INHBE* loss of function and abdominal obesity**
- **'Gene Y' for T2D**

Our Future Health

- 5 million participants
- Genotyping
- Health information
- Recontact of participants

- **Data coming 2023-2026**

RGC™ Regeneron Genetics Center

- Access to additional cohorts
- Data from health systems

- ***HSD17B13* for NASH**
- **Validation of *INHBE***

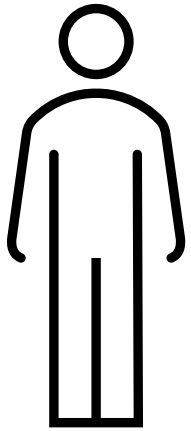
Alnylam® HUMAN GENETICS

INHBE Loss of Function Decreases Waist-to-Hip Ratio

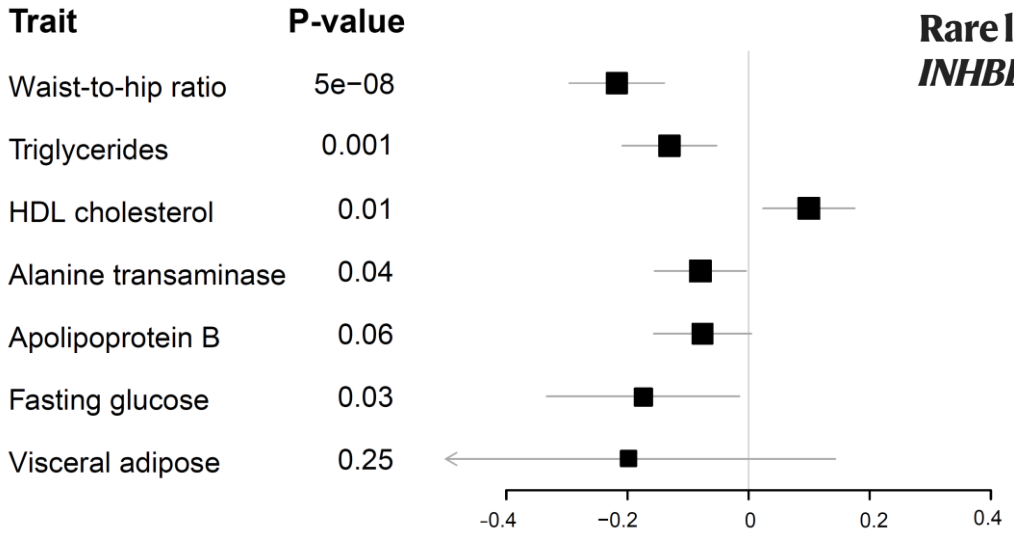
- Loss of function (LOF) in *INHBE* is associated with lower waist-to-hip ratio

Gene	Cohort	P-value	Effect (95% CI)	N	N carriers
***INHBE* LOF**	UK Biobank	5.0×10^{-8}	-0.22 (-0.30, -0.14)	362061	618
	T2D-GENES	9.4×10^{-4}	-1.03 (-1.60, -0.42)	13456	10

- Carriers have a favorable metabolic profile



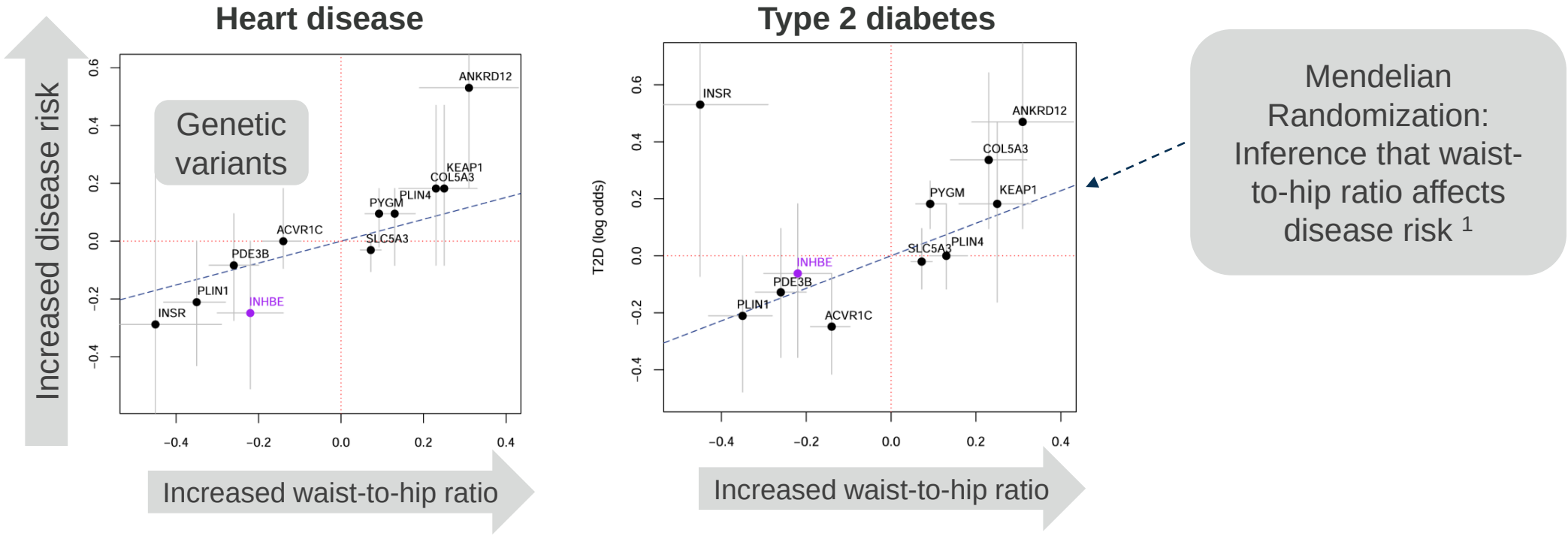
Genetic decrease in INHBE (~50%)



Deaton et al., Nat Comm 2022 https://doi.org/10.1038/s41467-022-31757-8

Fewer Cases of Heart Disease & Type 2 Diabetes for *INHBE* LOF Carriers

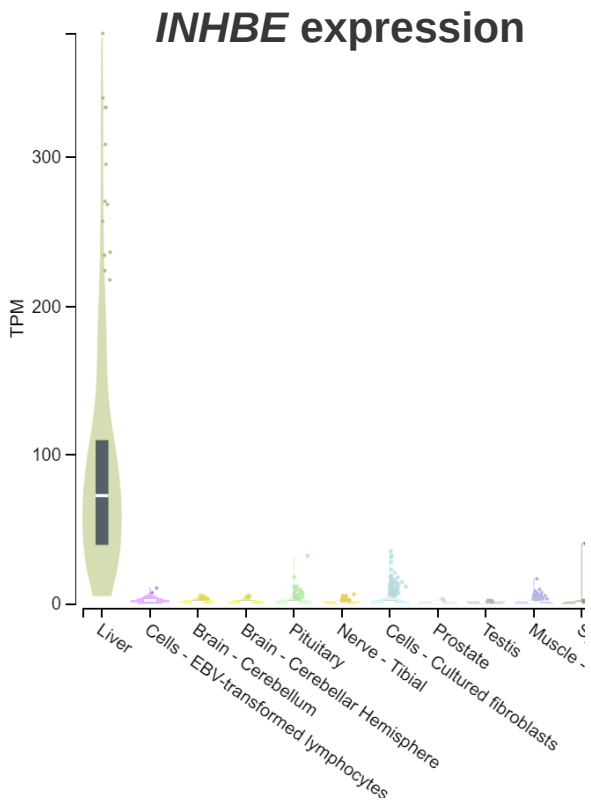
- Waist-to-hip ratio reflects abdominal fat and directly affects risk for cardiometabolic disease
- Fewer cases of coronary heart disease and type 2 diabetes for *INHBE* LOF carriers
  - Effect on disease is proportional to the effect on waist-to-hip ratio[1]

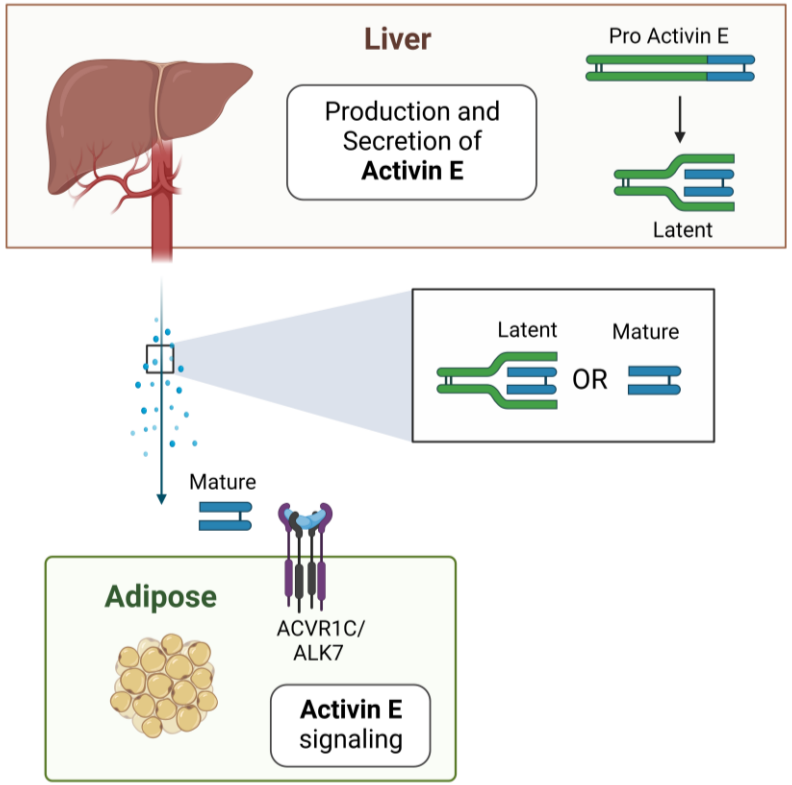


[1] Emdin et al., JAMA 2017 https://doi.org/10.1001/jama.2016.21042

INHBE Encodes the Hepatokine Activin E

- *INHBE* is exclusively hepatocyte-expressed
- Encodes the inhibin βE subunit of **activin E**, a secreted protein which likely binds to receptors on adipose tissue





RNAi suppression of INHBE may improve cardiometabolic disease in a way that is mechanistically distinct from current therapies

There is Unmet Need in Type 2 Diabetes

- Half of individuals with type 2 diabetes fail to achieve target HbA1c despite lifestyle changes and multiple treatment options
  - Low rate of compliance for many therapies

Proportion of Patients in HbA1c Range: Lack of Control in 50%	
HbA1c Range	**Percent of Individuals**
7 to 8%	22.4%
8 to 8.9%	13.2%
>9%	14.6%

No new class of medications since:

- 2013: Canaglifozin (SGLT2i)
- 2005: Byetta

- There is a medical need for additional treatments with orthogonal mechanisms to avoid insulin dependence

Liver

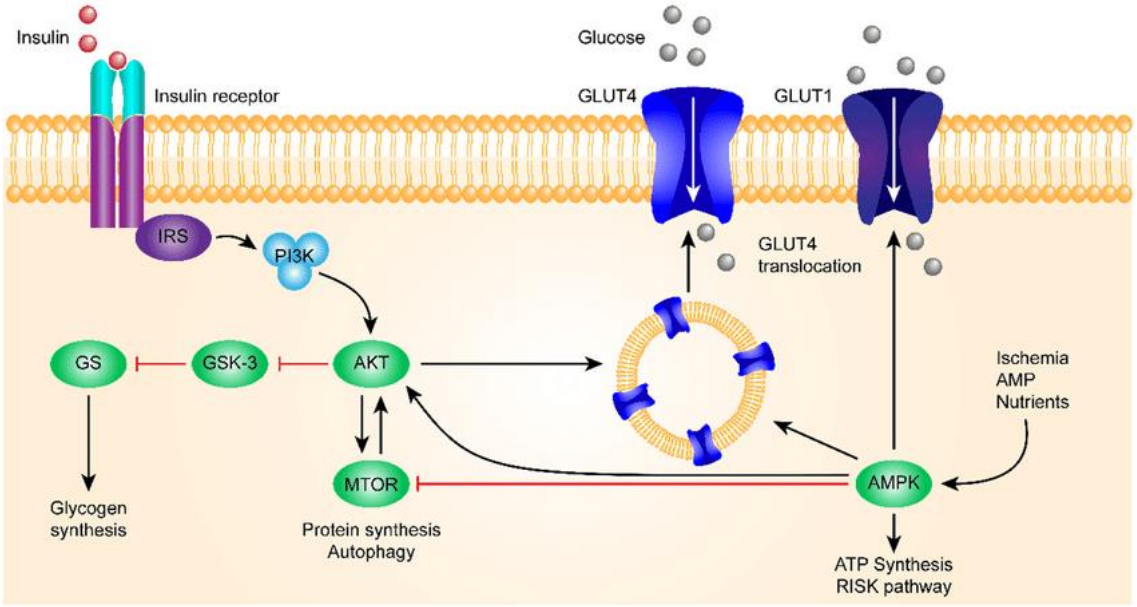
- Excessive hyperglycemia
- Steatosis
- Hepatic insulin clearance

