TTR Investor Day

October 9, 2024

Leadership Here Today

Yvonne Greenstreet, MBChB
Chief Executive Officer

Pushkal Garg, M.D.
Chief Medical Officer

Jeff Poulton
Chief Financial Officer

Tolga Tanguler
Chief Commercial Officer

John Vest, M.D.
Senior Vice President,
TTR Global
Development Lead

John P. Kennedy
Vice President,
TTR Franchise
Commercialization Lead

Mark Soued
Senior Vice President,
Head of U.S. & TTR Lead

Jason Gidelson
Vice President,
U.S. Market Access

Christine Lindenboom
Chief Corporate
Communications Officer

TTR Investor Day Agenda

8:30-8:45 AM	**Alnylam: A Leading Global Biotech**	Yvonne Greenstreet	15 min
8:45-9:05 AM	**ATTR-CM Disease & Unmet Needs**	Dr. Ahmad Masri	20 min
9:05-9:30AM	**The Promise of Vutrisiran for TTR Patients**	John Vest	25 min
9:30-9:50 AM	**Q&A**	Pushkal Garg (moderator)	20 min
9:50-10:15 AM	Break		25 min
10:15-10:30 AM	**Building a Flagship Franchise in ATTR-CM**	Tolga Tanguler	15 min
10:30-10:45 AM	**Driven by Patient Needs**	John Kennedy	15 min
10:45-11:10AM	**Unlocking the US Opportunity in ATTR-CM**	Mark Soued Jason Gidelson	25 min
11:10-11:40 AM	**Q&A**	Tolga Tanguler (moderator)	30 min
11:40-11:50 AM	**Our Innovative Pipeline in TTR and Beyond**	Yvonne Greenstreet	10 min

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Event Logistics

Event scheduled to end at **~12:00 p.m. ET**

Two moderated **Q&A sessions** during the meeting

Replay will be available on Investors Page of our website later today

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Alnylam Forward Looking Statements

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. All statements other than historical statements of fact regarding Alnylam's expectations, beliefs, goals, plans or prospects including, without limitation, Alnylam's expectations regarding the safety and efficacy of vutrisiran for the treatment of ATTR amyloidosis with cardiomyopathy (ATTR-CM), including its potential to be first-line standard of care in ATTR-CM; the potential for vutrisiran to halt disease progression that patients experience with ATTR-CM, including across key measures of disease burden; Alnylam's estimations regarding the size of the potential patient population; the potential for Alnylam's TTR franchise to drive robust and sustained growth; the potential for vutrisiran to obtain regulatory approval for the treatment of ATTR amyloidosis with cardiomyopathy; Alnylam's belief that vutrisiran is well positioned to address unmet medical need as the first and only RNAi therapeutic for both polyneuropathy and cardiomyopathy manifestations of ATTR amyloidosis; the potential for vutrisiran's clinical profile to support first-line positioning in newly diagnosed patients and in those patients who continue to experience disease progression with stabilizers; Alnylam's expectations regarding favorable market access dynamics in ATTR-CM; the potential for vutrisiran to have a market-leading profile, positioning Alnylam to win in ATTR-CM; the potential for vutrisiran to unlock future growth and value creation; Alnylam's expectations regarding its ability to increase the number of clinical programs in its pipeline by the end of 2025, and Alnylam's expectations regarding its ability to achieve its "*Alnylam P^{5}x25*" strategy should be considered forward-looking statements.

Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation, risks and uncertainties relating to: Alnylam's ability to successfully execute on its *"Alnylam P^{5}x25 "* strategy; Alnylam's ability to successfully demonstrate the efficacy and safety of its product candidates; the pre-clinical and clinical results for Alnylam's product candidates, including vutrisiran; actions or advice of regulatory agencies and Alnylam's ability to obtain regulatory approval for its product candidates, as well as favorable pricing and reimbursement, including vutrisiran; successfully launching, marketing and selling Alnylam's approved products globally, including vutrisiran; and any delays, interruptions or failures in the manufacture and supply of Alnylam's product candidates or its marketed products, including vutrisiran; as well as those risks more fully discussed in the "Risk Factors" section including within Alnylam's 2023 Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC), as may be updated from time to time by Alnylam's subsequent Quarterly Reports on Form 10-Q and in its other SEC filings. In addition, any forward-looking statements represent Alnylam's views only as of today and should not be relied upon as representing its views as of any subsequent date. Alnylam explicitly disclaims any obligation, except to the extent required by law, to update any forward-looking statements.

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Alnylam: A Leading Global Biotech

Yvonne Greenstreet, MBChB
Chief Executive Officer

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Key Themes You'll Hear Today

Alnylam is at a Major Inflection Point

High Unmet Need in ATTR-CM
A devastating, progressive disease with a large, addressable, and growing market

AMVUTTRA Poised to Be the Standard of Care for 1L Patients in ATTR-CM
Strong clinical evidence in a population reflective of today's TTR patients supports treatment as early as possible

Well-Positioned for TTR Leadership
Demonstrated and durable TTR capabilities

Flagship Franchise Will Drive Our Robust and Sustained Growth
Anticipated inflection in revenues to support reinvestment in our innovative pipeline

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

Leading Biotech Profile

Outstanding R&D Productivity

Validated **RNAi class** of medicines

5
medicines approved in <4 years

Robust and High-Yielding Pipeline

15
clinical programs

Up to **15**
additional programs expected in clinic by end of 2025

Leading Commercial Capabilities

>60
countries with commercial presence through direct or distributor sales

33% YoY
growth in net product revenue through 1H 2024

Strong Financial Position

>$2.6B
cash balance, based on performance through Q2 2024

Increased 2024 net product revenue guidance range to **$1.575B** to **$1.650B**

On track towards *Alnylam P^{5}x25*

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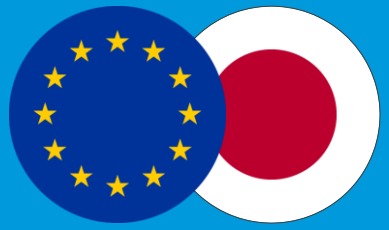
Vutrisiran sNDA for ATTR-CM Submitted to FDA

HELIOS·B

Priority Review Voucher to accelerate FDA review period

Additional global regulatory submissions – late 2024



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

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Flagship Franchises & Category Leadership Catalyze Growth

GILEAD

Viread 300 mg tablets
tenofovir disoproxil fumarate

REGENERON

EYLEA (aflibercept) Injection 2 mg

VERTEX

kalydeco (ivacaftor) tablets 150 mg oral granules 5.8•13.4•25•50•75 mg

AMGEN

EPOGEN INJECTION (EPOETIN ALFA) RECOMBINANT

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Poised for Leadership in TTR

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

amvuttra (vutrisiran) injection 25 mg/0.5 mL

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

Marc

Living with wild-type ATTR amyloidosis with cardiomyopathy

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ATTR-CM Disease & Unmet Needs

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Guest Speaker

Dr. Ahmad Masri, M.D., M.S.

Associate Professor of Medicine,
Division of Cardiovascular Medicine,
Oregon Health & Science University

Dr. Masri heads the Cardiomyopathy Section, the Cardiac Amyloidosis Program, and the Hypertrophic Cardiomyopathy Center at the Oregon Health & Science University in Portland, Oregon, where he is also an Associate Professor of Medicine.

Dr. Masri obtained his medical degree from Jordan University of Science and Technology in Jordan prior to joining the Cleveland Clinic where he completed Internal Medicine Residency training. He later joined the University of Pittsburgh where he completed Cardiology and Cardiac Imaging fellowships, a T32 post-doctoral fellowship, and obtained a graduate degree in Epidemiology and Statistics. Dr. Masri leads a multidisciplinary translational, imaging, and clinical research program which focuses on cardiomyopathies.

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ATTR-CM

Ahmad Masri, MD MS

Cardiomyopathy Section Head

Director, Cardiac Amyloidosis Program

Director, Hypertrophic Cardiomyopathy Center

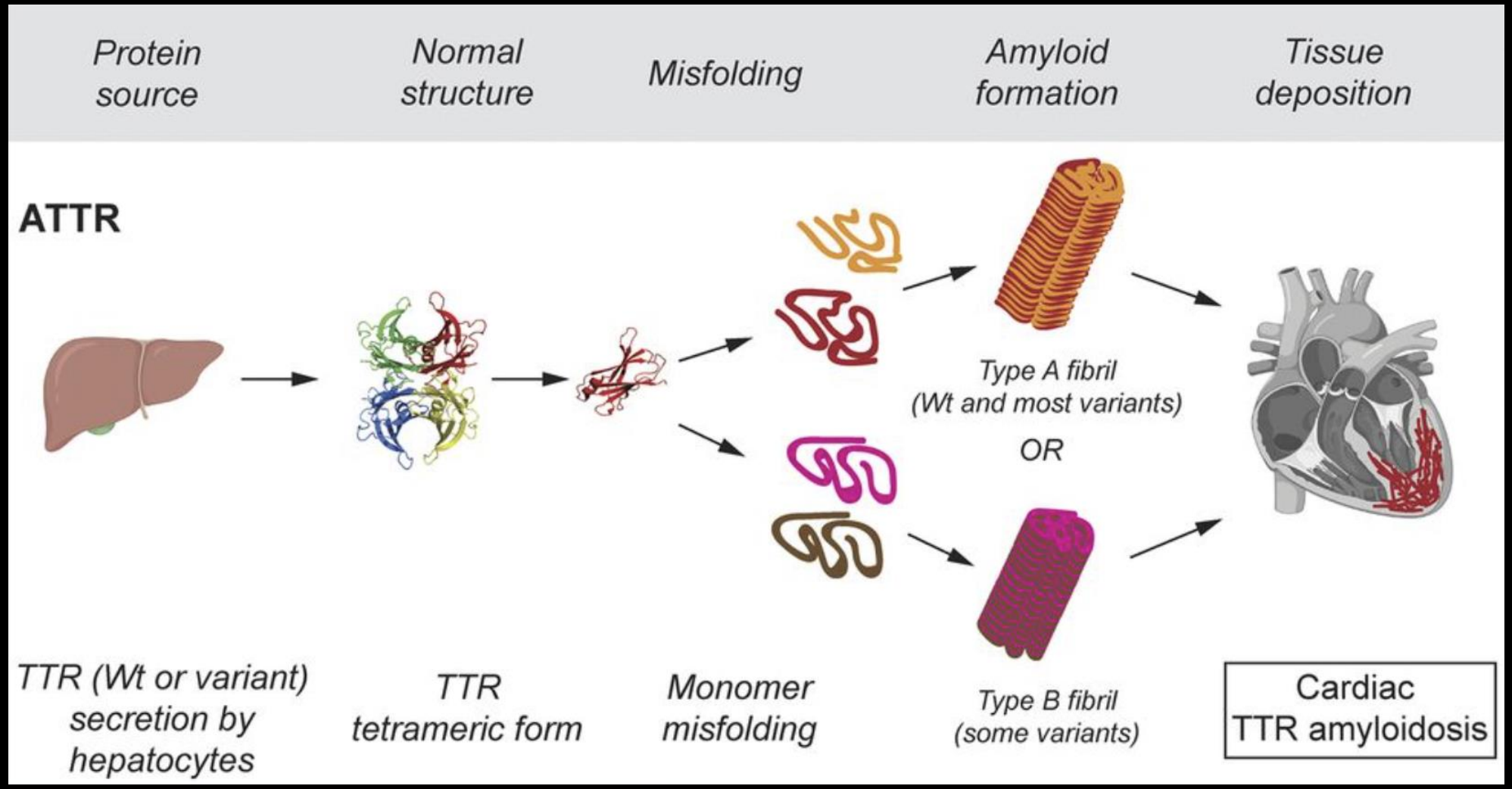
Associate Professor of Medicine

Oregon Health & Science University

Disclosures

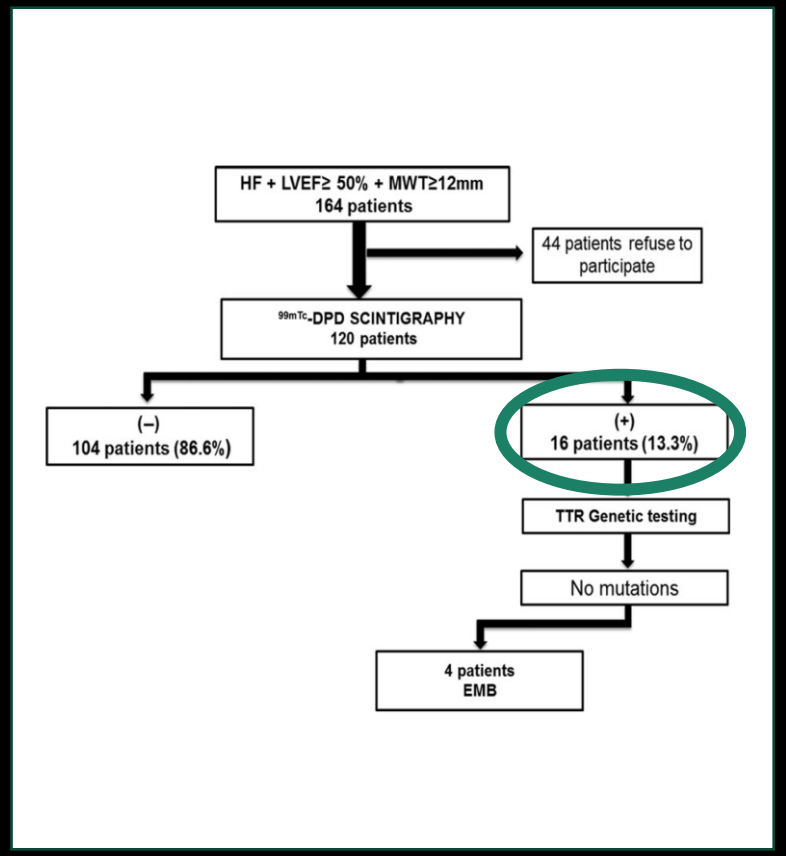
- Research Grants from Pfizer, Ionis, Attralus, and Cytokinetics.
- Fees from Cytokinetics, BMS, Eidos/BridgeBio, Pfizer, Ionis, Lexicon, Attralus, Alnylam, Haya, Alexion, Akros, Lexeo, Prothena, BioMarin, AstraZeneca, and Tenaya.

Transthyretin Amyloid Cardiomyopathy

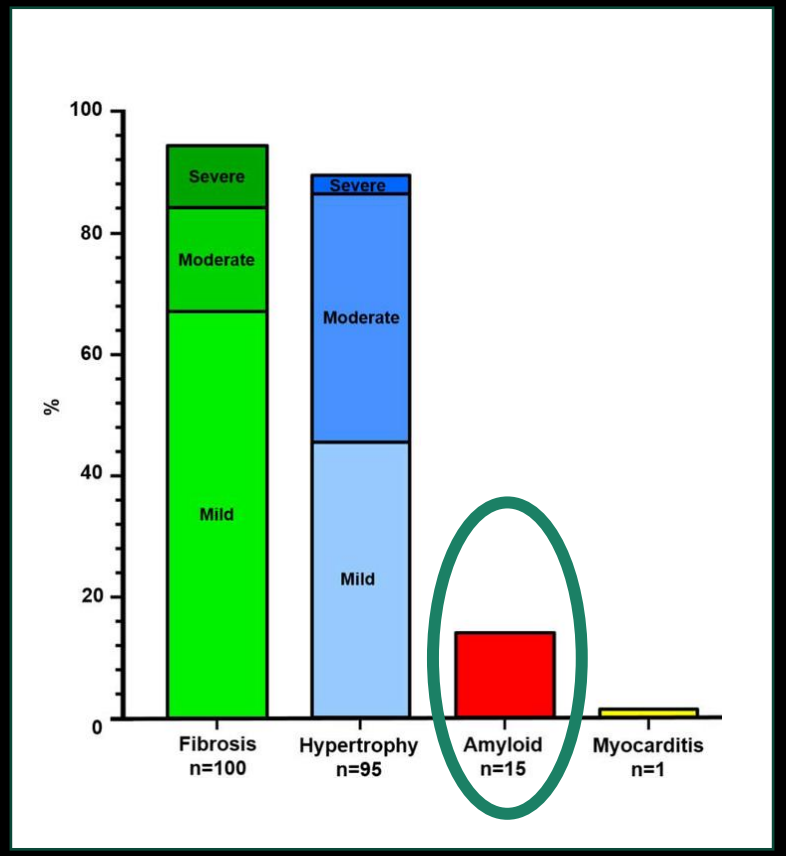


Masri A et al. J Nucl Med. 2020;61:965-970.

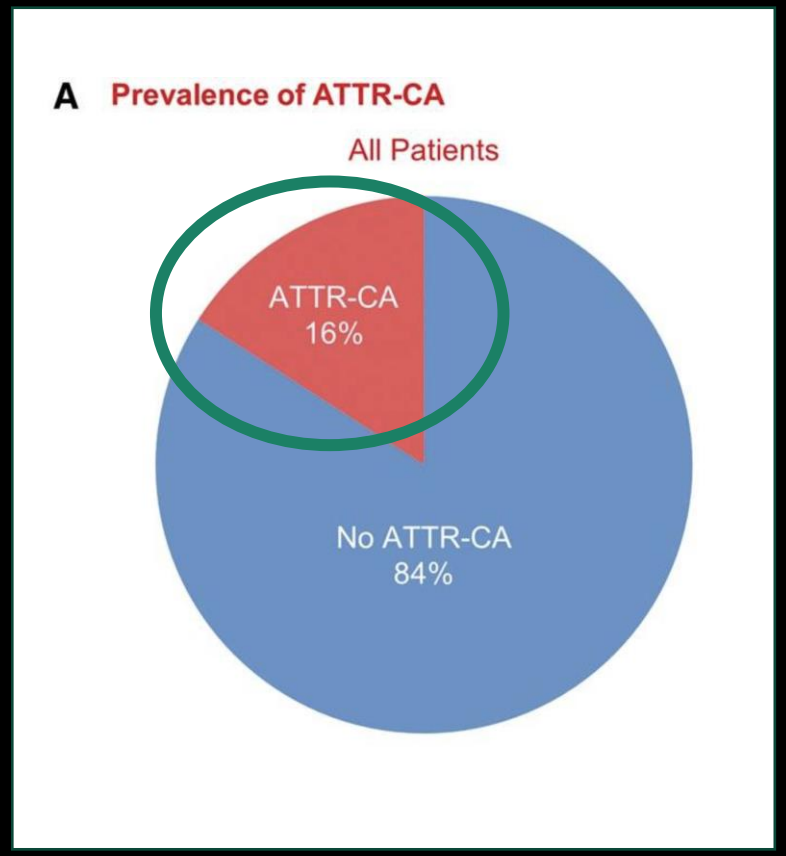
ATTR-CM is Prevalent in Heart Failure and in Aortic Stenosis



Gonzalez-Lopez E et al. Eur Heart J. 2015;36:2585-94.



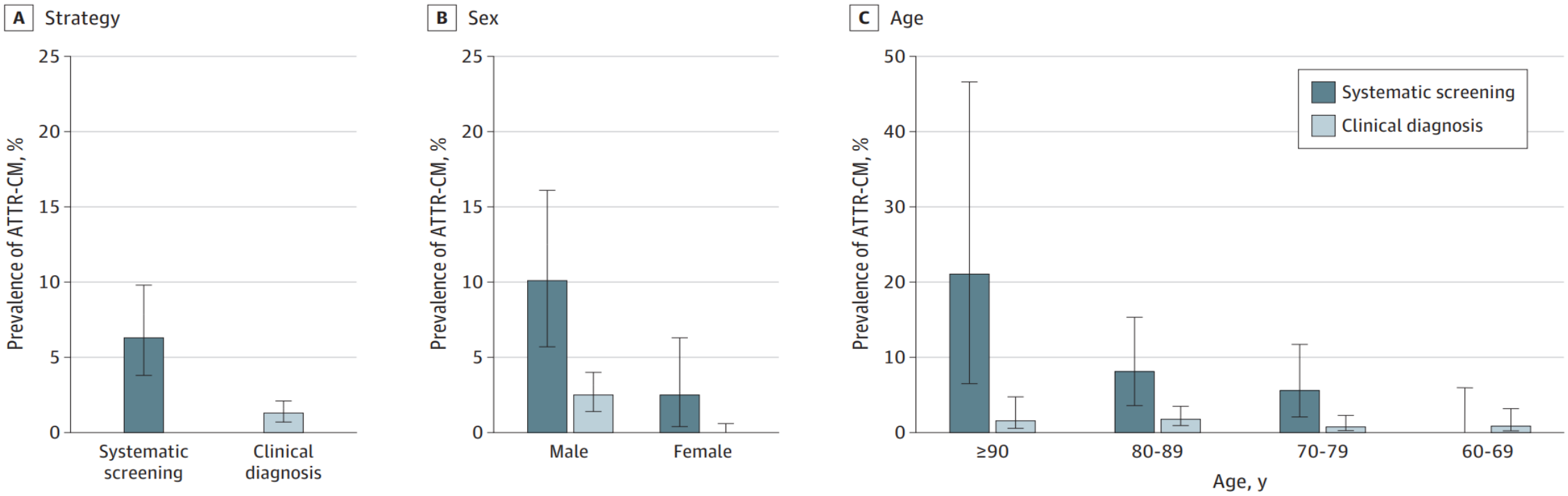
Hahn VS et al. JACC HF. 2020;8:712–724.



Castano A et al. Eur Heart J. 2017;38:2879-2887.,

Systematic Screening Strategy is Better Than Clinical Evaluation

Figure 2. Prevalence of Transthyretin Amyloid Cardiomyopathy (ATTR-CM) in Heart Failure With Preserved Ejection Fraction



Error bars indicate 95% CIs.

AbouEzzeddine OF et al. JAMA Cardiol. 2021;6:1267-1274.

Tenosynovial and Cardiac Amyloidosis in Patients Undergoing Carpal Tunnel Release

Brett W. Sperry, MD,[a,b] Bryan A. Reyes, MD,[c] Asad Ikram, MBBS,[a] Joseph P. Donnelly, MD,[a] Dermot Phelan, MD, PhD,[a] Wael A. Jaber, MD,[a] David Shapiro, MD,[c] Peter J. Evans, MD, PhD,[c] Steven Maschke, MD,[c] Scott E. Kilpatrick, MD,[d] Carmela D. Tan, MD,[d] E. Rene Rodriguez, MD,[d] Cecilia Monteiro, MD,[e] W.H. Wilson Tang, MD,[a] Jeffery W. Kelly, PhD,[c] William H. Seitz, Jr, MD,[c] Mazen Hanna, MD[b]

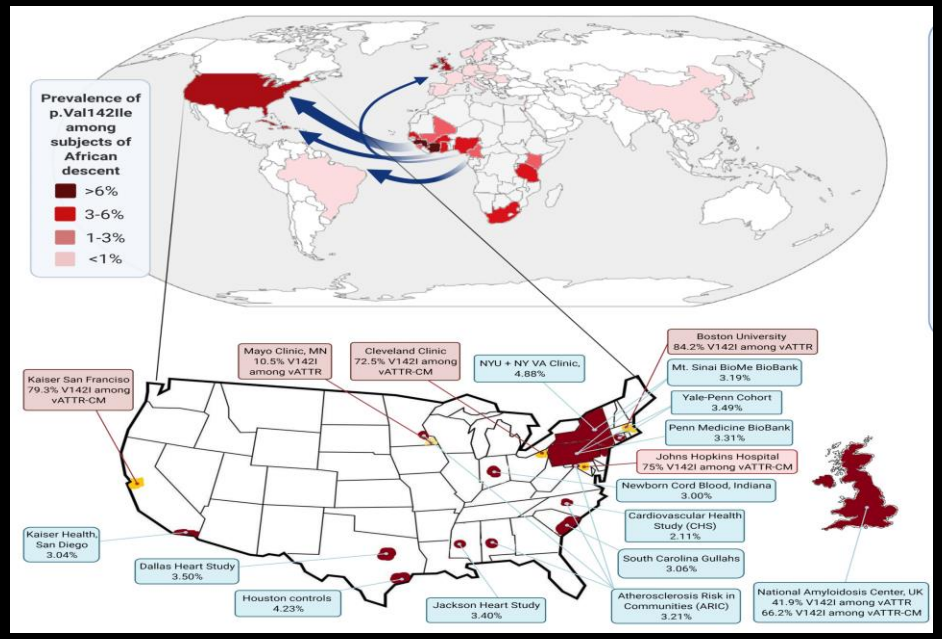
RESULTS Of 98 patients enrolled (median age 68 years, 51% male), 10 (10.2%) had a positive biopsy for amyloid (7 ATTR, 2 light chain [AL], 1 untyped). Two patients were diagnosed with hereditary ATTR (Leu58His and Ala81Thr), 2 were found to have cardiac involvement (1 AL, 1 ATTR wild-type), and 3 were initiated on therapy. In those patients who had biopsy-diagnosed ATTR, there was no difference in plasma TTR concentration or tetramer kinetic stability.

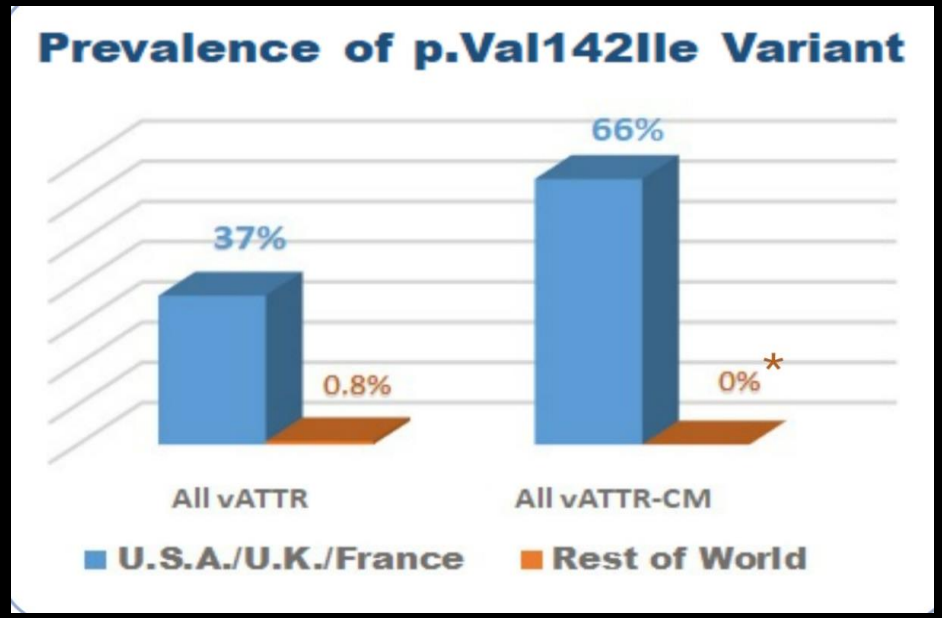
- **10%** of biopsies from carpal tunnel release surgery had amyloid deposits
- **2%** had hereditary ATTR
- **2%** had cardiac disease
- **3%** were initiated on therapy

Sperry BW et al. J Am Coll Cardiol. 2018;72:2040-2050.

V122I (p.V142I)

- First described in 1988 in an African-American man
- Unique – predominantly in patients with African descent
- Age-dependent autosomal dominant
- Prevalence of ~3.4% of African Americans
  - 1.6 Million carriers*
  - ~150,000, aged ≥65 years*

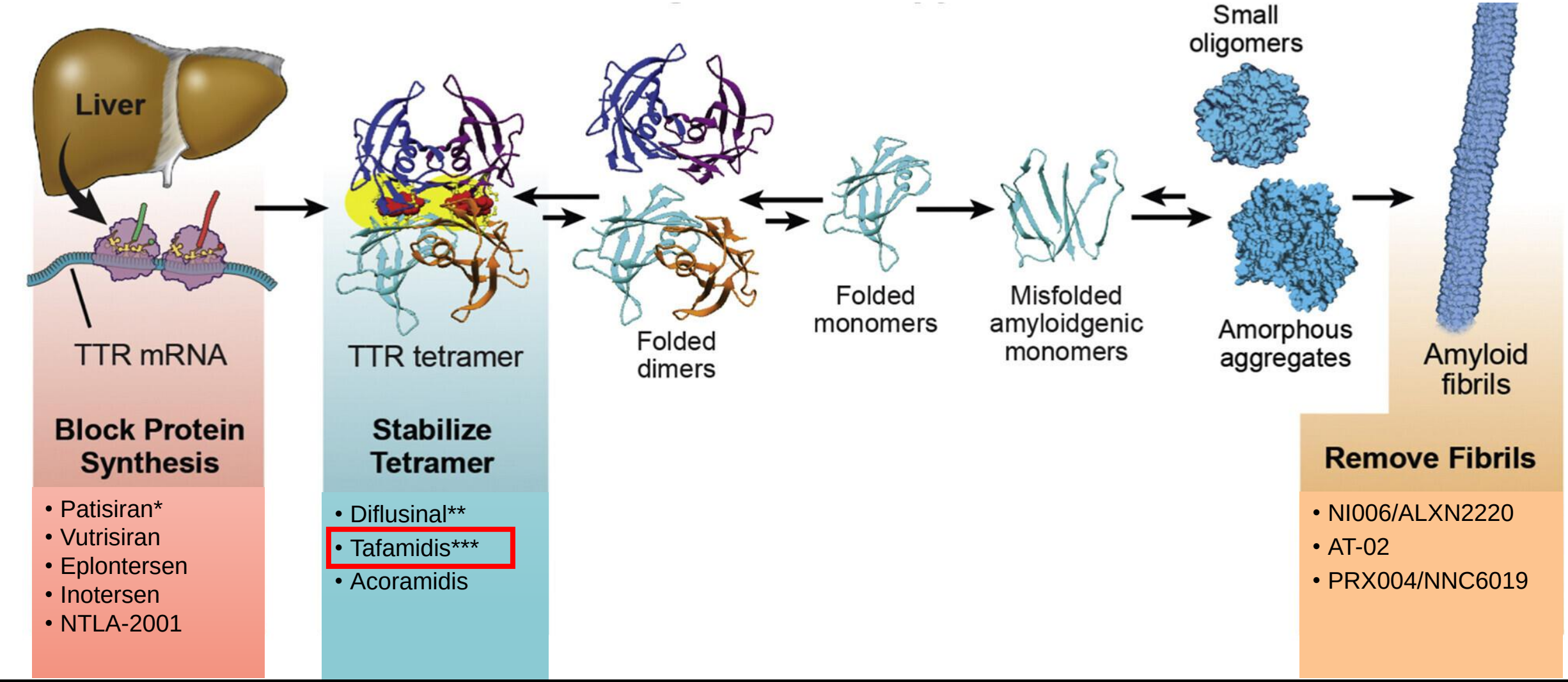




*Estimation based on US Census.