→

Type 2 Diabetes & Insulin Resistance

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

Liver ‘Gene Y’ is a Potential Target for Type 2 Diabetes



- Modulate insulin signaling to improve Type 2 Diabetes
- ‘Gene Y’ is liver-enriched and negatively regulates insulin signaling

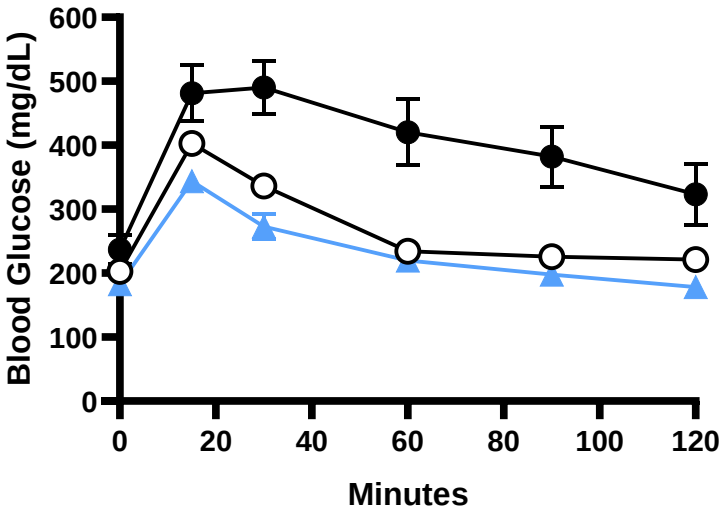
Reduced Type 2 Diabetes risk and HbA1c for a damaging missense variant of ‘Gene Y’

Gene	Variant Frequency	Variant Consequence	Trait	P-value	Effect
‘Gene Y’	2.4%	Missense	Type 2 Diabetes	6.7×10^{-10}	0.84 odds ratio
			HbA1c	0.002	0.79 mmol/mol

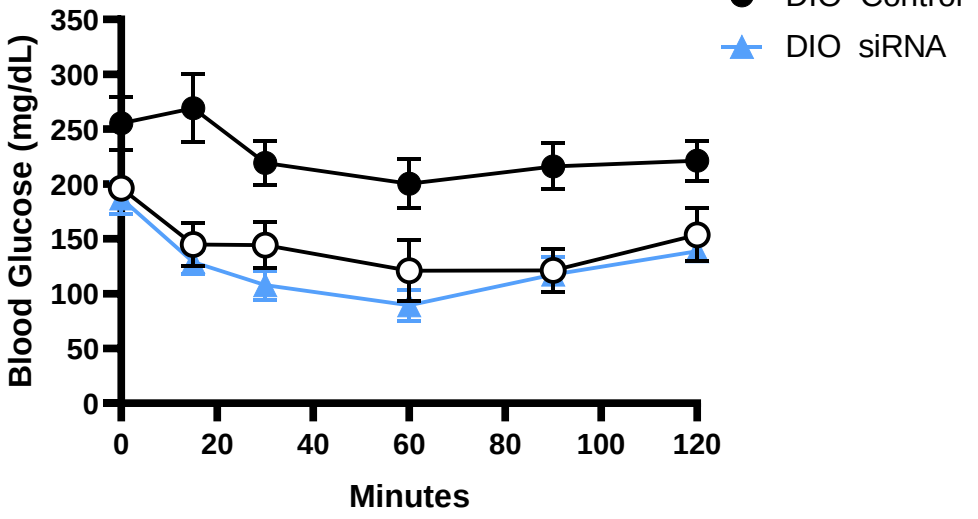
Knockdown of ‘Gene Y’ in Liver of Diet-Induced Obese (DIO) Mice Improved Glycemia and Reduced Liver Fat without Weight Gain

Different siRNAs Targeting ‘Gene Y’ Replicate This Effect of a Liver-Specific Insulin Sensitizer

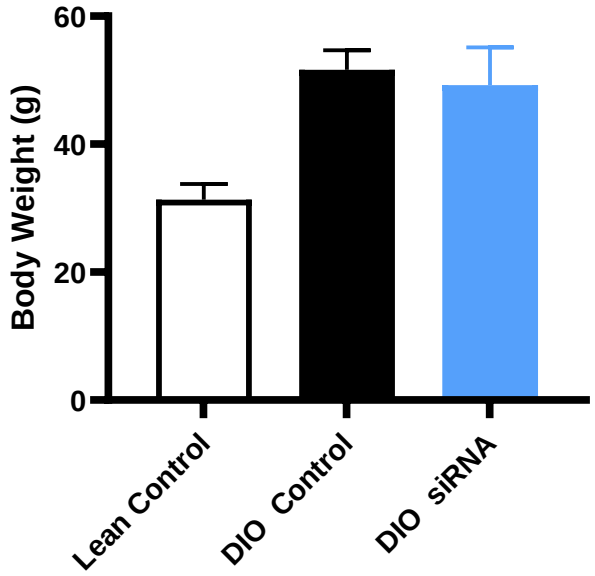
Blunting of hyperglycemic response



Improved insulin sensitivity



No body weight gain



Additional Observations with ‘Gene Y’ Knockdown in DIO Mice:

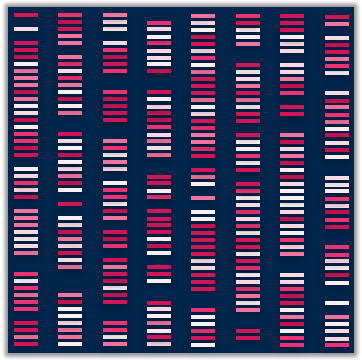
- Enhanced insulin sensitivity in liver & extrahepatic tissues
- Reduced liver fat
- Reduced homeostasis model assessment-estimated insulin resistance (HOMA-IR)

Summary

- Alnylam has made a significant commitment to genetics as targets with genetic validation are more likely to lead to approved drugs
- Association of *INHBE* LOF with lower waist-to-hip ratio supports potential of INHBE to be evaluated as novel therapeutic target for treatment of cardiometabolic disease
- Currently pursuing development candidate for INHBE using hepatocyte-directed siRNA, DC expected in 2023
- Genetics identified ‘Gene Y’ as novel target for type 2 diabetes. Consistent with this, hepatic silencing of ‘Gene Y’ improves insulin sensitivity in obese mice

Sources of Sustainable Innovation

Human Genetics



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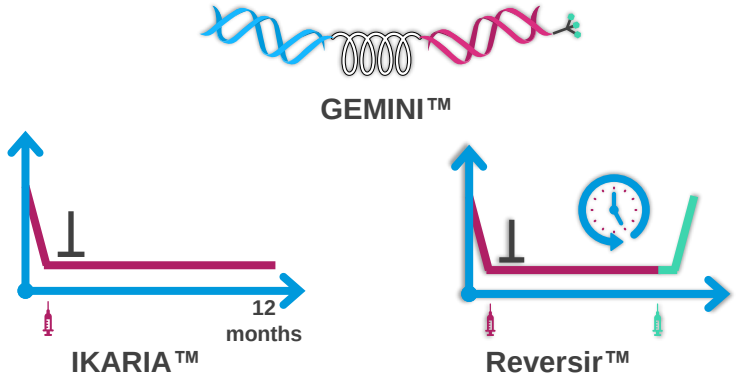

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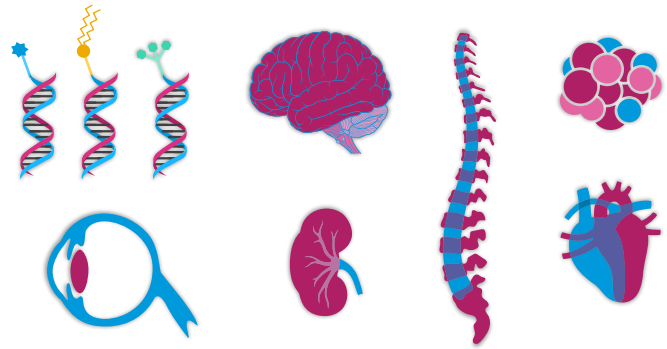

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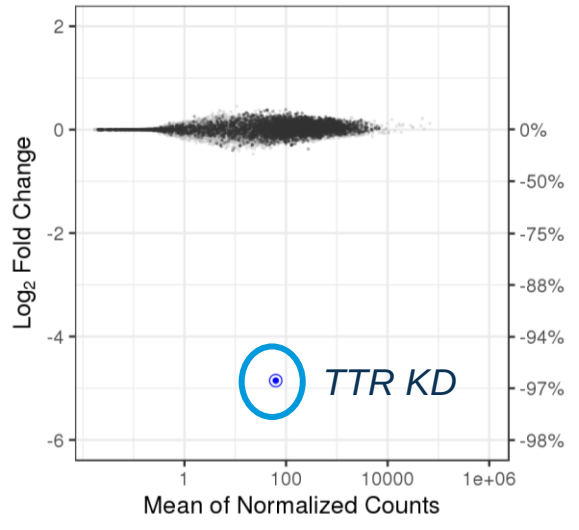
IKARIA™ Platform: Proprietary siRNA Design with Novel Chemistry

Super-Specific siRNAs May Enable Higher Doses to Achieve Annual Dosing

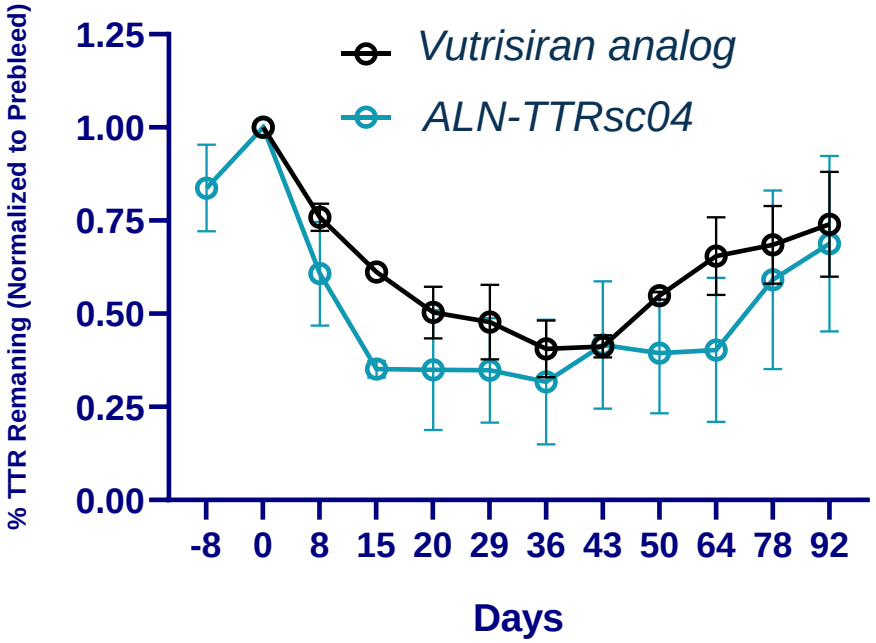
Exquisite specificity



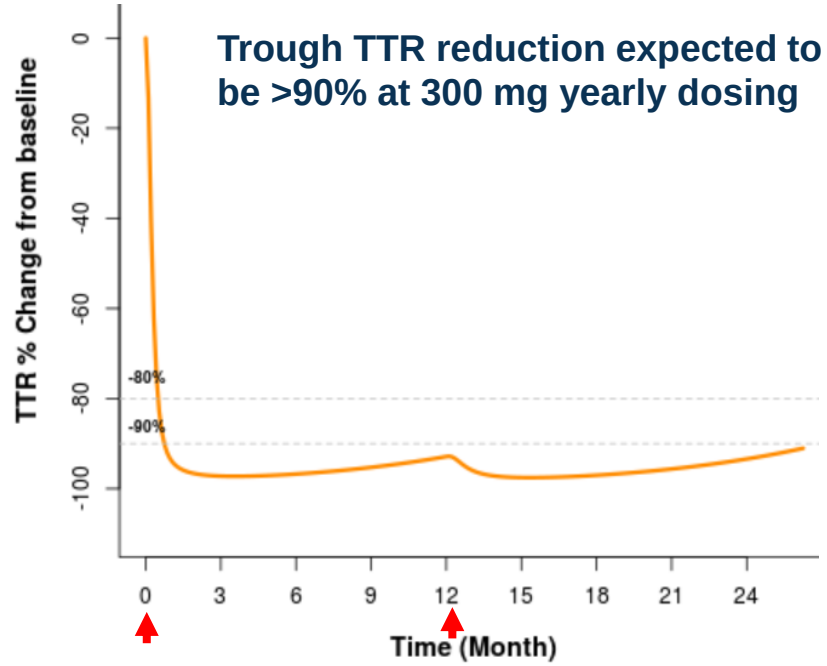
RNAseq analysis

High potency in NHP

0.5 mg/kg single SC dose



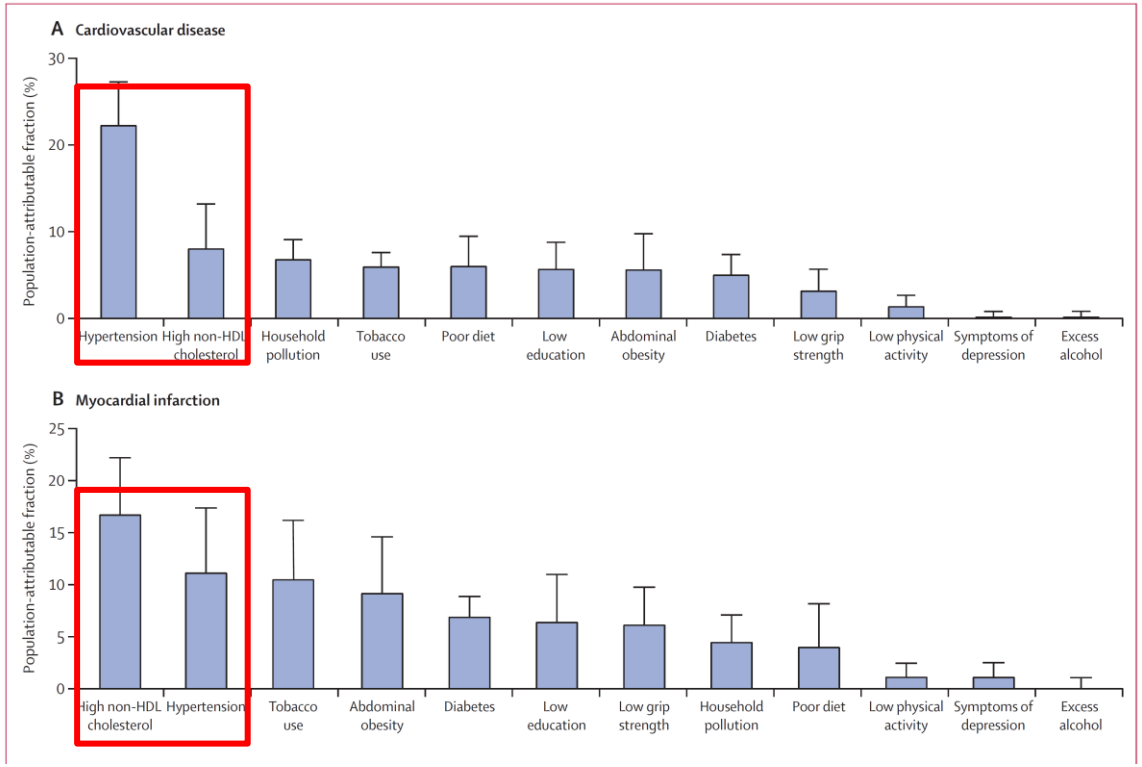
Human dose projection



Multiple siRNAs against different targets identified with IKARIA™ profile

Gemini/Bis-RNAi™ Platform: Potential Applications in Multi-Gene Indications

Elevated blood pressure and cholesterol are two leading CV risk factors

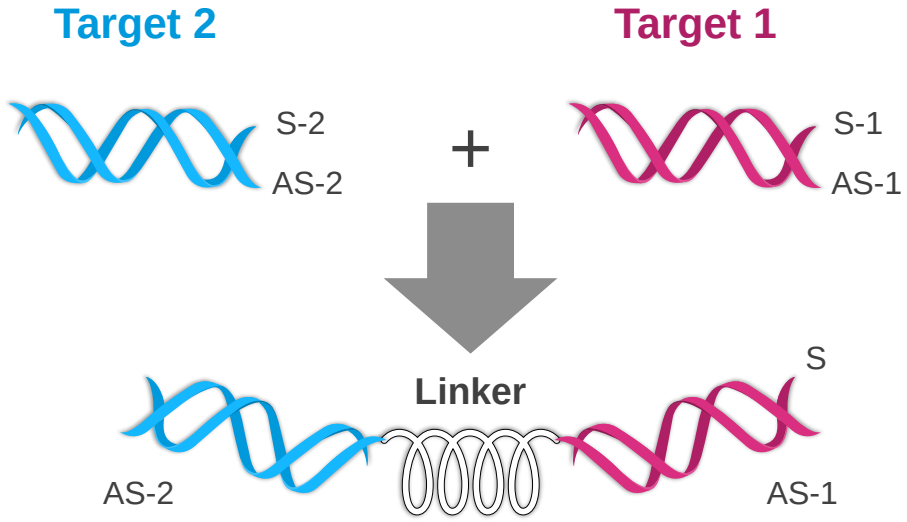


Gemini/Bis-RNAi™

- Effectively combine conjugate siRNAs for the simultaneous silencing of two transcripts or same (for viruses) using single chemical entity

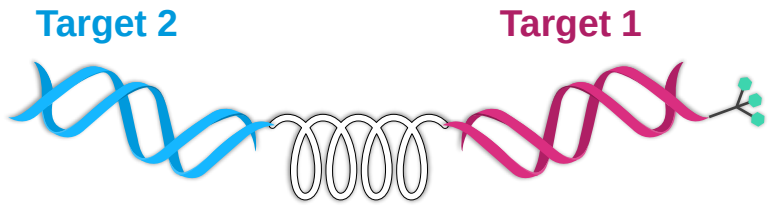
Benefits

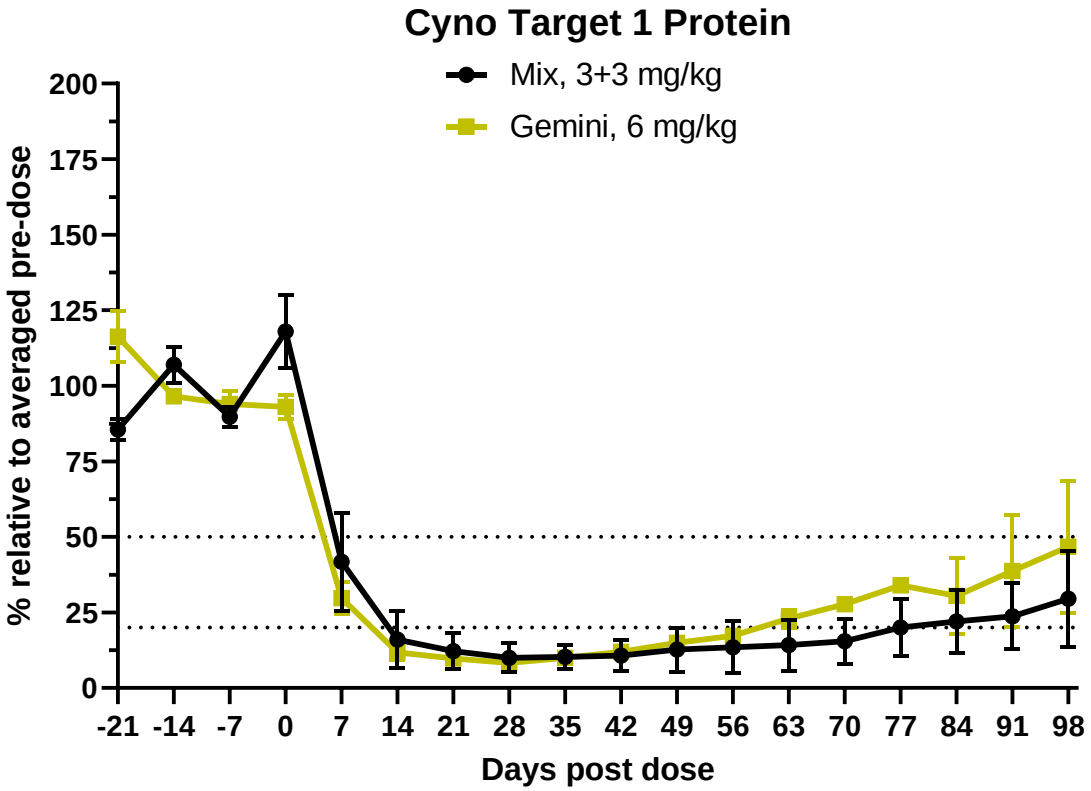
- Potentially simplified clinical development path compared to two entities or combo
- Ensures uptake of both siRNAs in same cell across tissue types (e.g. liver, CNS)
- Controlled, parallel reductions in two targets

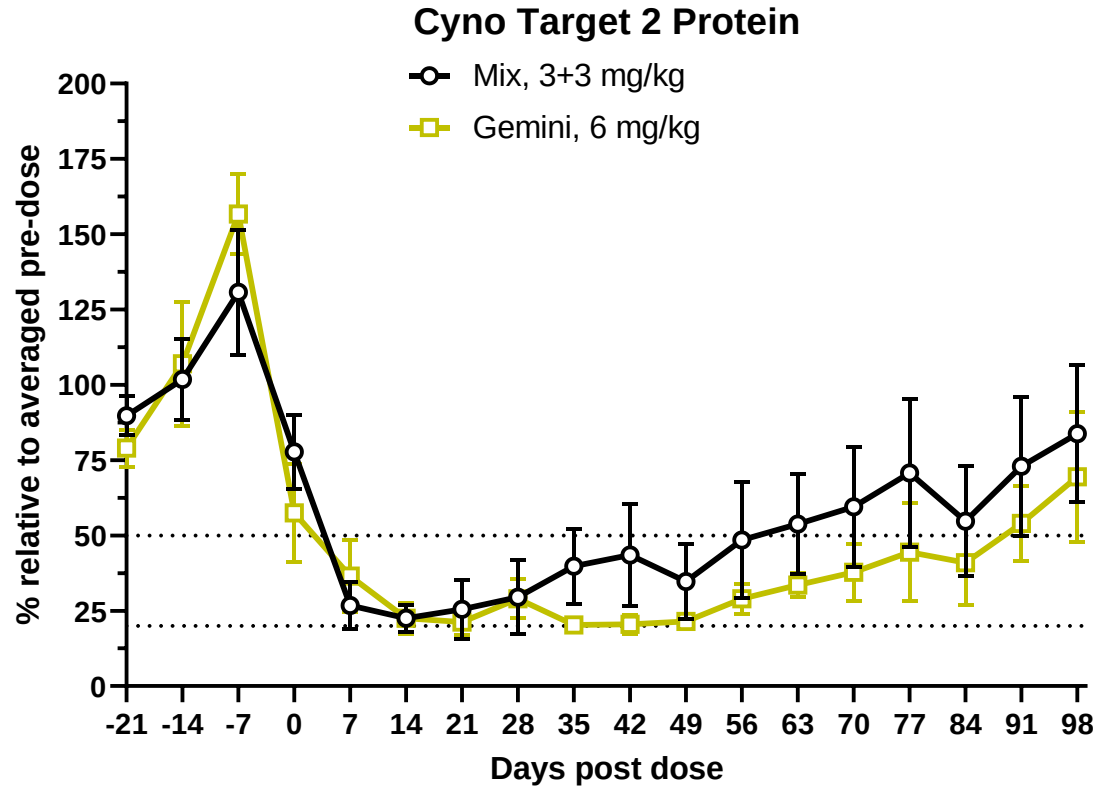


Yusuf et al, (2020) Lancet. Modifiable risk factors, cardiovascular disease, and mortality in 155,722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study

Gemini-GalNAc Candidate Compound with Optimal Linker Demonstrated Potent and Durable Activity in NHP