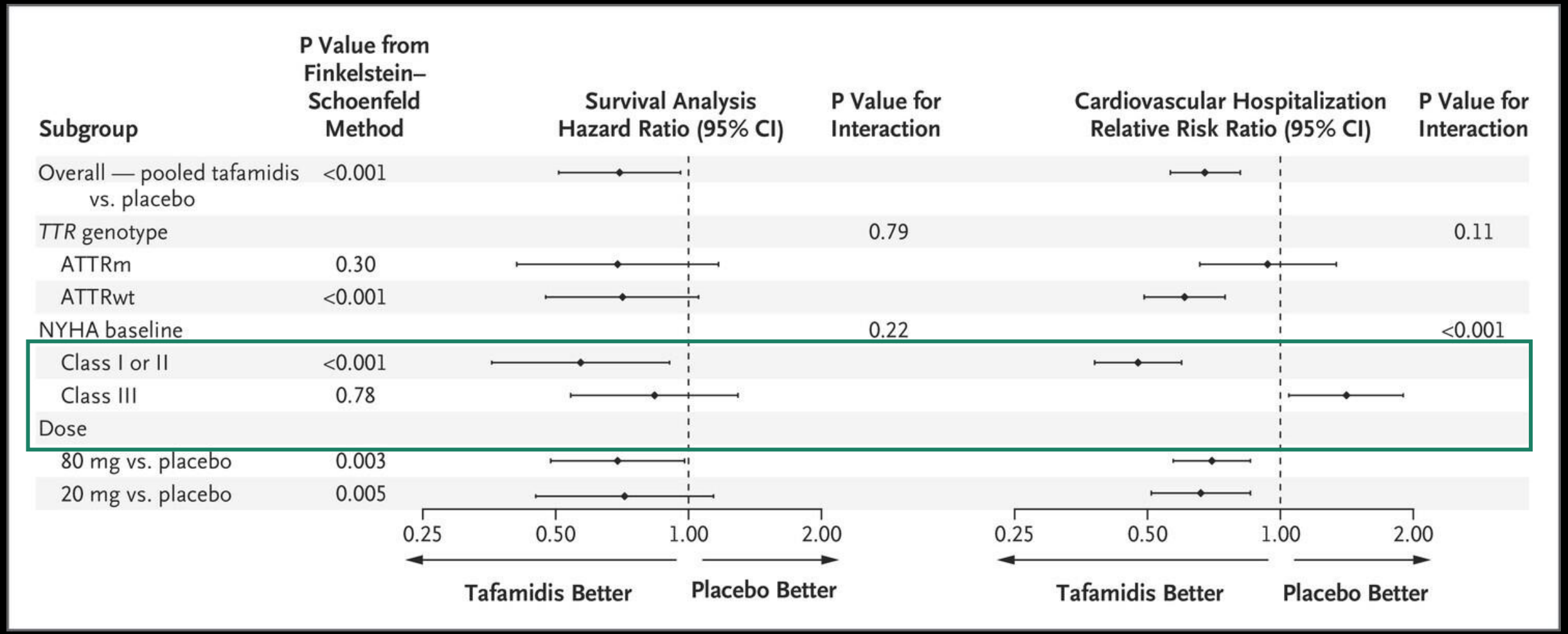
Chandrashekar P et al. Circ Genom Precis Med. 2021 Oct;14(5):e003356.

TTR Targets of Therapy



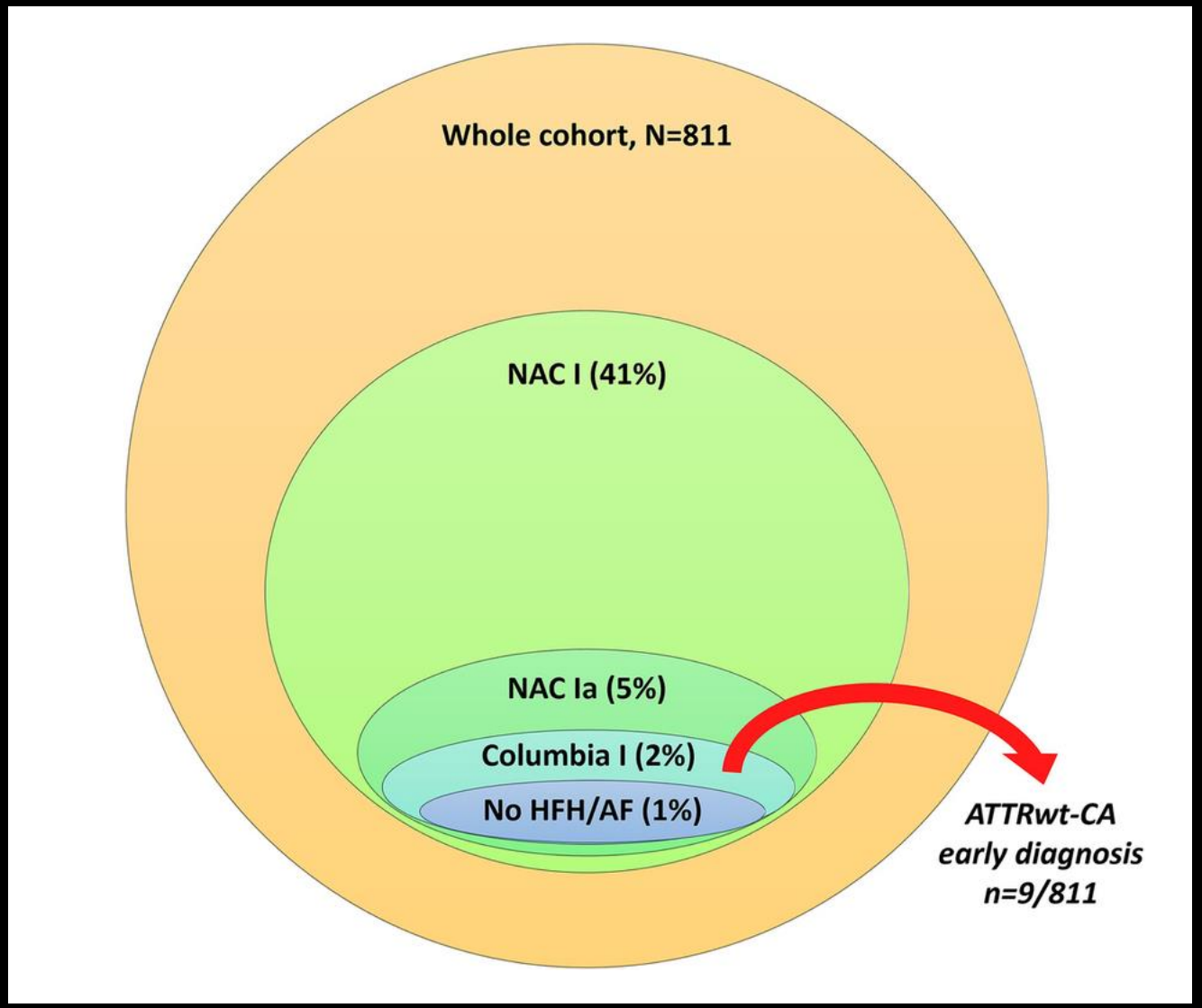
Ruberg et al. JACC 2019 (modified)

Early Diagnosis is Essential



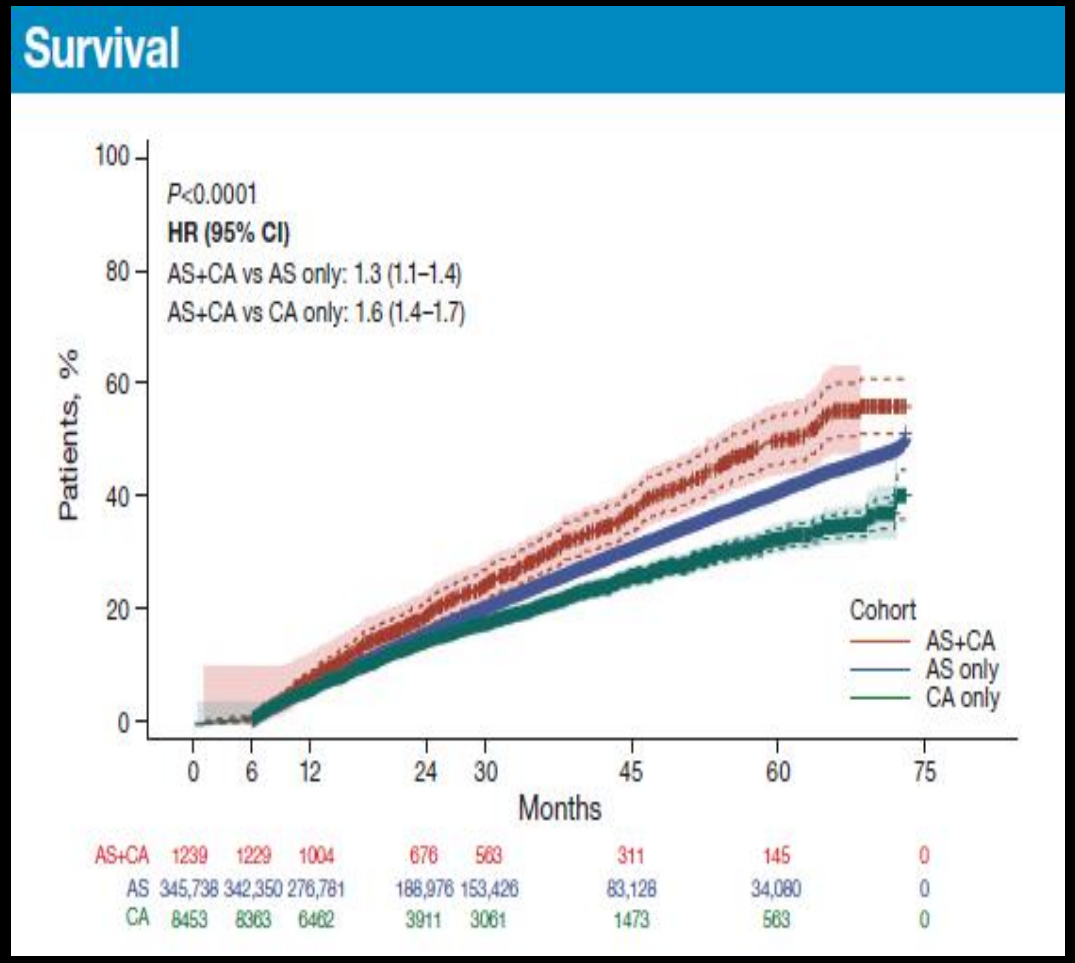
Maurer et al. NEJM 2018

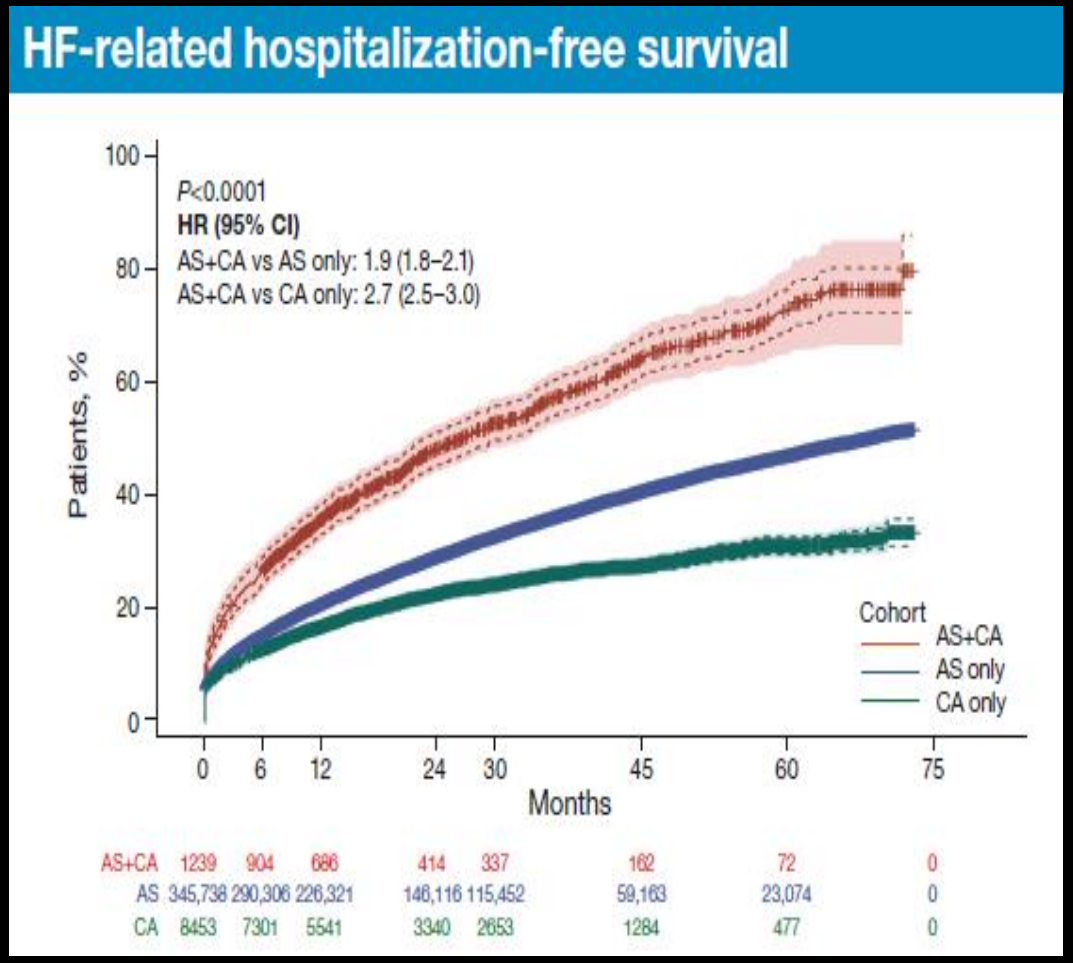
Unmet Need to Truly Achieve Early Diagnosis



Tini et al. ESC HF 2024

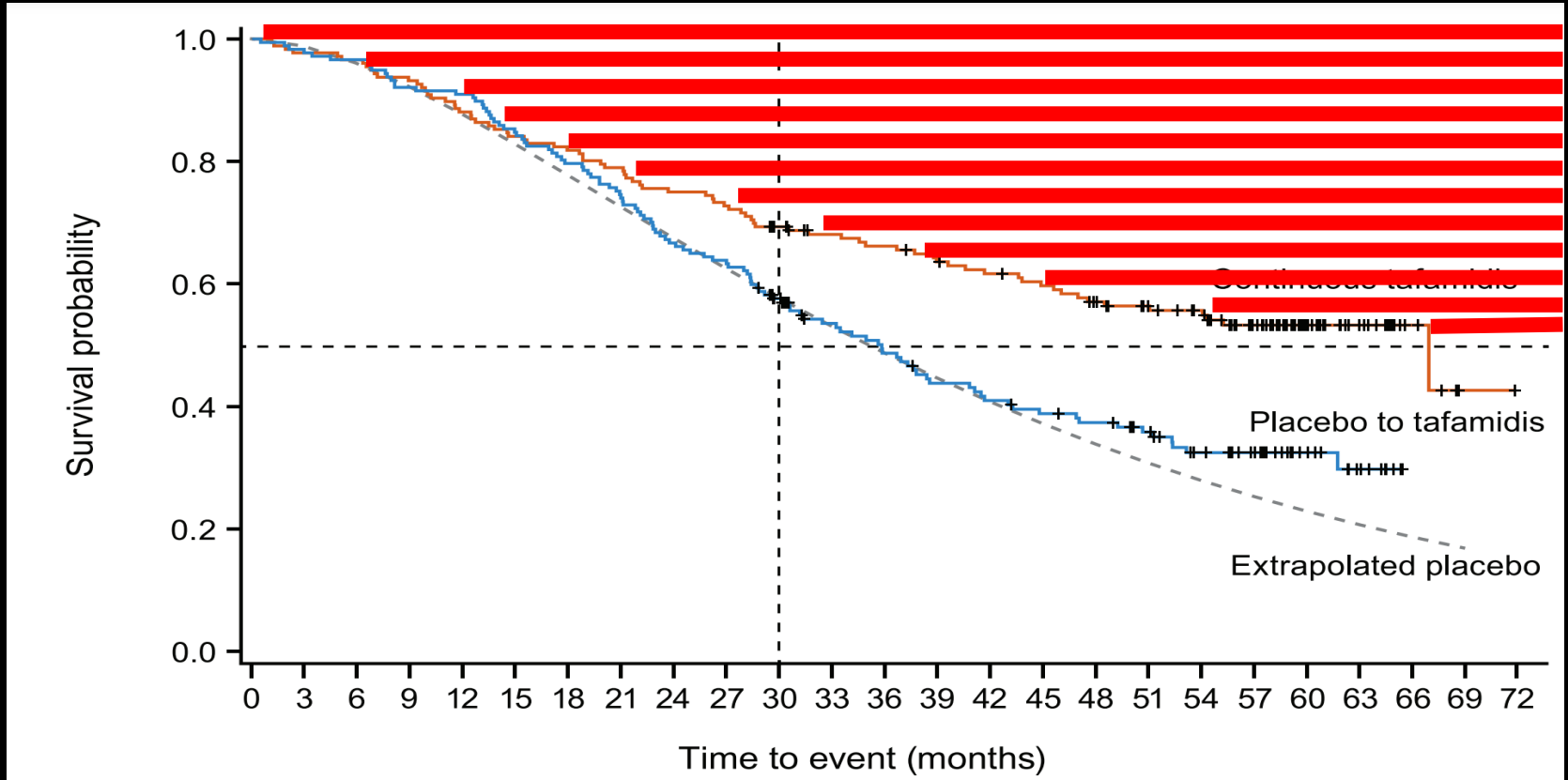
Concurrent AS+CA Was Associated with An Increased Risk of Death and HF-related Hospitalization Compared with AS Alone





Masri A et al. J Am Coll Cardiol. 2022;80 (12_Supplement): B175.

Significant Unmet Need on Tafamidis in ATTR-ACT and OLE

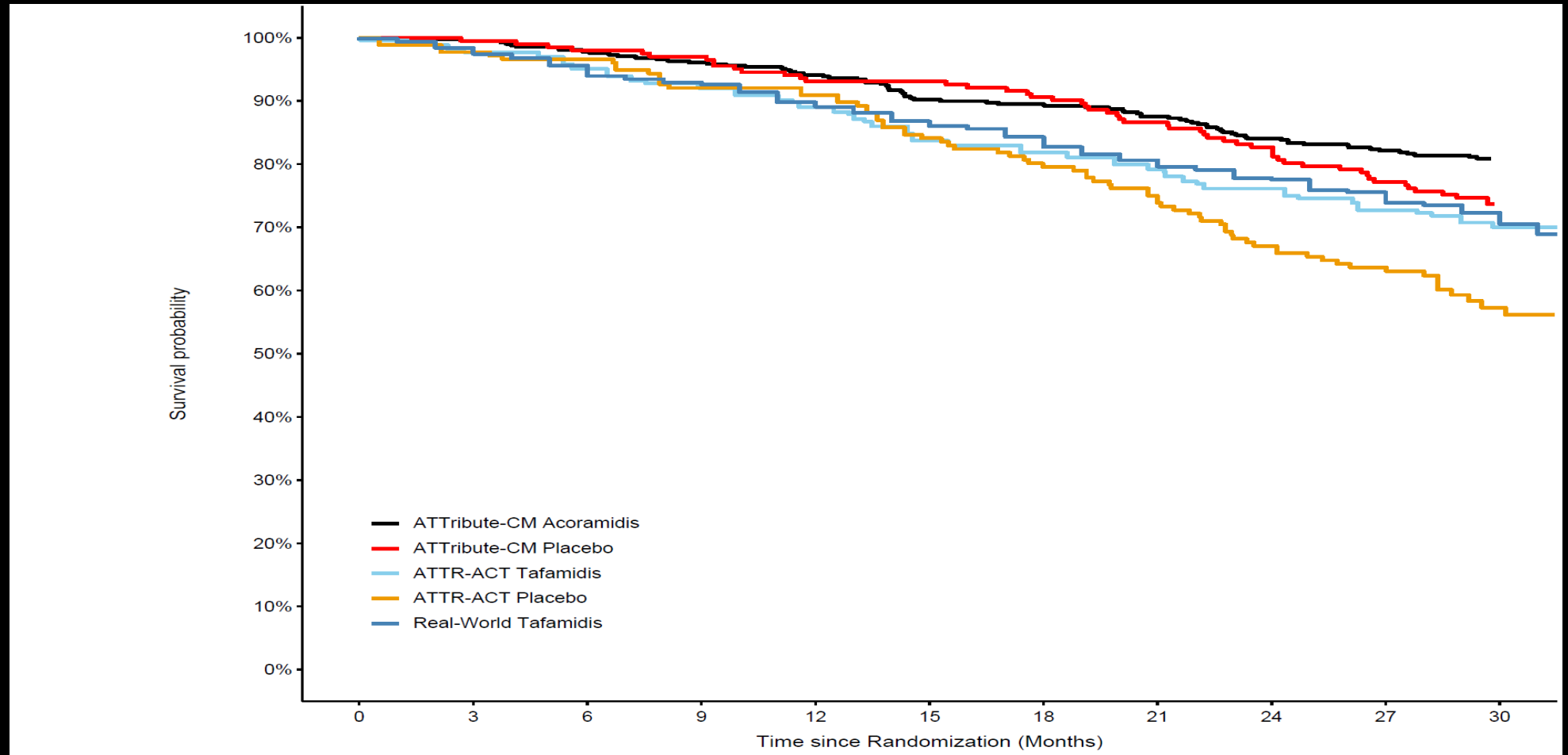


Patients remaining at risk (cumulative events)

Continuous tafamidis	176 (0)	172 (4)	170 (6)	164 (12)	155 (21)	148 (28)	144 (32)	139 (37)	132 (44)	128 (48)	117 (54)	107 (56)	104 (59)	99 (63)	95 (66)	91 (69)	85 (73)	78 (74)	72 (75)	56 (78)	30 (78)	17 (78)	6 (78)	1 (79)	0 (79)
Placebo to tafamidis	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	93 (75)	77 (81)	70 (88)	62 (95)	58 (99)	54 (102)	51 (104)	45 (106)	36 (110)	29 (110)	15 (110)	8 (111)	0 (111)	0 (111)	0 (111)

Elliott et al. Circ HF 2022

Real World Experience with Tafamidis and the Changing Natural History



Number at risk (number of events)

ATTribute-CM Acoramidis	409 (0)	407 (2)	401 (8)	393 (16)	385 (24)	369 (40)	365 (44)	358 (51)	344 (65)	336 (73)	0 (79)
ATTribute-CM Placebo	202 (0)	201 (1)	198 (4)	196 (6)	188 (14)	188 (14)	183 (19)	175 (27)	166 (36)	156 (46)	0 (52)
ATTR-ACT Tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)
ATTR-ACT Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)
Real-World Tafamidis	624 (1)	607 (16)	576 (37)	544 (45)	493 (65)	439 (81)	372 (96)	323 (109)	288 (117)	226 (129)	160 (137)

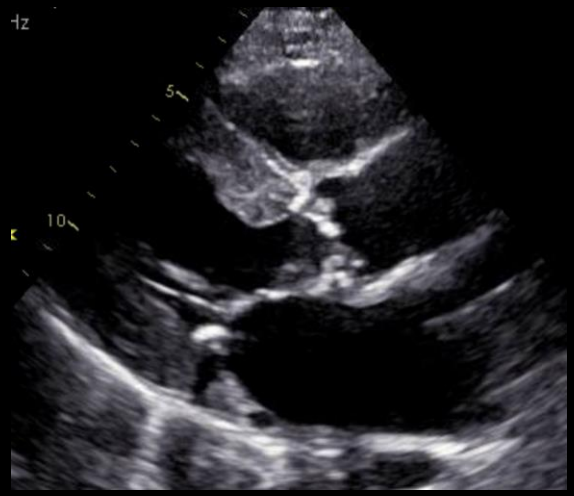
Masri et al. HFSA 2023

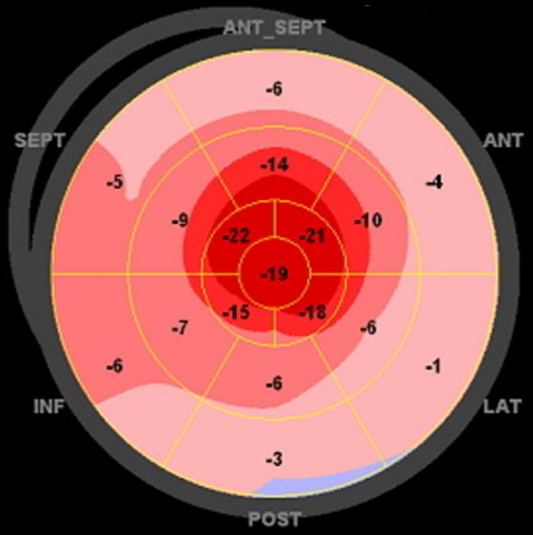
Monitoring ATTR-CM Progression

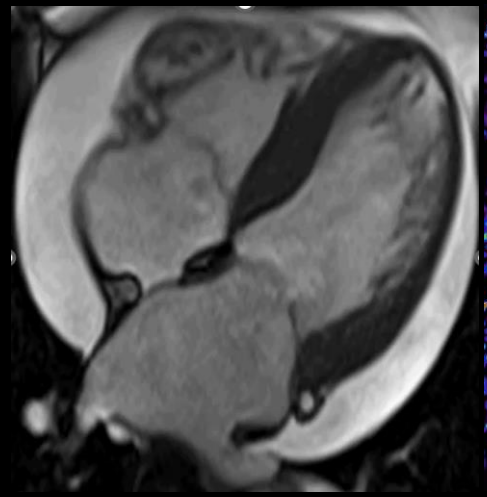
Mortality
CV Hospitalizations
Urgent visits
Diuretics
Intensification

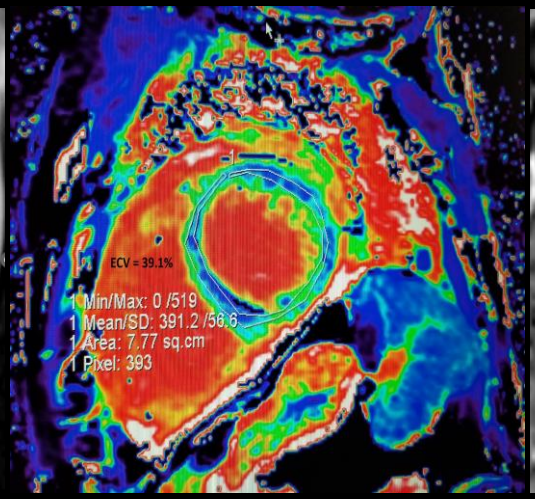
KCCQ
NYHA class
6MWT

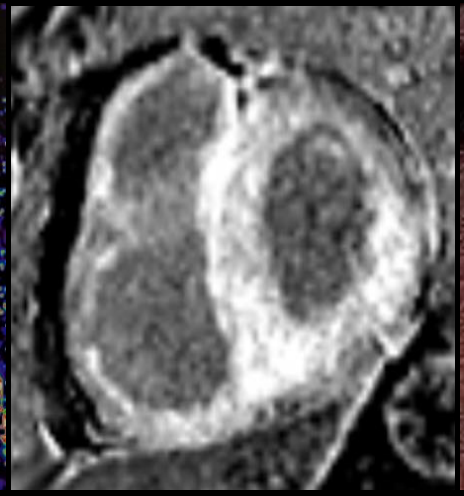
NT-proBNP
Troponin
TTR level

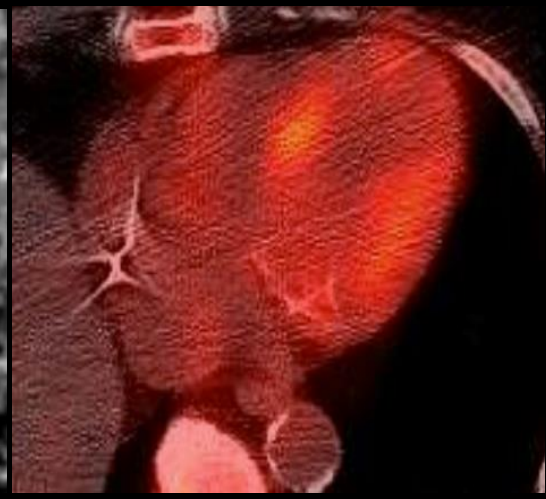


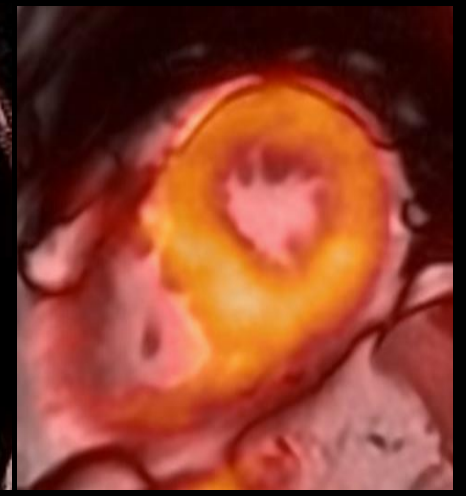












Future Goals in ATTR-CM

- Better disease control
- Improved survival and decreased hospitalizations
- Improved function and quality of life
- Addressing unintentional weight loss
- Disease regression
- Ongoing need for longer term studies

Conclusions

- While ATTR-CM is being transformed through earlier recognition, better overall management, and targeted therapy such as tafamidis, there remains a significant unmet need.
- New diagnostic approaches and new therapies open the door to further improving patients' outcomes.