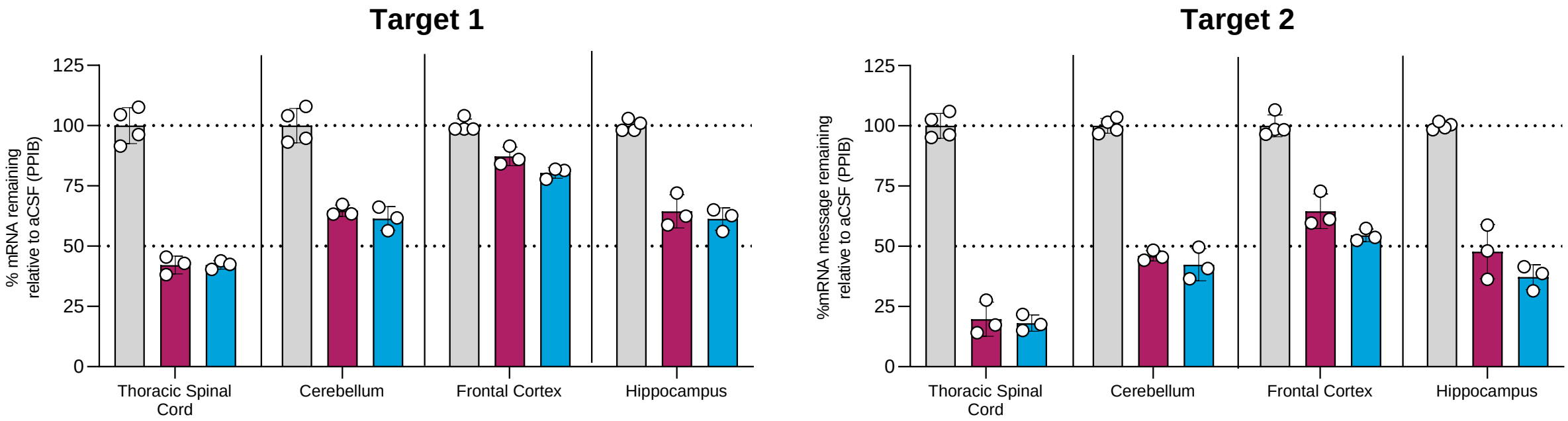




Gemini Approach Also Attractive for CNS Indications

Potential to Target Multiple Genes Implicated in Alzheimer's Disease, ALS, Parkinson's Disease and Others

GEMINI-C16 Candidate Compound Demonstrated High Potency in Rat CNS



aCSF

1+1 mix (0.3 mg + 0.3 mg)

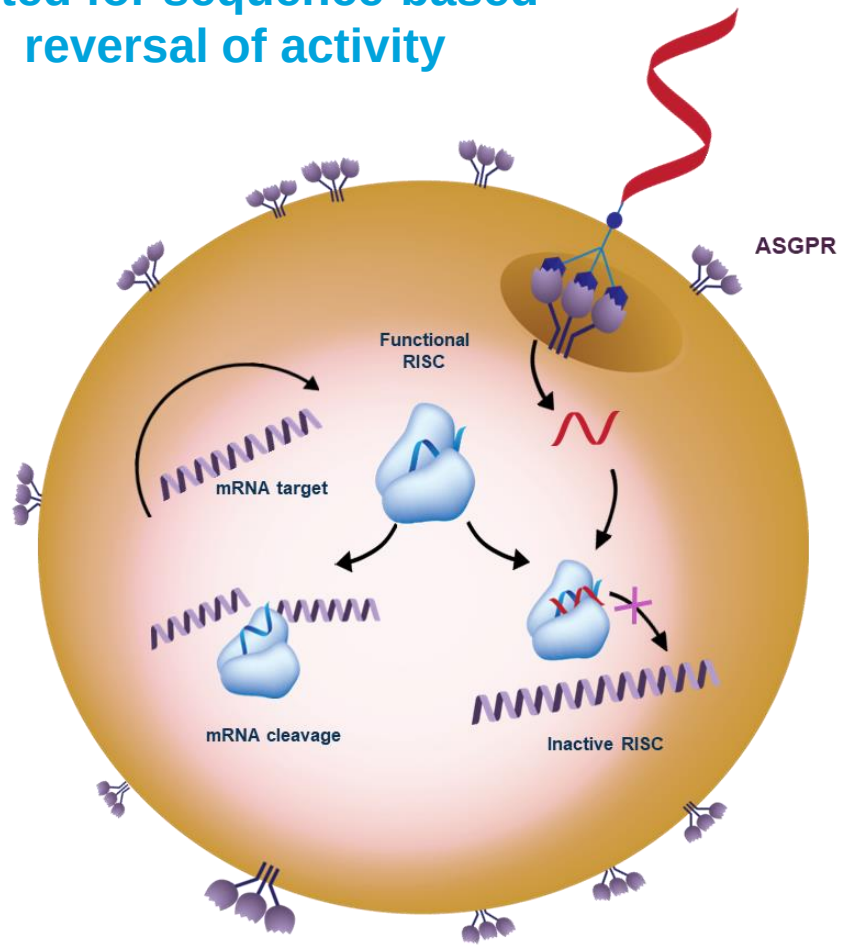
Gemini (0.6 mg)

REVERSIR™ Platform Provides Tailored Control of RNAi Pharmacology

Commonly used antidotes/reversal agents

Category	Drug	Antidote/ Reversal Agent
Analgesics	• Acetaminophen • Morphine	• Acetylcysteine • Naloxone
Anticoagulant	• Warfarin • Heparin • Dabigatran • Apixaban or Rivaroxaban	• Vitamin K • Protamine • PRAXBIND • ANDEXXA
Antidiabetic	• Insulin	• Glucose • Glucagon

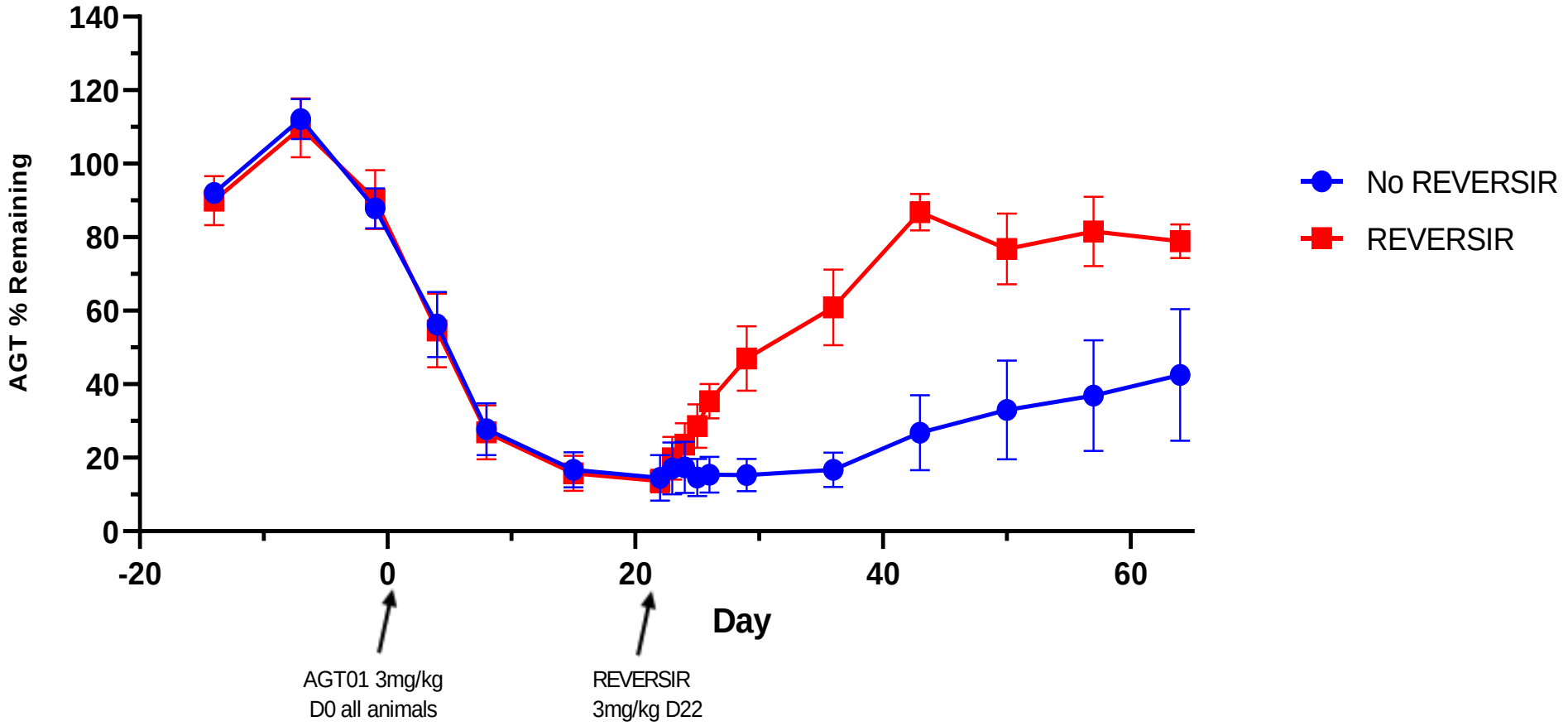
siRNA technology uniquely suited for sequence-based reversal of activity



Nature Biotechnology 36, 509–511 (2018)

REVERSIR Demonstrates Potent and Durable Reversal of Zilebesiran Activity in NHP

With long-acting pharmacology of zilebesiran, Reversir offers option for the rapid reversal of drug effect



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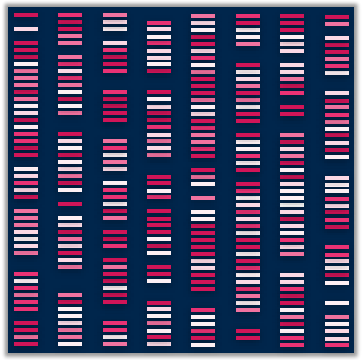

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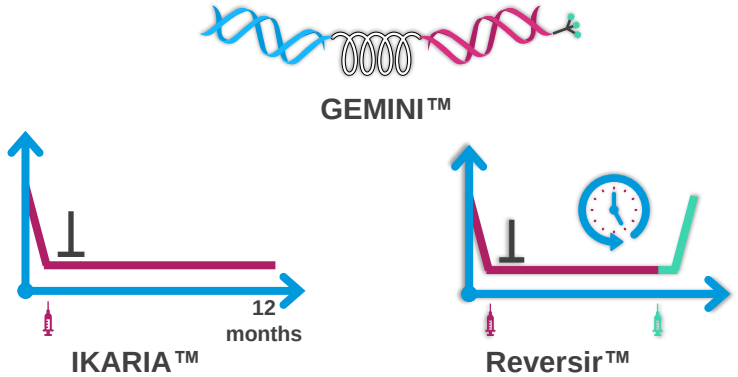

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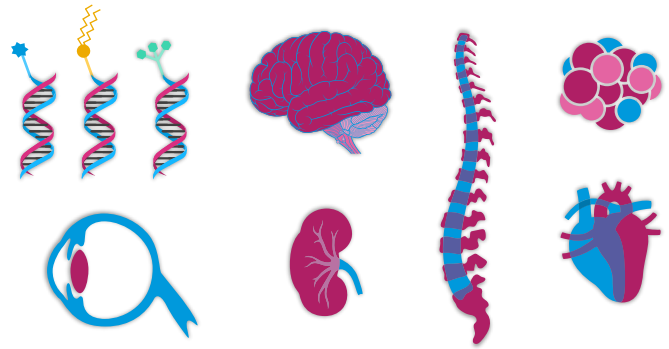

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RNAi Therapeutics for CNS Diseases

No Current Therapies to Prevent Neurodegenerative Disease

Very high unmet need for new treatments for CNS Diseases

- Genetically defined neurodegenerative diseases include
  - Alzheimer's disease
  - Amyotrophic lateral sclerosis (ALS)
  - Frontotemporal dementia
  - Huntington's disease
  - Parkinson's disease
  - Prion disease
  - Spinocerebellar ataxia
  - Many other orphan genetic diseases with CNS component

- Number of genetically validated targets known but no current disease modifying therapies for these devastating, life-threatening disorders
- Significant opportunity for RNAi therapeutics directed to disease-causing, CNS-expressed genes
- Based on pre-clinical studies, potential for increased potency and duration of effect, and improved systemic safety profile

RNAi Therapeutics Can Be Delivered to the CNS

Potent, Durable Gene Silencing Achieved in Animals with CNS Conjugates

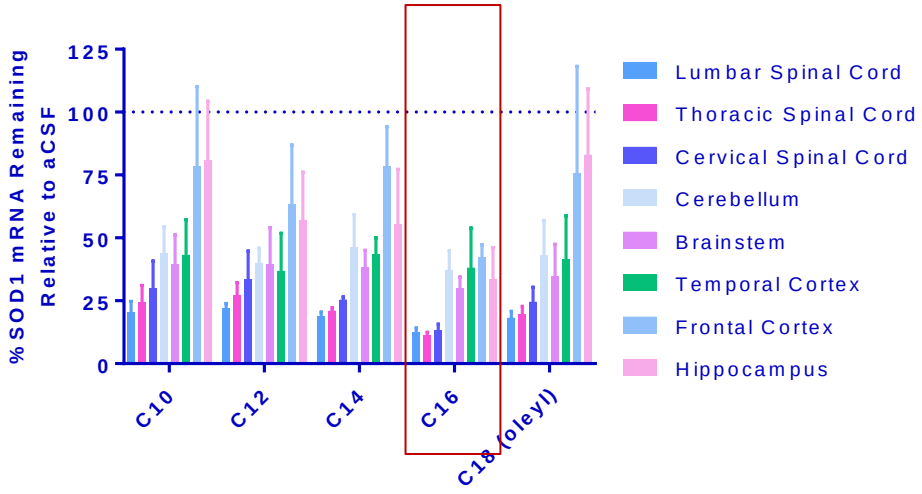
C16 conjugate platform designed to optimize potency, durability, and safety

- Exhaustive optimization of siRNA lipophilic moiety, position, and design chemistry
- Backbone modifications to enable similar metabolic stability to liver platform (e.g., ESC+)
- Vinylphosphonate (VP) modification improves potency through enhanced RISC-binding

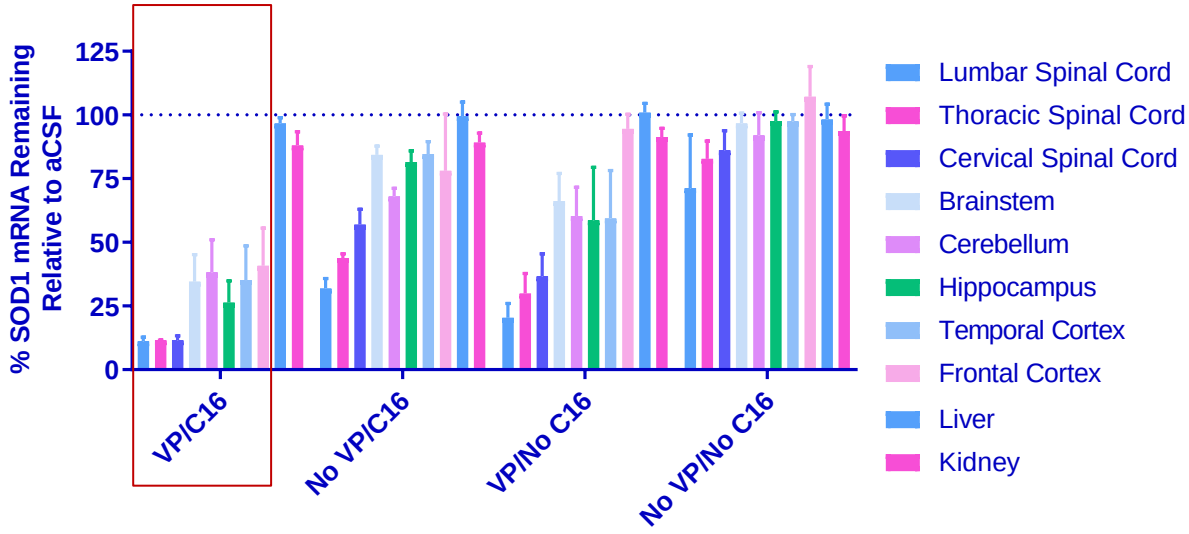
OTS Paper of the Year 2022

Nature Biotechnology
Expanding RNAi therapeutics to extrahepatic tissues with lipophilic conjugates
Brown, et al.

Single 0.9 mg IT Dose Rat (Day 14)



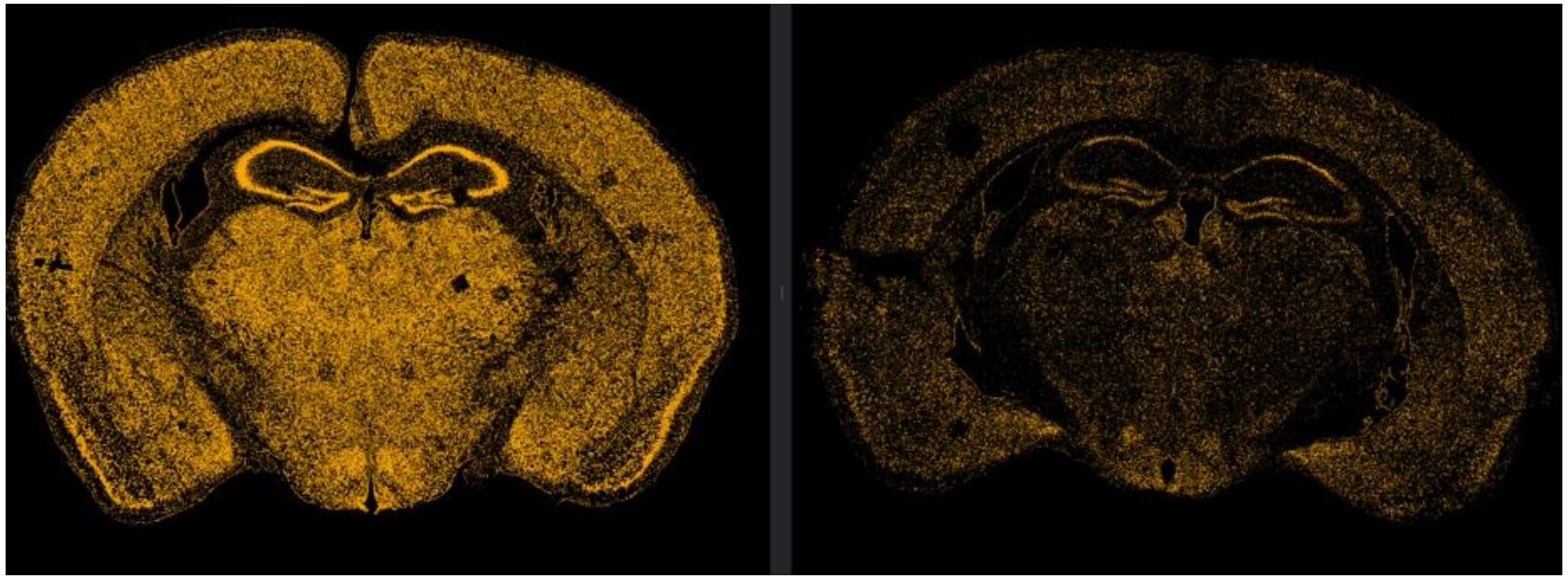
Single 0.9 mg IT Dose (Day 28)



Robust Knockdown Across Brain Regions of Mice

Single Intracerebroventricular (ICV) Dose in Mice at Day 21 Post-Dose

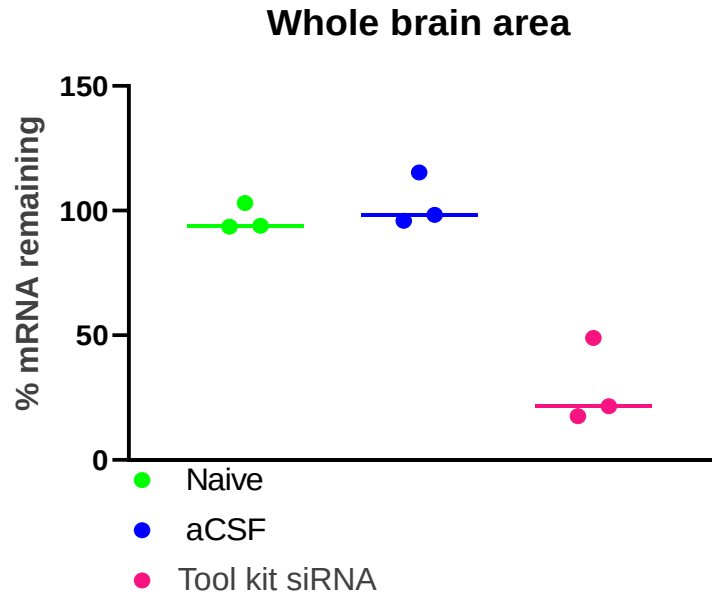
MERFISH reveals spatial resolution of target mRNA knockdown



Control

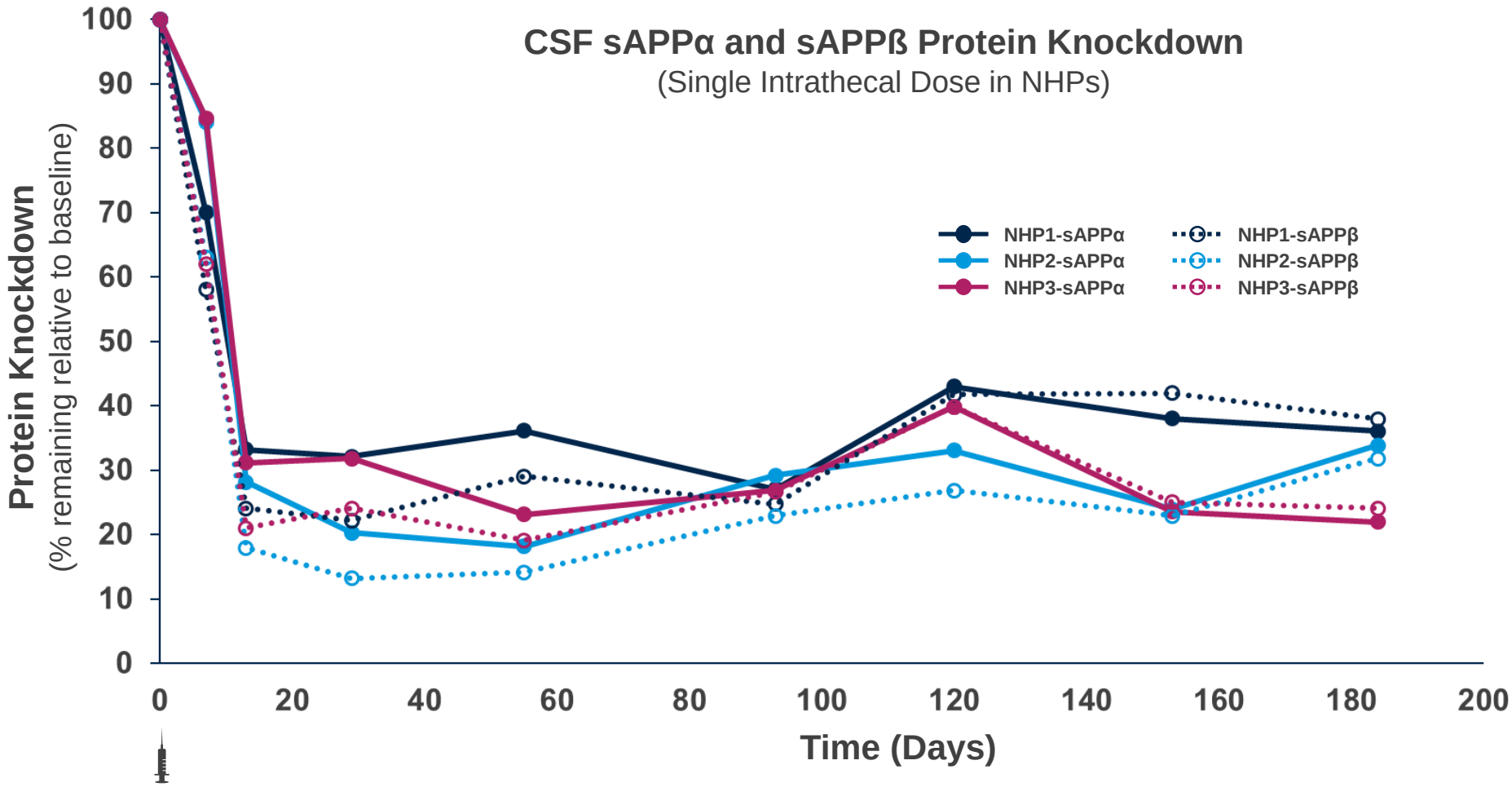
Tool kit siRNA

Quantification of target KD



Highly Durable Amyloid Precursor Protein (APP) Knockdown in NHP

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



ALN-APP Phase 1 ongoing

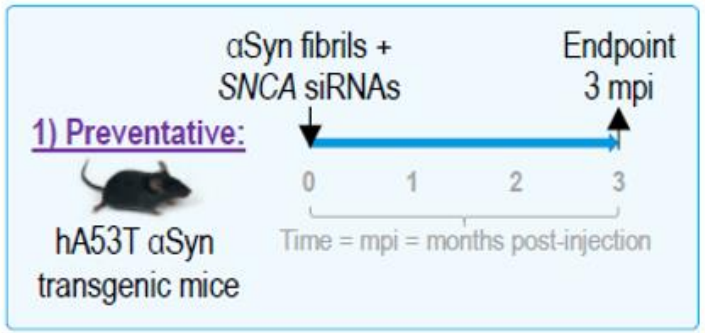
Initial data expected early 2023

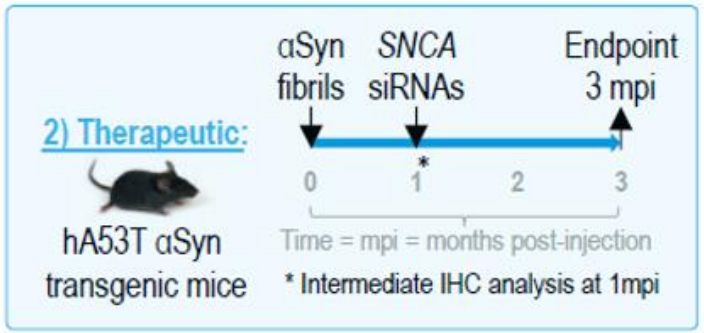
Pre-Clinical Evaluation of *SNCA* siRNA in a Synucleinopathy Mouse Model of Parkinson's Disease