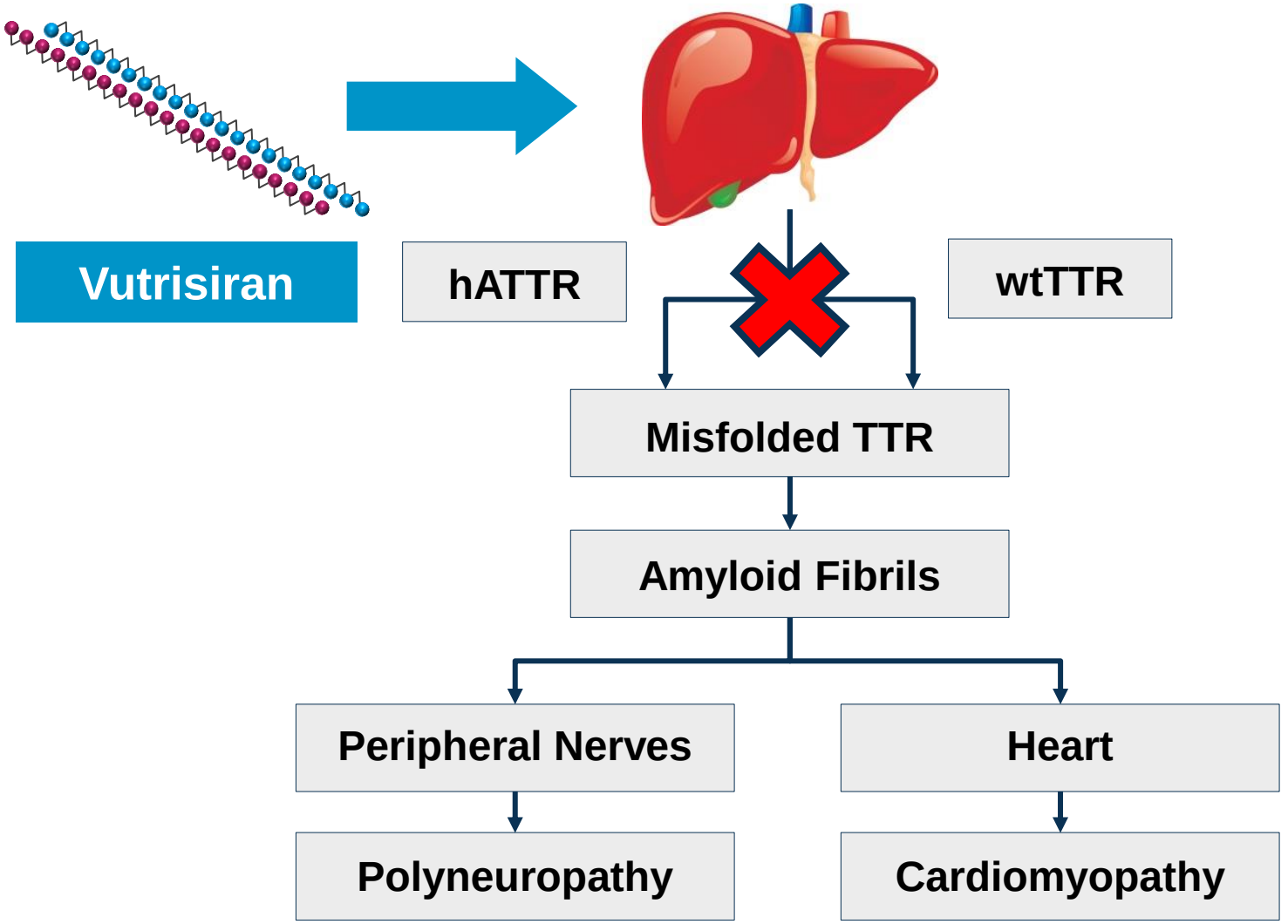
The Promise of Vutrisiran for TTR Patients

John Vest, M.D.
SVP, TTR Global Development Lead

Alnylam®

RNAi Therapeutic Hypothesis in ATTR Amyloidosis

Silencing TTR Gene Expression to Address Underlying Cause of Disease



Vutrisiran is a RNAi therapeutic targeting hepatic TTR production; dosing 25 mg once every 3 months

Characterized by rapid knockdown

Approved for the treatment of hATTR with polyneuropathy

HELIOS-B evaluated efficacy and safety of vutrisiran in ATTR (wt or hereditary) with cardiomyopathy

Abbreviations: hTTR, hereditary transthyretin-mediated; RNAi, RNA interference; siRNA, small interfering RNA; TTR, transthyretin; wt, wild type

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Profile of RNAi Therapeutics in Hereditary ATTR Amyloidosis with Polyneuropathy

Transformational Profile in hATTR-PN

Consistent results observed with both vutrisiran (HELIOS-A) and patisiran (APOLLO)

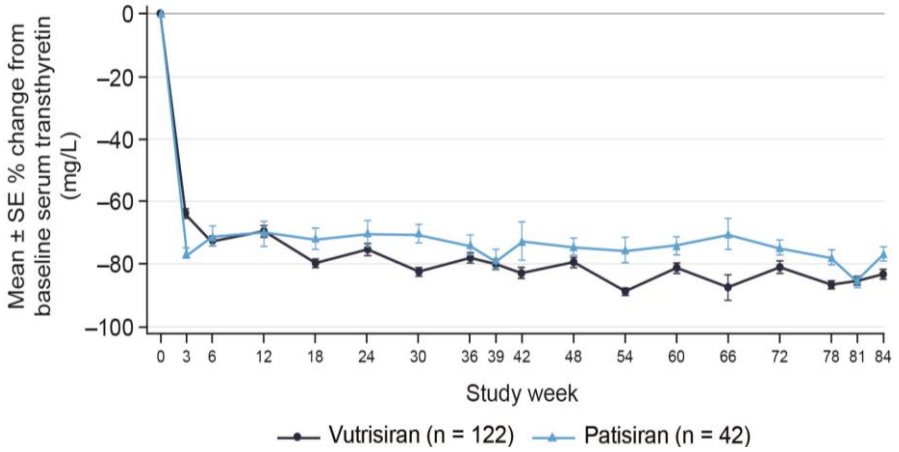
Stabilization or improvement in **neuropathy**

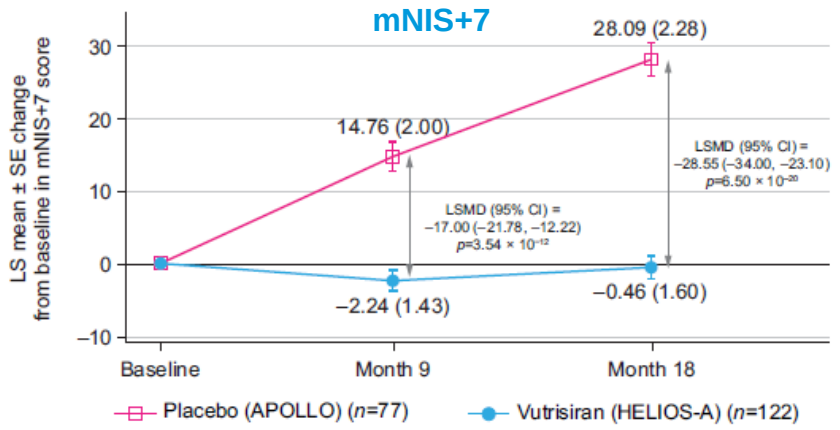
Stabilization or improvement in **quality of life**

Beneficial effects on **functional and nutritional status**

HELIOS·A

Percent Change from Baseline in Serum TTR Levels





SD, standard deviation; SE, standard error; TTR, transthyretin; Adams, et al. Amyloid, 2023; Garcia Pavia, et al. European Journal of Heart Failure, 2024; Adams, et al. New England Journal of Medicine, 2018.Solomon, et al. Circulation, 2018.

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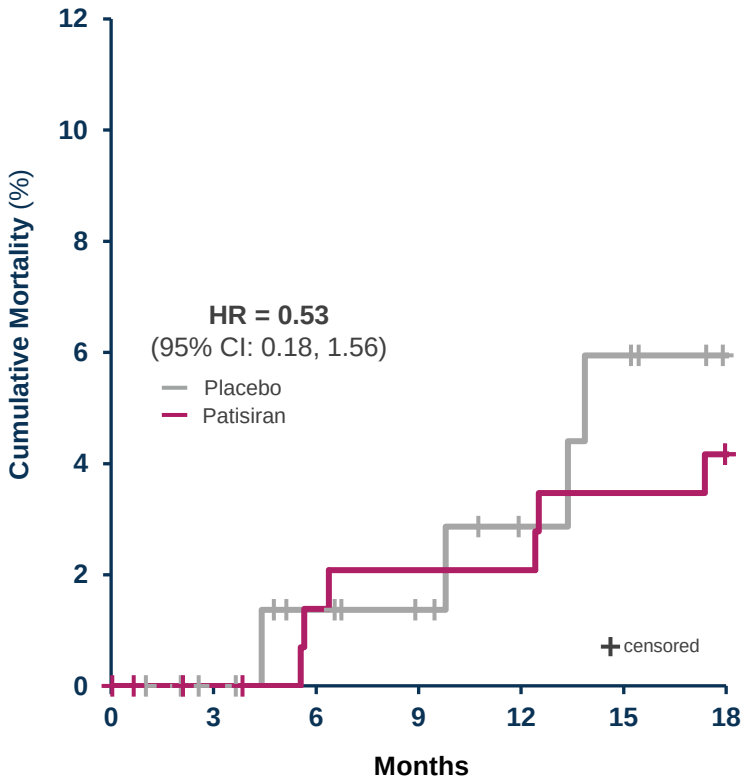
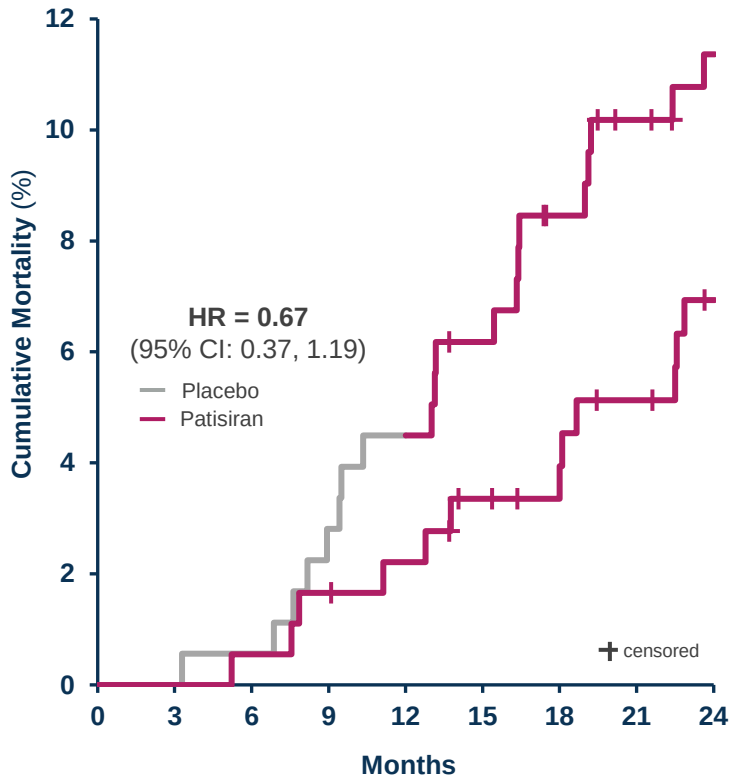
Exploratory Analyses of All-Cause Mortality from APOLLO and APOLLO-B

Previous Data From Patisiran Supported Potential for RNAi to Reduce Mortality

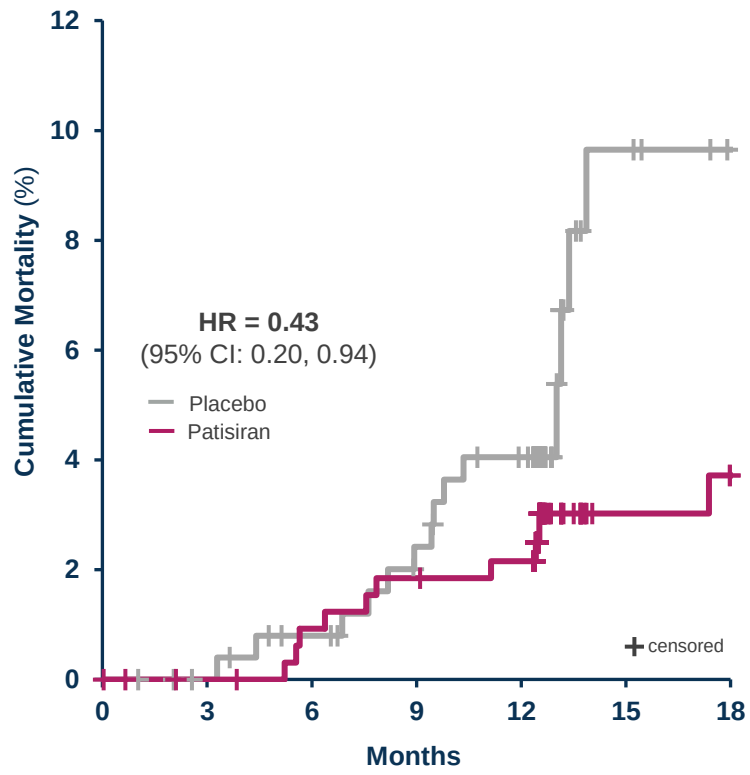
APOLLO



APOLLO-B



Pooled APOLLO and APOLLO-B



Vutrisiran HELIOS·B Phase 3 Study

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

Patient Population

(N=655)

- ATTR: wild-type or any TTR variant
- Confirmed cardiomyopathy and medical history of symptomatic HF
- NYHA Class ≤III; 6-MWT ≥150 m; NT-proBNP limits[1] at baseline
- Approximately 40% of patients on tafamidis at baseline

Select Exclusion Criteria:

- NYHA Class IV HF
- PND Score ≥III at the screening visit
- Received prior TTR lowering treatment

1:1 RANDOMISATION[2]

Vutrisiran SC q3M 25 mg

or

Placebo SC q3M

Primary Endpoints

- Composite outcome of all-cause mortality and recurrent CV events during double-blind (DB) period (**Month 33-36**) in:
  - Overall population
  - Monotherapy population (patients not on tafamidis at baseline)

Secondary Endpoints[3]

- Change from BL to **Month 30** in 6-MWT distance
- Change from BL to **Month 30** in KCCQ-OS
- All-cause mortality through **42 Months**
- Change from BL to **Month 30** in NYHA class

Vutrisiran SC q3M 25 mg

Vital status was ascertained for 99.8% of patients

Day -45 — **Screening period** — Day 1 (Baseline) — **DB period** — M33 — M36 — M42 — **OLE** — M60

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

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

HELIOS-B Enrolled Population Reflective of Today's Patient

HELIOS·B

Milder Patients on Substantial Background Therapy; Underscores Magnitude of Treatment Effect and Relevance of Data to Real World

Use of Substantial Background Medications

~50%

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

~30%

of patients started SGLT2 inhibitors during the DB period

~80%

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

Patient Characteristics

	Real World Data*			HELIOS-B Overall (n=654)
	2002-2006 (n=35)	2012-2016 (n=704)	2017-2021 (n=968)	
NT-proBNP (ng/L), median	4466	3040	2505	1920
NYHA Class, n (%)				
I	0 (0.0)	83 (11.8)	136 (14.0)	84 (12.8)
II	6 (17.1)	444 (63.1)	657 (67.9)	508 (77.7)
III	10 (28.6)	153 (21.7)	134 (13.8)	62 (9.5)
IV	6 (17.1)	17 (2.4)	5 (0.5)	-
missing	13 (37.1)	7 (1.0)	36 (3.7)	-
NAC Stage, n (%)				
I	12 (34.3)	309 (43.9)	516 (53.3)	437 (66.8)
II	10 (28.6)	265 (37.7)	302 (31.2)	187 (28.6)
III	8 (22.9)	126 (17.9)	106 (11.0)	30 (4.6)
missing	5 (14.3)	4 (0.5)	44 (4.9)	-

*Retrospective observational study of patients referred to National Amyloidosis Center between 2002 – 2021 (Ioannou et al., Circulation, 2022)

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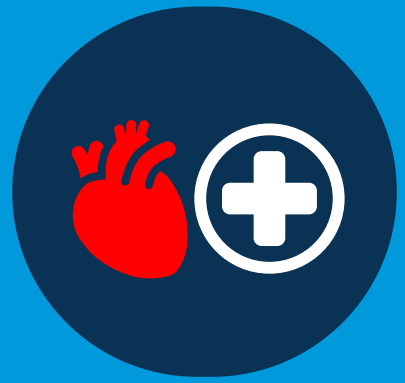
Alnylam®

Favorable Impact Across Sequential Parameters in ATTR Amyloidosis with Cardiomyopathy

Observed Clinical Benefit Occurs Early and Cascades in a Biologically Rational Manner

Rapid TTR Knockdown

Cardiac Biomarkers and Echocardiographic Improvements



Functional, Health Status, and QoL Benefit

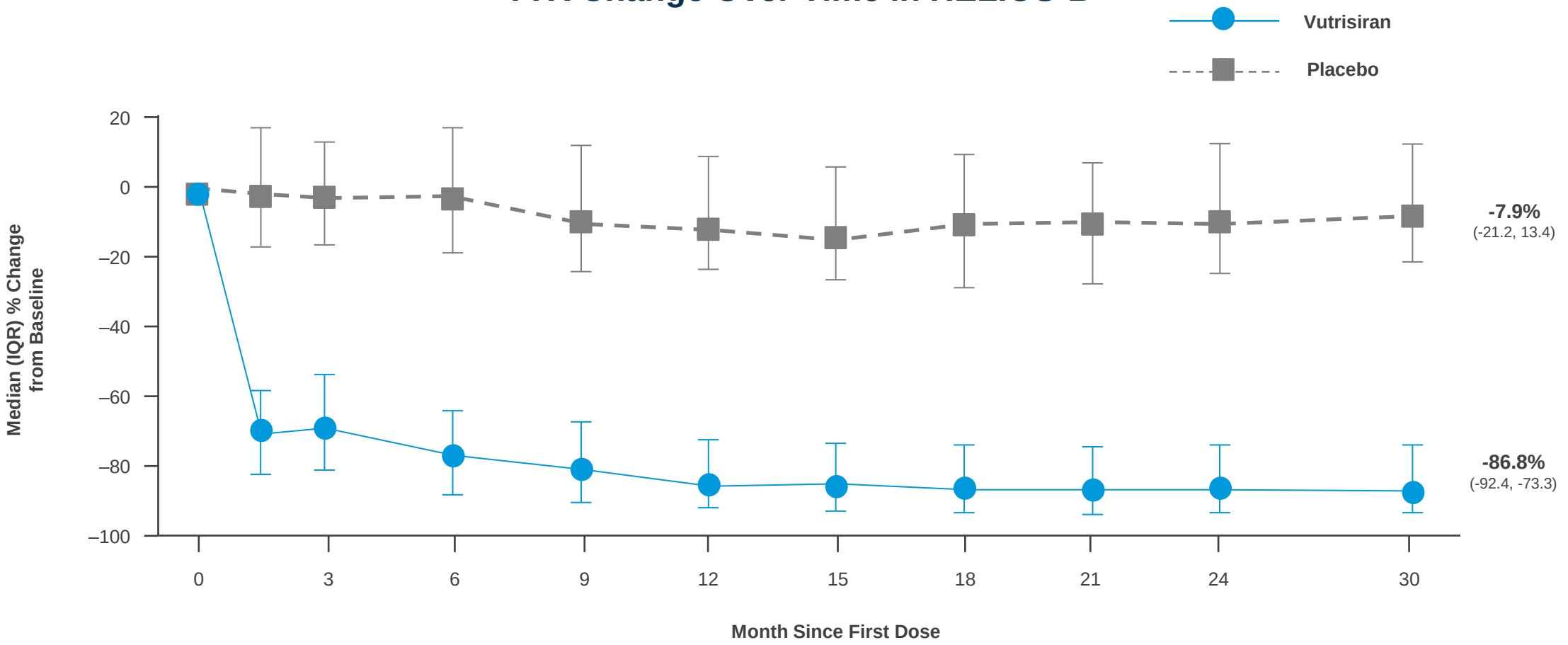
Outcomes Benefit

Alnylam®

Rapid TTR Knockdown and Durable Impact

HELIOS·B

TTR Change Over Time in HELIOS-B



TTR % change at Month 30: Mean (SD): placebo -1.98 (35.4); vutrisiran -80.98 (16.1)

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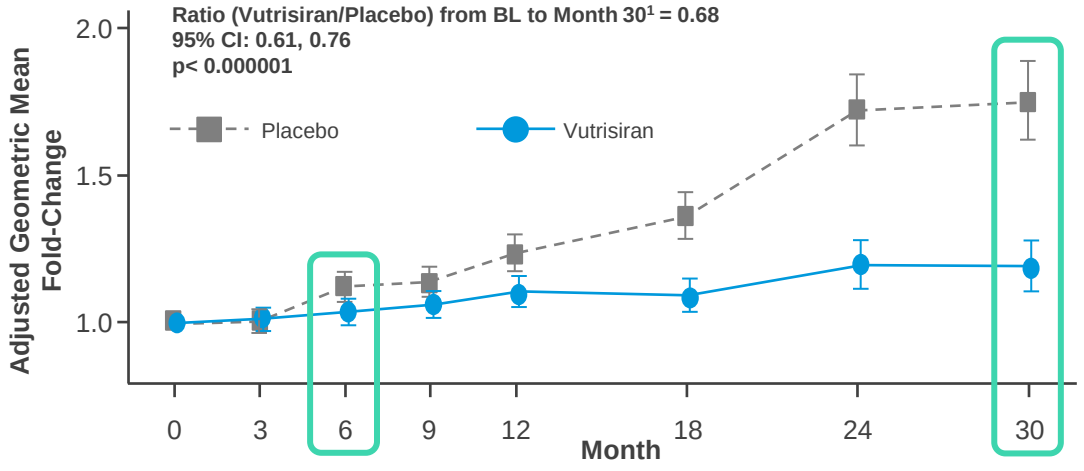
Vutrisiran Maintained Relative Stability of NT-proBNP and Troponin I Compared with Placebo

HELIOS-B

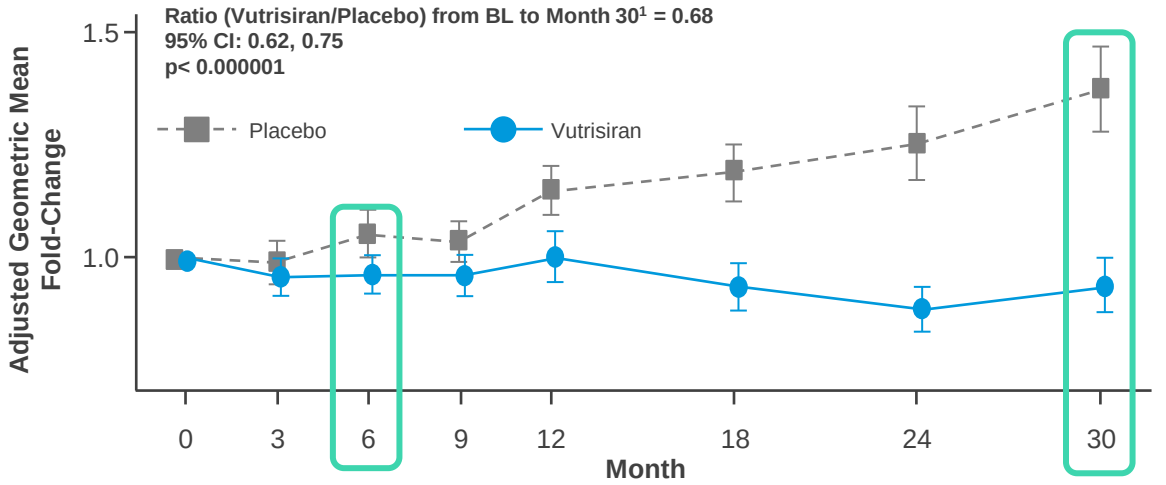
Favorable Treatment Effect Observed as Early as 6 Months on Exploratory Endpoints, and Grew Over Time

32% Relative Reduction for Both Biomarkers at Month 30

NT-proBNP



Troponin I



NT-proBNP and Troponin I are well established biomarkers predictive of mortality in ATTR-CM both in published data and within HELIOS-B[2]

[1]Adjusted geometric mean fold-change and 95% CIs obtained by exponentially back-transforming the LS mean of log-transformed NT-proBNP or troponin I and the corresponding 95% CI. In the MMRM model, the outcome variable is change from baseline in log-transformed NT-proBNP or troponin I. The model includes log-transformed baseline value as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR, and age group. [2]Maurer, Annual Scientific Meeting of the Heart Failure Society of America 2024. Abbreviations: BL, baseline; CI, confidence interval; LS, least squares; M, Month; MMRM, mixed models for repeated measures.

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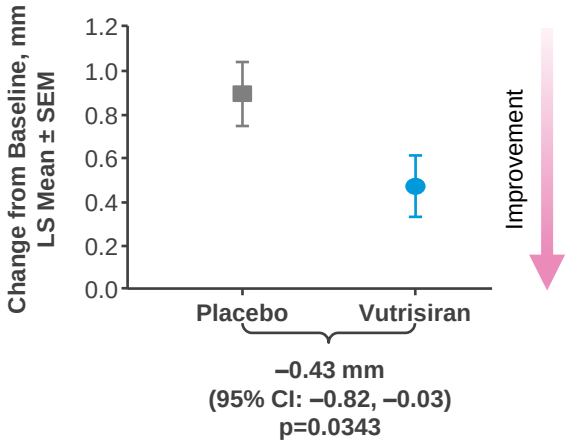
Vutrisiran Improved Cardiac Structure and Function

Exploratory Echocardiographic Assessments at M30 Provide Supportive Evidence of Disease-Modifying Effect