Synucleinopathy Mouse Model

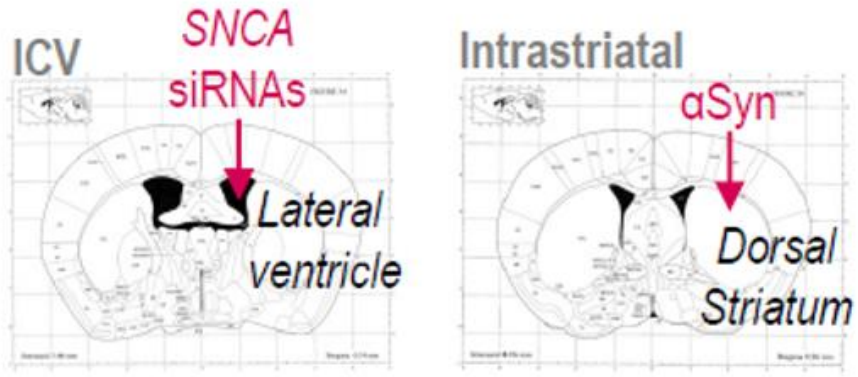
- Homozygous transgenic mice overexpressing human A53T α-synuclein under the prion promoter (line M83, V. Lee's lab)
- Seeded with 3µg of A53T α-synuclein fibrils (or monomer) into the dorsal striatum (V. Lee's lab)
- Within 3 months, these mice show accumulation and spread of pathological αSyn throughout CNS, neuroinflammation, neurodegeneration, motor deficits progressing to paralysis and early lethality

Two experimental paradigms for SNCA siRNA treatment





Injection sites

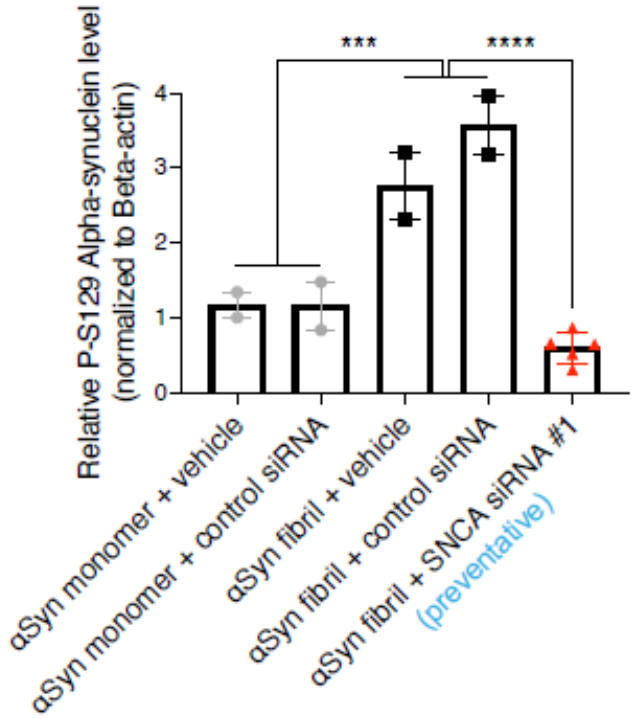


Giasson et al., 2002; Luk et al., 2012

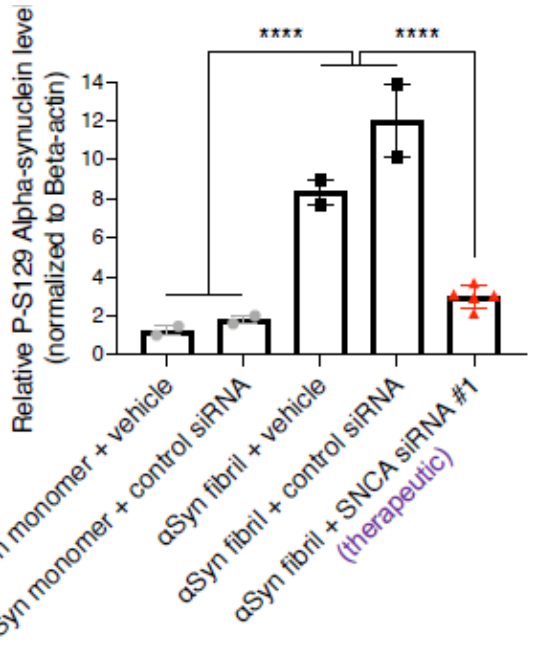
SNCA siRNAs Prevent αSyn Aggregation/Spread & Motor Deficits in Mouse Model

Western-blot quantification of pathological αSyn in the contralateral brainstem (Pons/Medulla)

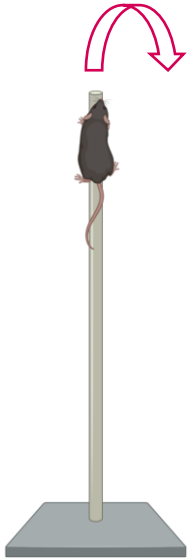
Prevention paradigm

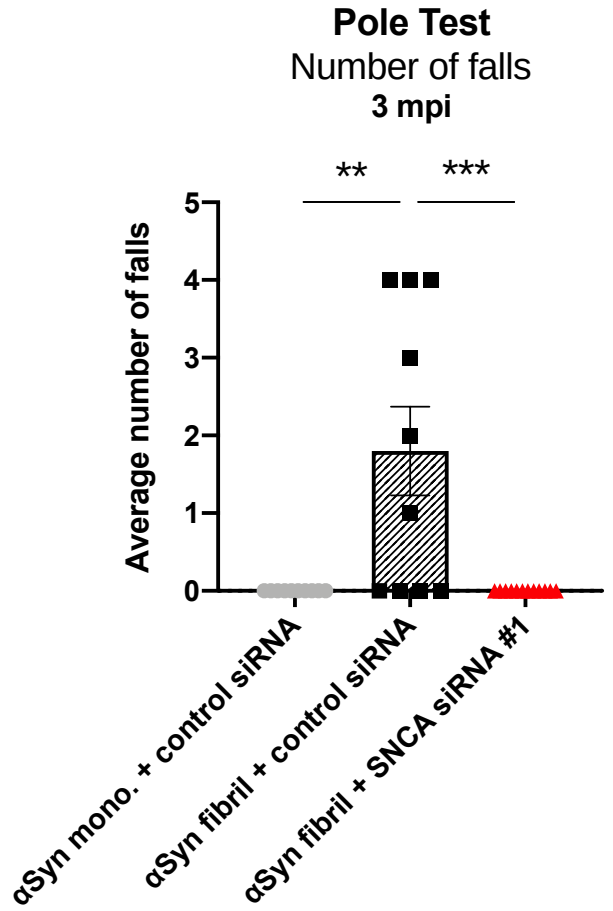


Therapeutic paradigm



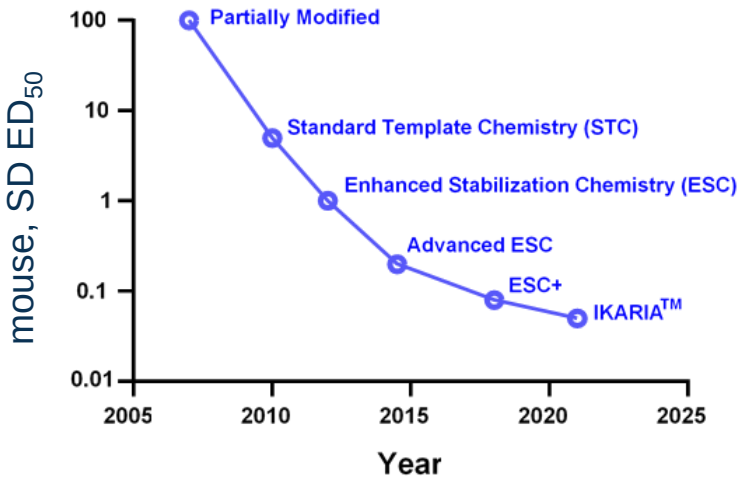
Pole test: Behavioral test assessing movement disorders related to basal ganglia shows SNCA siRNAs prevent motor deficits





Broadening Range of Ligands and Key Attributes of Tissue-Specific Receptors for Targeted Delivery

Learnings from liver delivery serve as a blueprint to expedite extrahepatic delivery efforts



Potency of GalNAc-siRNA conjugate over time

New Ligand Approaches

- Protein
- Peptide
- Lipid
- Small molecule

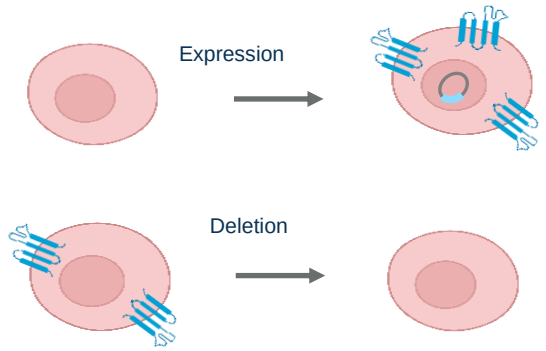
Conjugate →

- CNS
- Kidney
- Eye
- Muscle
- Adipose

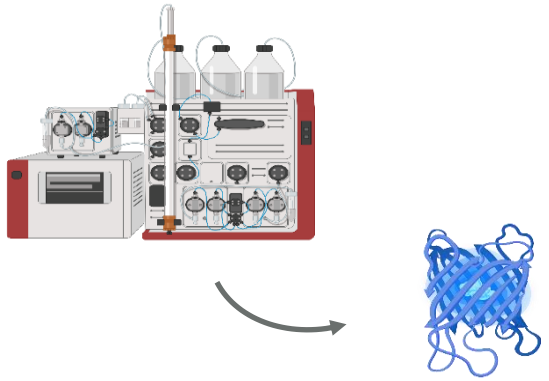
Range of ligands

Established Core Capabilities to Identify, Generate, and Characterize Novel Ligand-Receptor Pairs for Extra-Hepatic siRNA Delivery