HELIOS-B

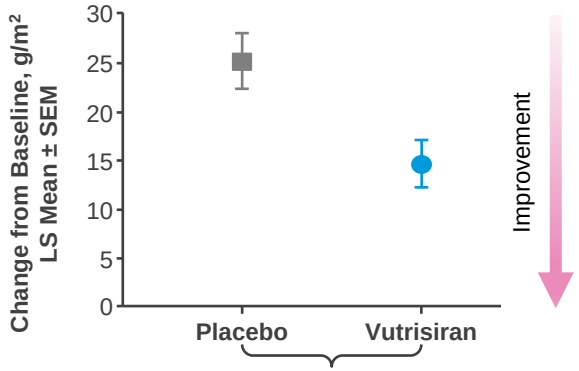
Cardiac Structure

Mean LV Wall Thickness



–0.43 mm
(95% CI: –0.82, –0.03)
p=0.0343

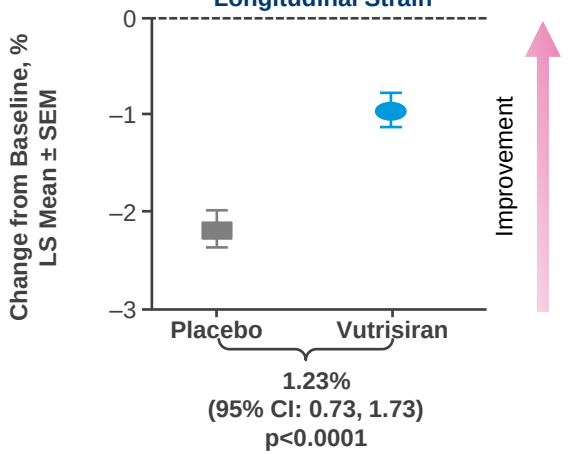
LV Mass Index



–10.6 g/m²
(95% CI: –18.0, –3.3)
p=0.0047

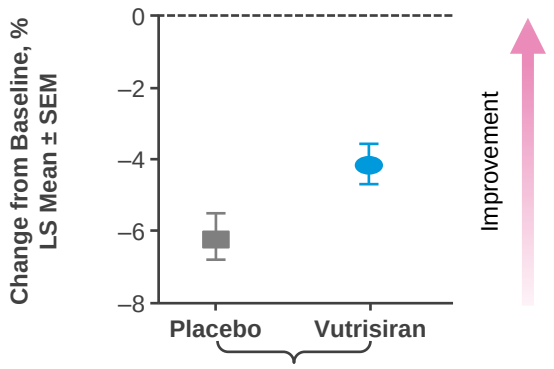
Systolic Function

Absolute Global Longitudinal Strain



1.23%
(95% CI: 0.73, 1.73)
p<0.0001

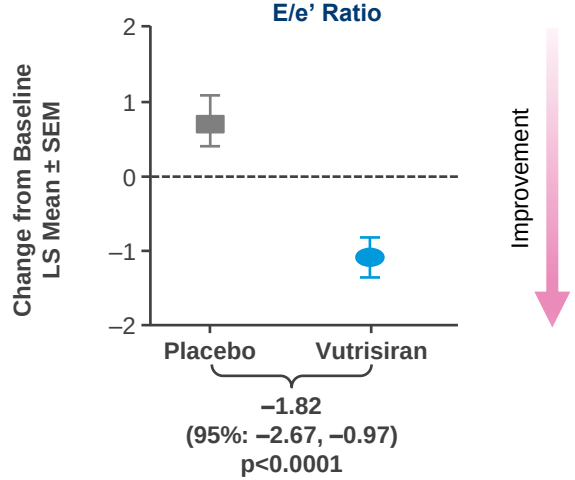
LV Ejection Fraction



2.03%
(95% CI: 0.34, 3.73)
p=0.0190

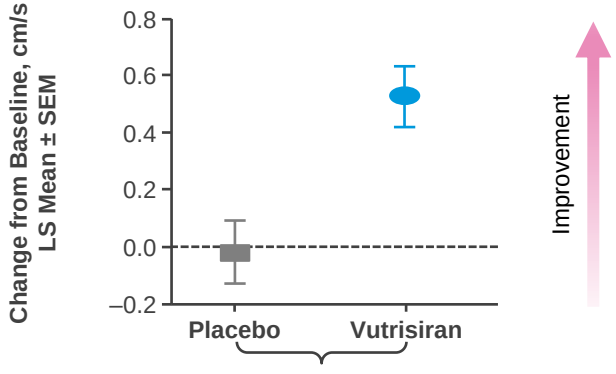
Diastolic Function

E/e' Ratio



–1.82
(95%: –2.67, –0.97)
p<0.0001

TDI Lateral e'



0.55 cm/s
(95% CI: 0.24, 0.85)
p=0.0005

Results are from a MMRM with baseline as a covariate and fixed effect terms including treatment group, visit, treatment-by-visit interaction, baseline tafamidis use, treatment-by-baseline tafamidis use interaction, type of ATTR amyloidosis, and age group. Abbreviations: E/e', ratio of early mitral inflow velocity to lateral early diastolic mitral annular velocity; LS, least squares; LV, left ventricular.

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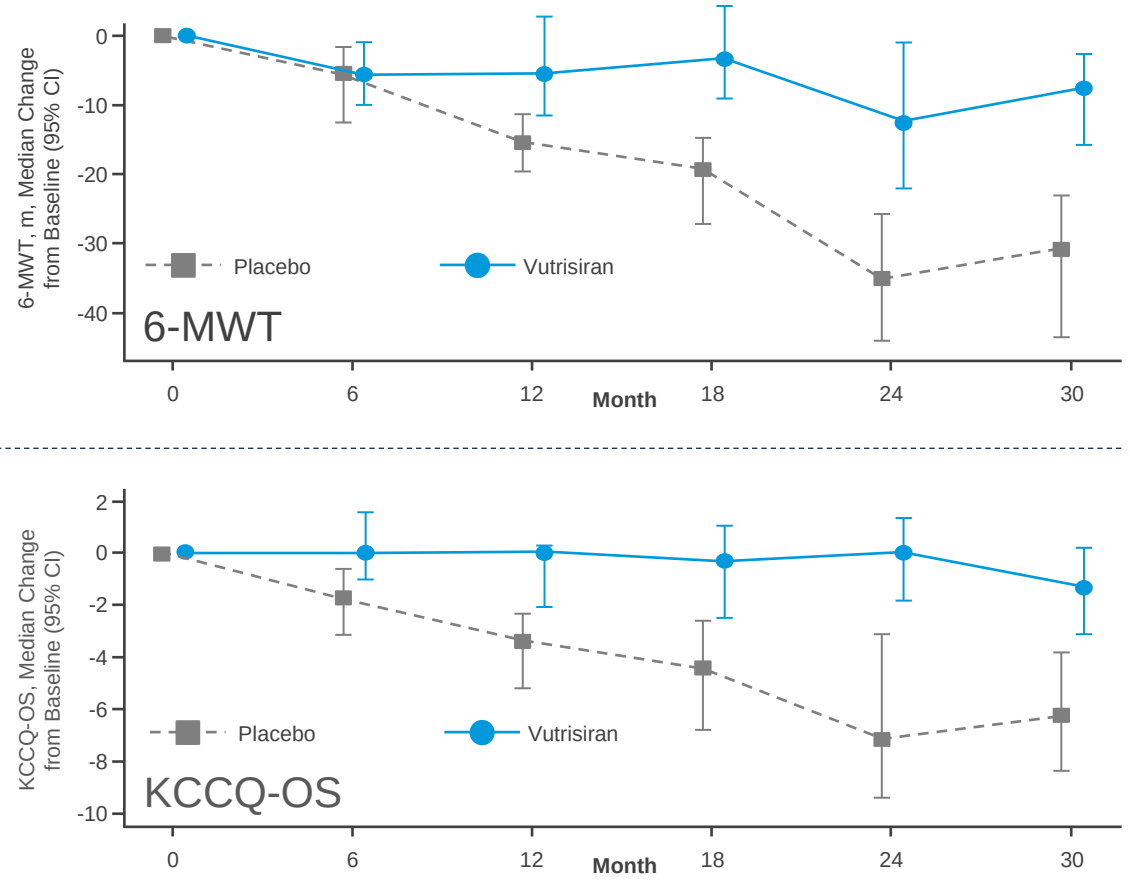
Favorable Impact on Multiple Measures of Disease Progression

HELIOS-B

Preserved Functional Capacity, Health Status, and Quality of Life over 30 Months; Statistically Significant Impact Relative to Placebo

Change from Baseline at Month 30	Overall Population	
	Placebo (N=328)	Vutrisiran (N=326)
6-MWT, n	**285**	**294**
Median	-30.65	-7.50
LS mean (SEM)	-71.88 (4.79)	-45.42 (4.62)
LS mean difference (95% CI)	—	26.46 (13.38, 39.55)
p-value	—	0.00008
KCCQ-OS, n	**298**	**306**
Median	-6.25	-1.30
LS mean (SEM)	-15.49 (1.26)	-9.68 (1.19)
LS mean difference (95% CI)	—	5.80 (2.40, 9.20)
p-value	—	0.0008
NYHA Class, n	**328**	**326**
Stable or improved %	61	68
Difference in % patients stable or improved (95% CI)	—	8.7 (1.3, 16.1)
p-value	—	0.0217

Median Change over Time (Observed)



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

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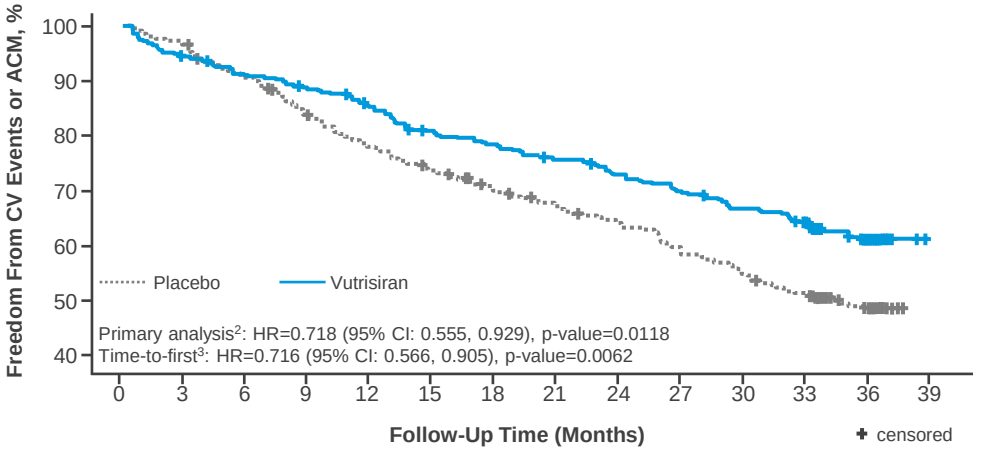
Reduction in All-Cause Mortality and Recurrent CV Events

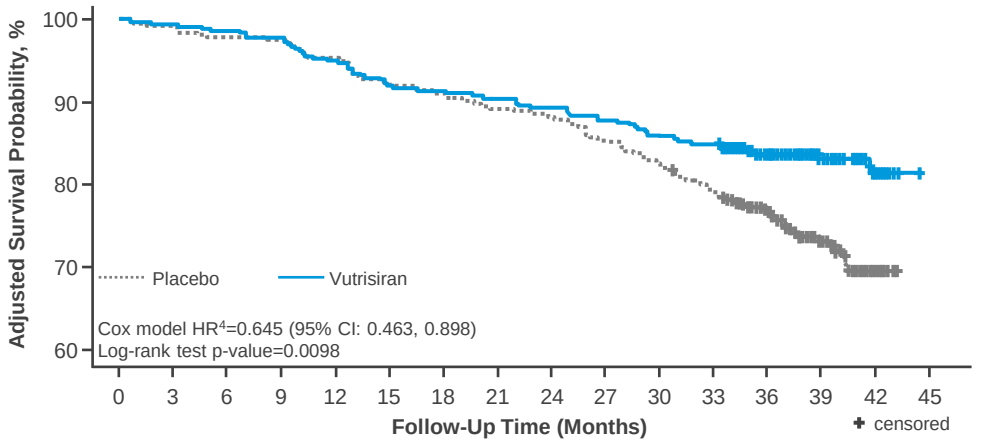
HELIOS-B

Time to First CV Event or All-Cause Mortality[1]



	Overall population (N = 654)
Primary endpoint: all-cause mortality and recurrent CV events up to month 36 (LWYY)	
HR (95% CI)	**0.718** (0.555, 0.929)
p-value	**0.0118**
Components	
All-cause mortality (DB period)	
HR (95% CI)	**0.694** (0.490, 0.982)
Log-rank p-value	**0.0389**
Recurrent CV events (Poisson regression)	
Relative rate ratio (95% CI)	**0.733** (0.610, 0.882)
p-value	**0.0010**

Time to All-Cause Mortality[1]



	Overall population (N = 654)
Secondary endpoint: all-cause mortality up to 42 months (Cox PH model)	
HR (95% CI)	**0.645** (0.463, 0.898)
p-value	**0.0098**

All-cause mortality includes heart transplantation and left ventricular assist device placement. 1Based on IPTW-adjusted Kaplan-Meier curves; 2Primary analysis based on the modified Andersen-Gill model, also known as LWYY; 3Time-to-first event HR derived from Cox PH model, p-value derived from Log-rank test. 4Time to all-cause mortality includes data from the double-blind period and up to 6 months in the OLE, deaths after end of study are included in the analysis, HR derived from Cox PH model. Abbreviations: ACM, all-cause mortality; CI, confidence interval; CV, cardiovascular; DB, double-blind; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LWYY, Lin, Wei, Yang , and Ying; PH, proportional hazard.

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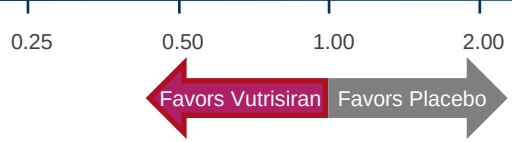
Consistent Efficacy Across All Prespecified Subgroups

HELIOS-B

Magnitude of Treatment Effect and Outsized Benefit in Key Subgroups Highlight Relevance to Today's Patients and Supports First-Line Positioning

Composite Outcome of All-Cause Mortality & Recurrent CV Events

Subgroup		Vutrisiran/Placebo	HR	95% CI
Overall	(N=654)		0.718*	(0.555, 0.929)
Age	<75 (N=257)		**0.545**	**(0.348, 0.854)**
	≥75 (N=397)		0.806	(0.584, 1.114)
Baseline tafamidis use	No (N=395)		0.672	(0.487, 0.929)
	Yes (N=259)		**0.785**	**(0.511, 1.207)**
ATTR disease type	hATTR (N=76)		0.922	(0.494, 1.724)
	wtATTR (N=578)		0.674	(0.506, 0.898)
NYHA class	I/II (N=592)		0.727	(0.552, 0.958)
	III (N=62)		0.681	(0.330, 1.406)
Baseline NT-proBNP	≤2000 (N=342)		**0.525**	**(0.349, 0.788)**
	>2000 (N=312)		0.798	(0.562, 1.133)



Secondary Endpoint of All-Cause Mortality Through 42 Months

Vutrisiran/Placebo	HR	95% CI
	0.645†	(0.463, 0.898)
	0.552	**(0.293, 1.040)**
	0.686	(0.464, 1.013)
	0.655	(0.440, 0.973)
	0.588	**(0.320, 1.081)**
	0.891	(0.390, 2.033)
	0.609	(0.424, 0.875)
	0.663	(0.467, 0.940)
	0.578	(0.198, 1.689)
	0.348	**(0.183, 0.659)**
	0.827	(0.553, 1.236)

- Trends toward greater efficacy seen in patients with earlier disease (i.e, age <75 and NT-proBNP ≤2000), with 46% and 48% reduction, respectively, in primary composite, and 45% and 65% reduction, respectively, in all-cause mortality
- Consistent benefit in patients with or without baseline tafamidis

All-cause mortality includes heart transplantation and left ventricular assist device placement. Abbreviations: ATTR, transthyretin amyloidosis; CI, confidence interval; CV, cardiovascular; hATTR, hereditary transthyretin amyloidosis; HR, hazard ratio; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; wtATTR, wild-type transthyretin amyloidosis.