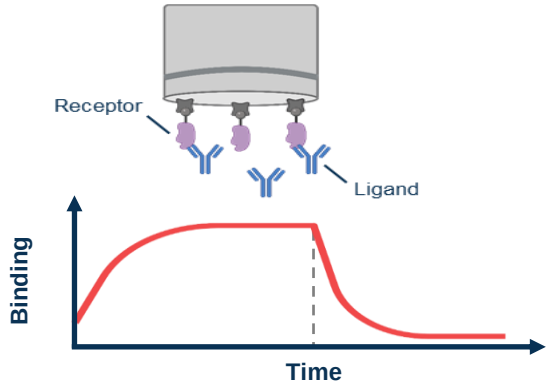
Cell Line Engineering



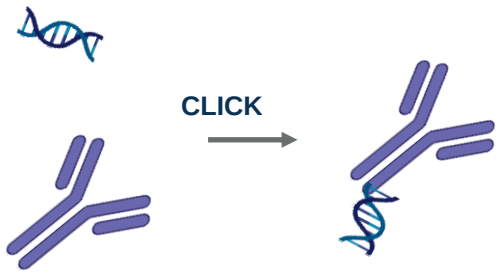
Protein Production



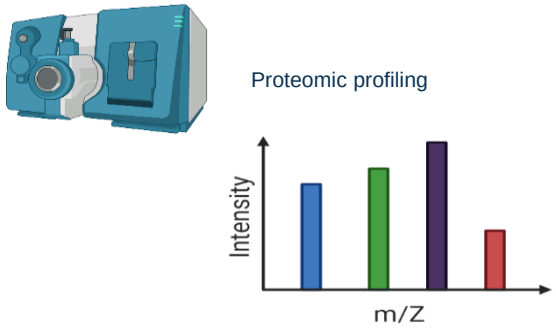
Receptor ↔ Ligand



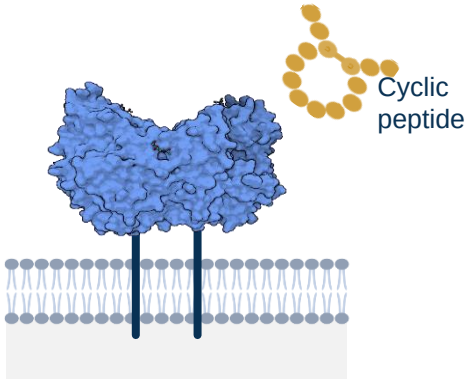
Conjugation



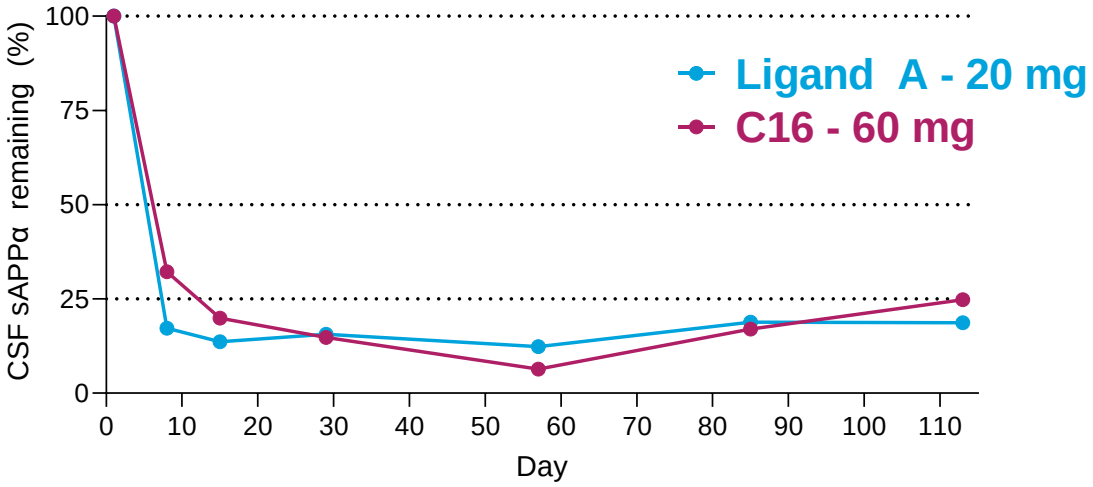
Receptor ID

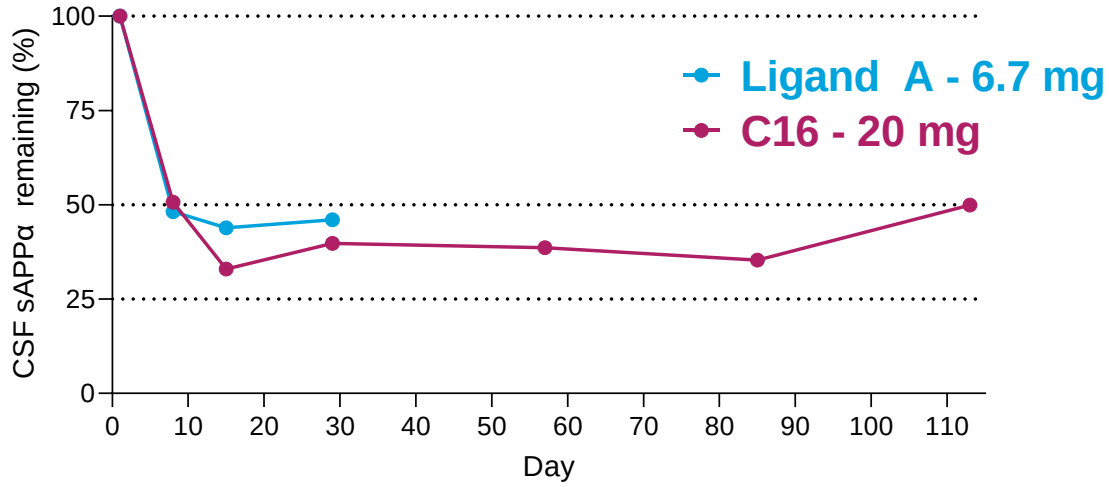


Ligand Discovery



‘Ligand A’ Exhibits 3-Fold Potency Enhancement Over C16 in NHP Following IT Administration



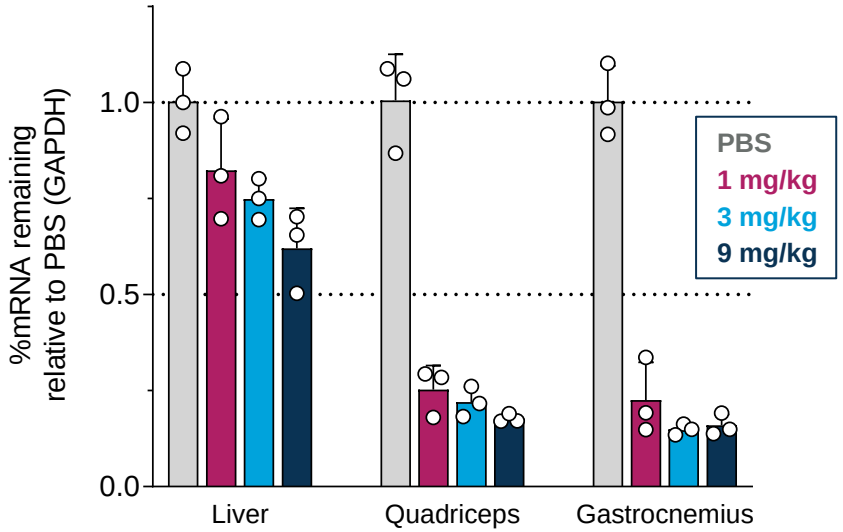


Potent, Durable Knockdown in Rodent Skeletal Muscle After Single Dose of 'Ligand B' Conjugate

Potent in Skeletal Muscle and Minimally Active in Liver

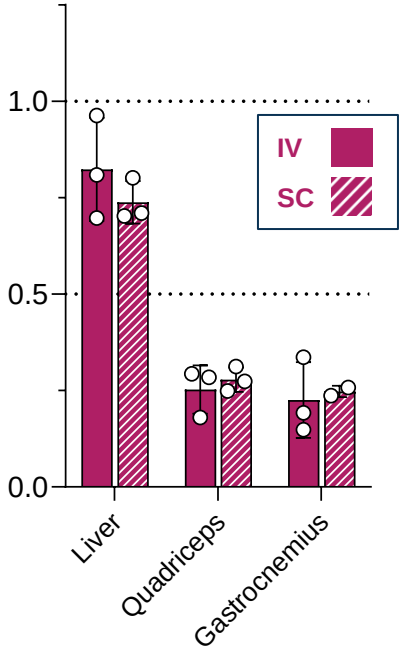
Dose dependent KD

·IV · D21



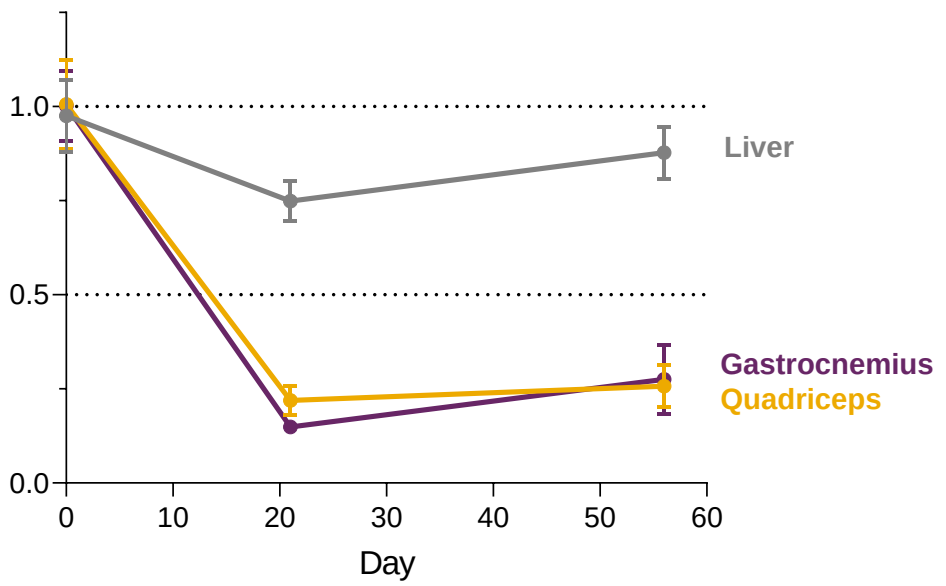
Amenable to IV/SC

1 mg/kg · D21



Durability

Duration · IV · 3 mg/kg

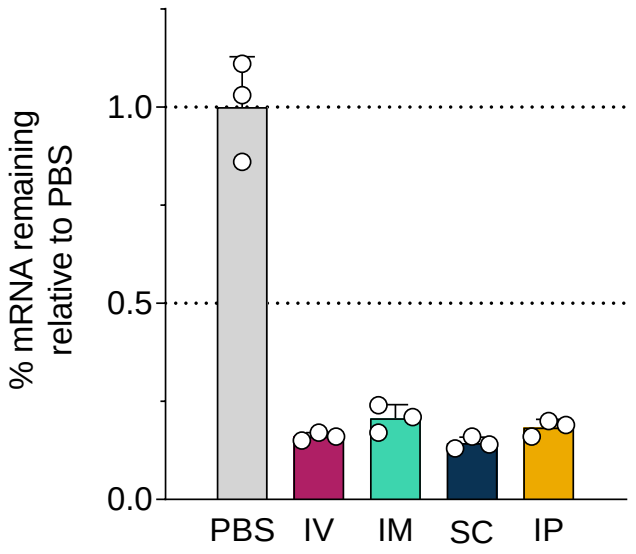


‘Ligand C’ Conjugate Demonstrates Robust and Durable KD in Heart

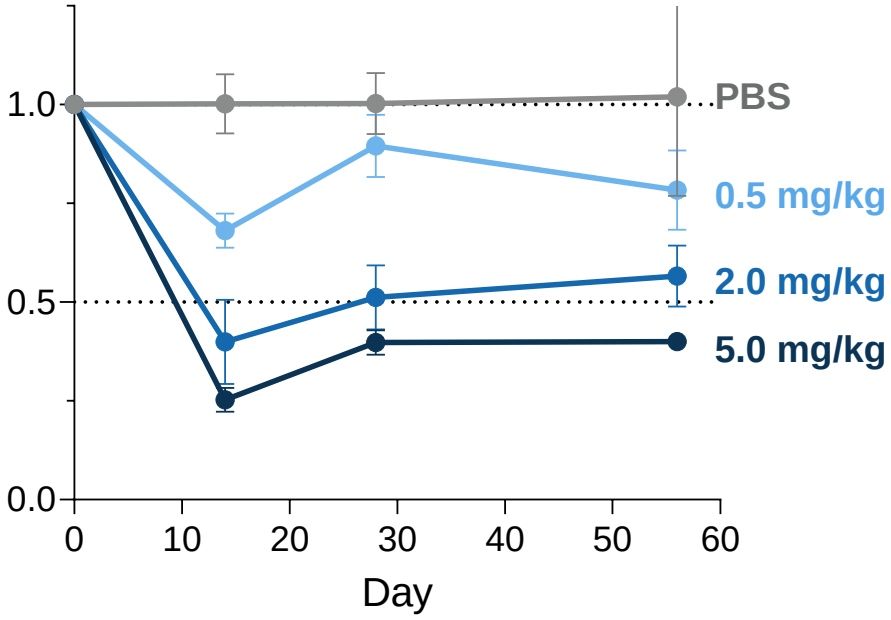
Confirmed Translation to NHP

Rodent

5 mg/kg Ligand C-siRNA · D21

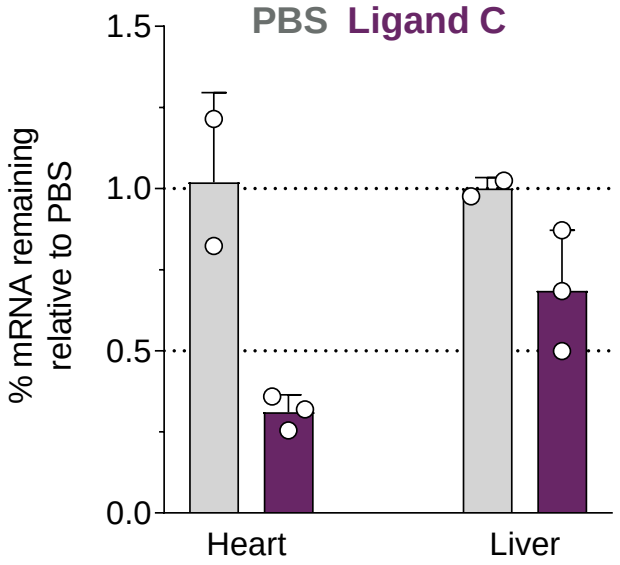


Ligand C-siRNA · SC



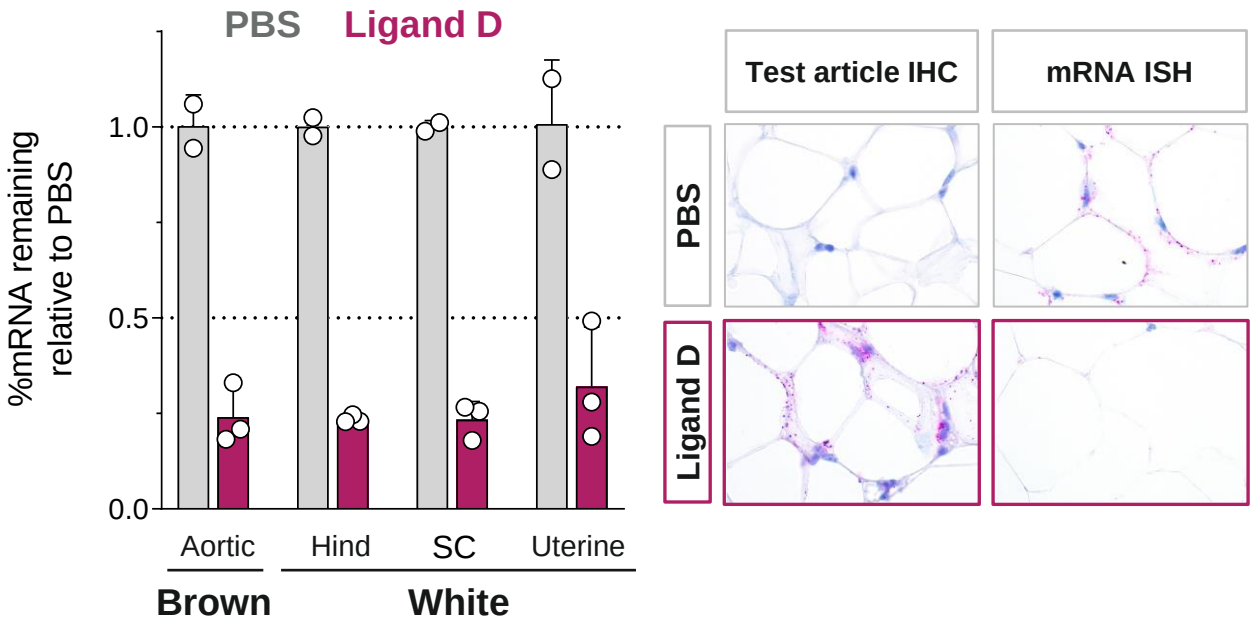
NHP

3 mg/kg Ligand C-siRNA · IV · D29

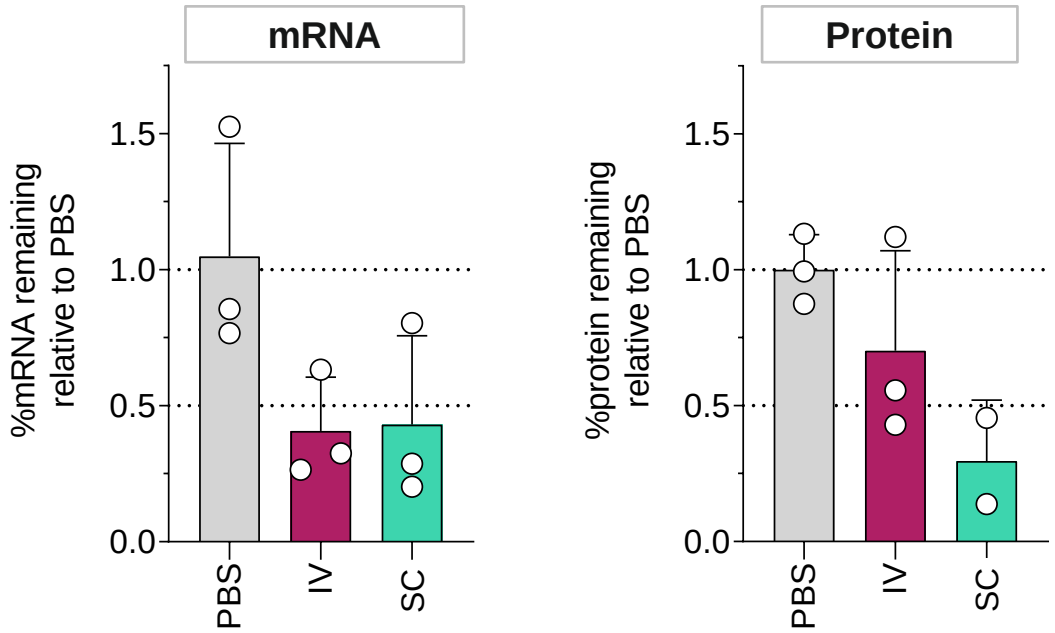


Robust Knockdown in Multiple NHP Adipose Depots Following IV or SC Administration of 'Ligand D' Conjugate

3 mg/kg Ligand D-siRNA · IV · D29



3 mg/kg Ligand D-siRNA · IV/SC · D64

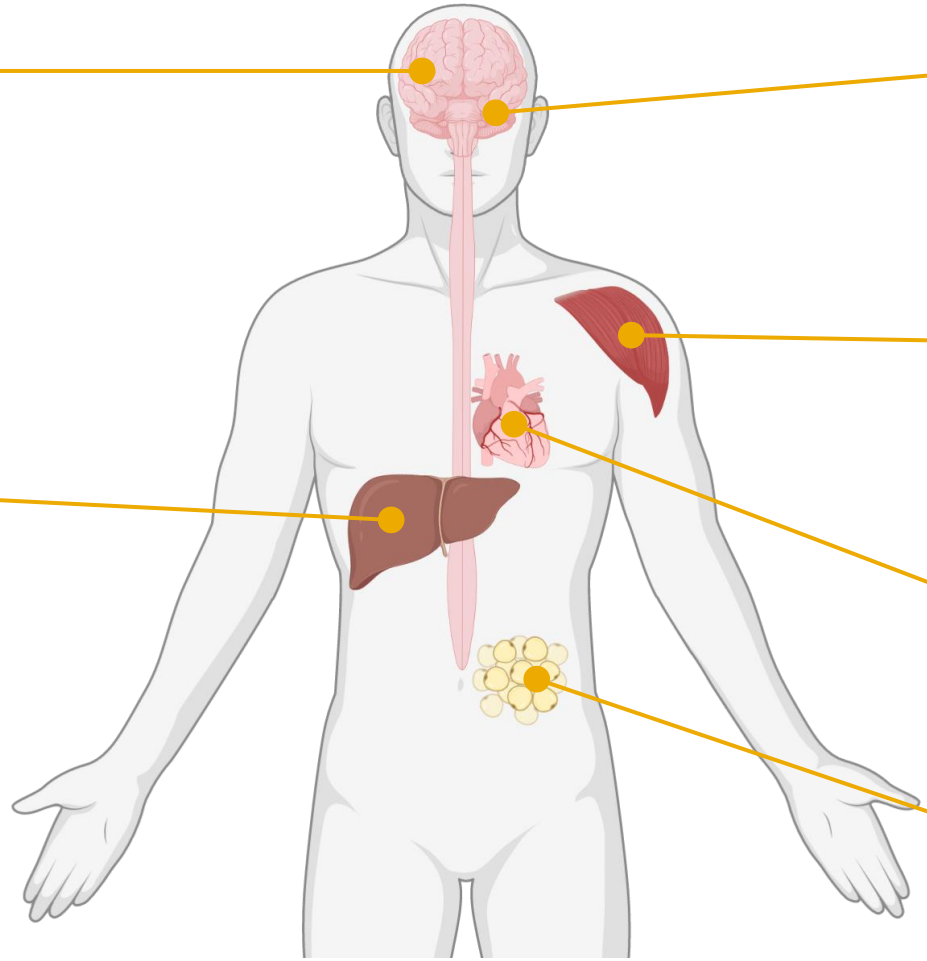


Delivery Advances Open Door to Potential Therapeutic Target Opportunities Across Range of Tissues

Many With Very High Unmet Need for New Treatments; Uniquely Suitable for RNAi

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

LIVER
- *ATTR Amyloidosis*
- *Acute Hepatic Porphyria*
- *Primary Hyperoxaluria*
- *Hypercholesterolemia*
- *Hemophilia*
- *Hepatitis B Virus*
- *Hypertension*
- *NASH*
- *Gout*
- *Cardiometabolic diseases*
- *Diabetes*

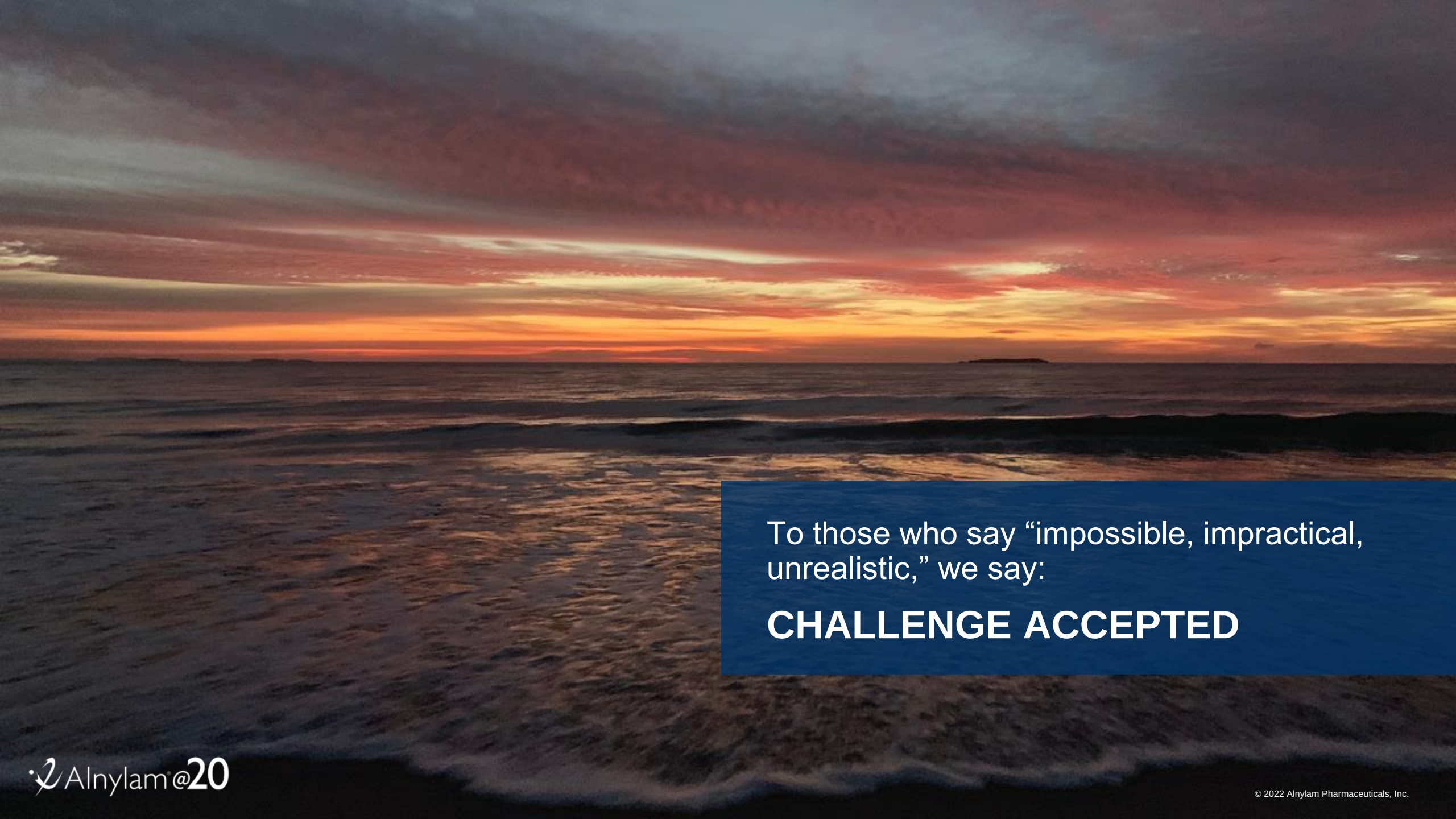


EYE
- *Glaucoma*
- *Age-related Macular Degeneration*
- *Stargardt Disease*

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

HEART
- *Heart Failure*
- *Atrial Fibrillation*

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



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