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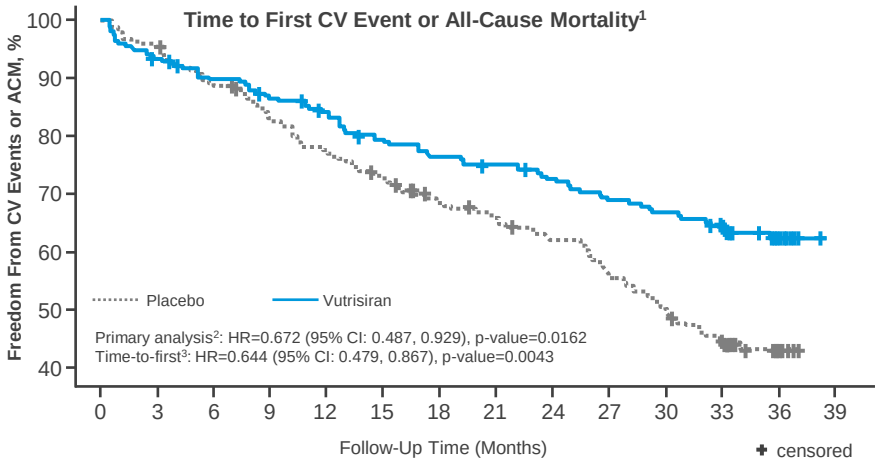
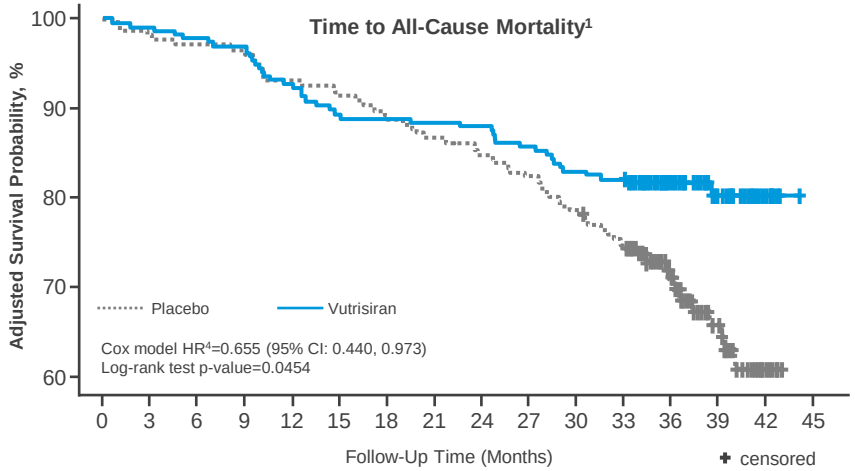
Significant Outcomes Benefit with Vutrisiran Monotherapy and Favorable Trends in Baseline Tafamidis Subgroup

HELIOS-B

Monotherapy Population

33% reduction in primary composite of all-cause mortality and recurrent CV events

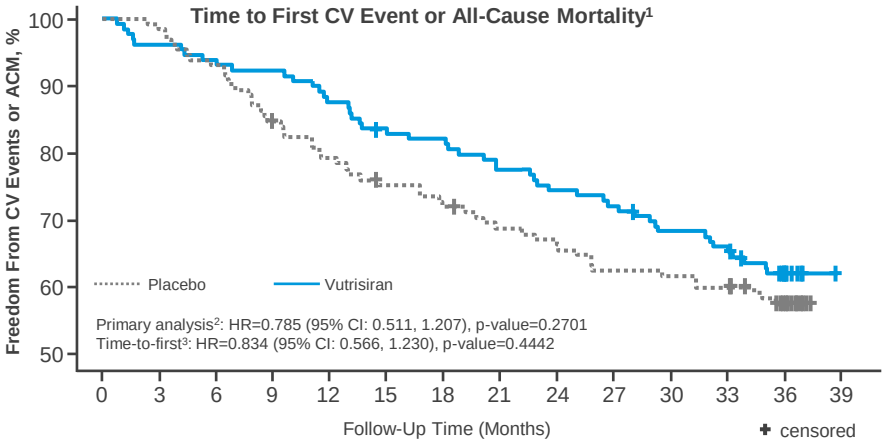


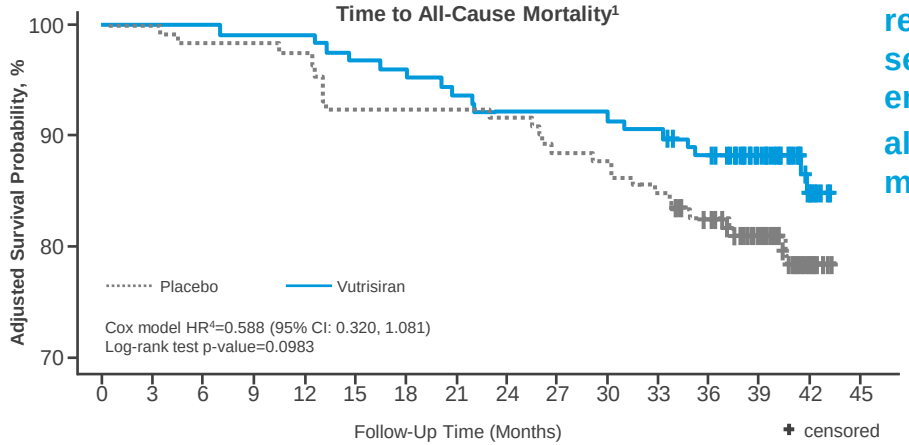


35% reduction in secondary endpoint of all-cause mortality

Tafamidis Subgroup

22% reduction in primary composite of all-cause mortality and recurrent CV events





41% reduction in secondary endpoint of all-cause mortality

All-cause mortality includes heart transplantation and left ventricular assist device placement. [1]Based on IPTW-adjusted Kaplan-Meier curves; [2]Primary analysis based on the modified Andersen-Gill model, also known as LWYY; [3]Time-to-first event HR derived from Cox PH model, p-value derived from Log-rank test; [4]Time to all-cause mortality includes data from the double-blind period and up to 6 months in the OLE, deaths after end of study are included in the analysis, HR derived from Cox PH model; Abbreviations: ACM, all-cause mortality; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LWYY, Lin, Wei, Yang , and Ying; PH, proportional hazard.

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Key Takeaways From HELIOS-B

HELIOS·B

In a population reflective of today's patients, on substantial background therapy, HELIOS-B demonstrated profound benefit on outcomes

Clinical effect seen early, starting with effects on well-established biomarkers predictive of outcomes in real world and within HELIOS-B

Improvements compared to placebo were seen in cardiac structure, as well as systolic and diastolic function; all important elements of underlying pathophysiology

Early benefit on functional status and quality of life, which was preserved over 30 months

Treatment effect was consistent across all subgroups, including patients on background tafamidis

Particularly profound effects on outcomes were observed for patients with evidence of early disease

Acceptable safety and tolerability profile, as previously established

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Putting It All Together; Vutrisiran Well-Positioned for 1L Use

HELIOS-B results were observed in a population reflective of today's patients on substantial background therapy

Magnitude of benefit was profound

Trends of substantial benefit observed in patients on background tafamidis, highlighting unmet need in this patient population despite currently available therapies

Outsized benefit on patients with milder disease, demonstrating importance of early treatment

Preserved functional status and quality of life based on key measures of disease progression, critical in a disease marked by irreversible decline

Collectively, data indicate it is imperative to identify patients early and initiate treatment with effective therapy

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

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Q&A Chat With Clinical Leadership and ATTR-CM Expert

Pushkal Garg, M.D.
Executive Vice President,
Chief Medical Officer

MODERATOR

Dr. Ahmad Masri, M.D., M.S.
Oregon Health & Science University

John Vest, M.D.
Senior Vice President,
TTR Global
Development Lead

Alnylam®

TTR Investor Day

October 9, 2024

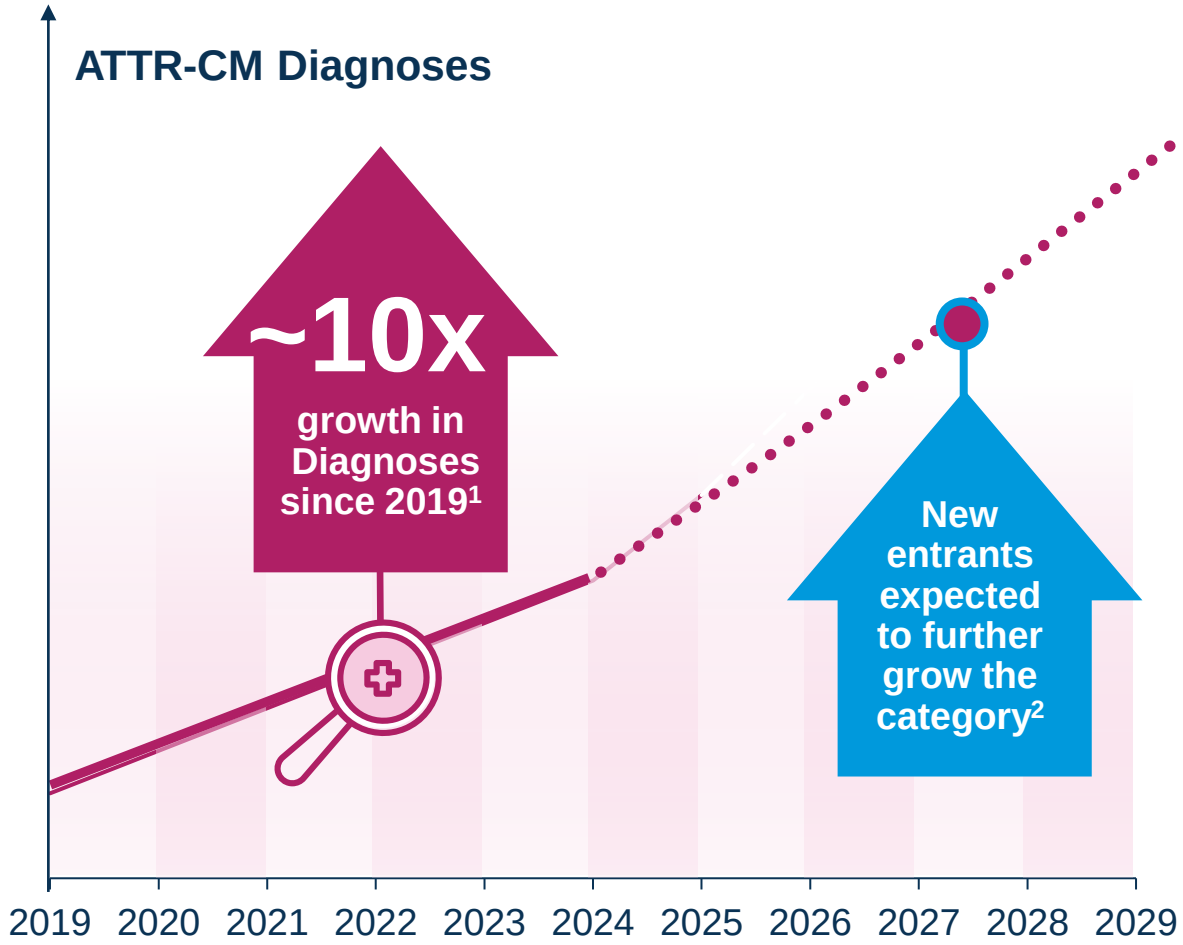
Building a Flagship Franchise in ATTR-CM

Tolga Tanguler
EVP, Chief Commercial Officer

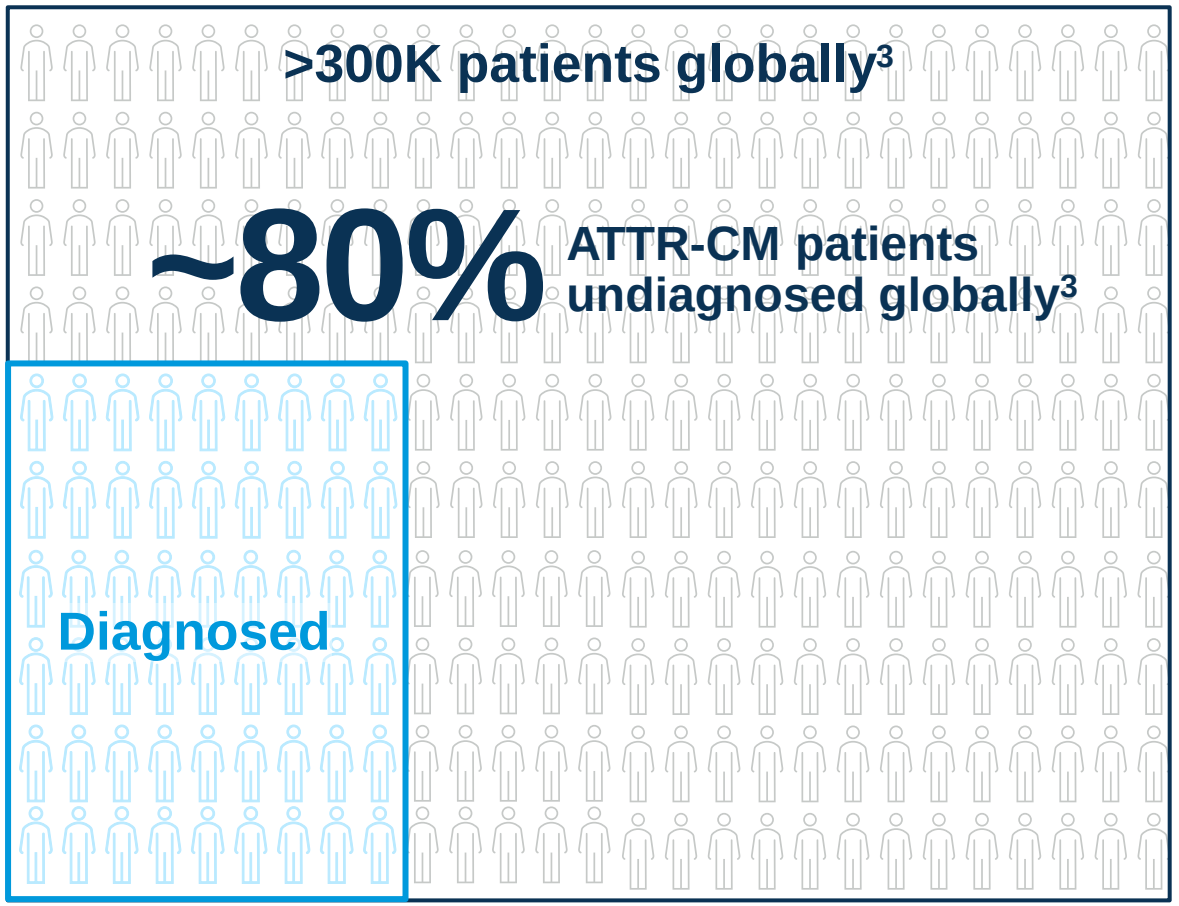
Alnylam®

Large and Growing Category with Significant Unmet Need

Growing Category with Rapidly Improving Dx



Large and Untapped Opportunity

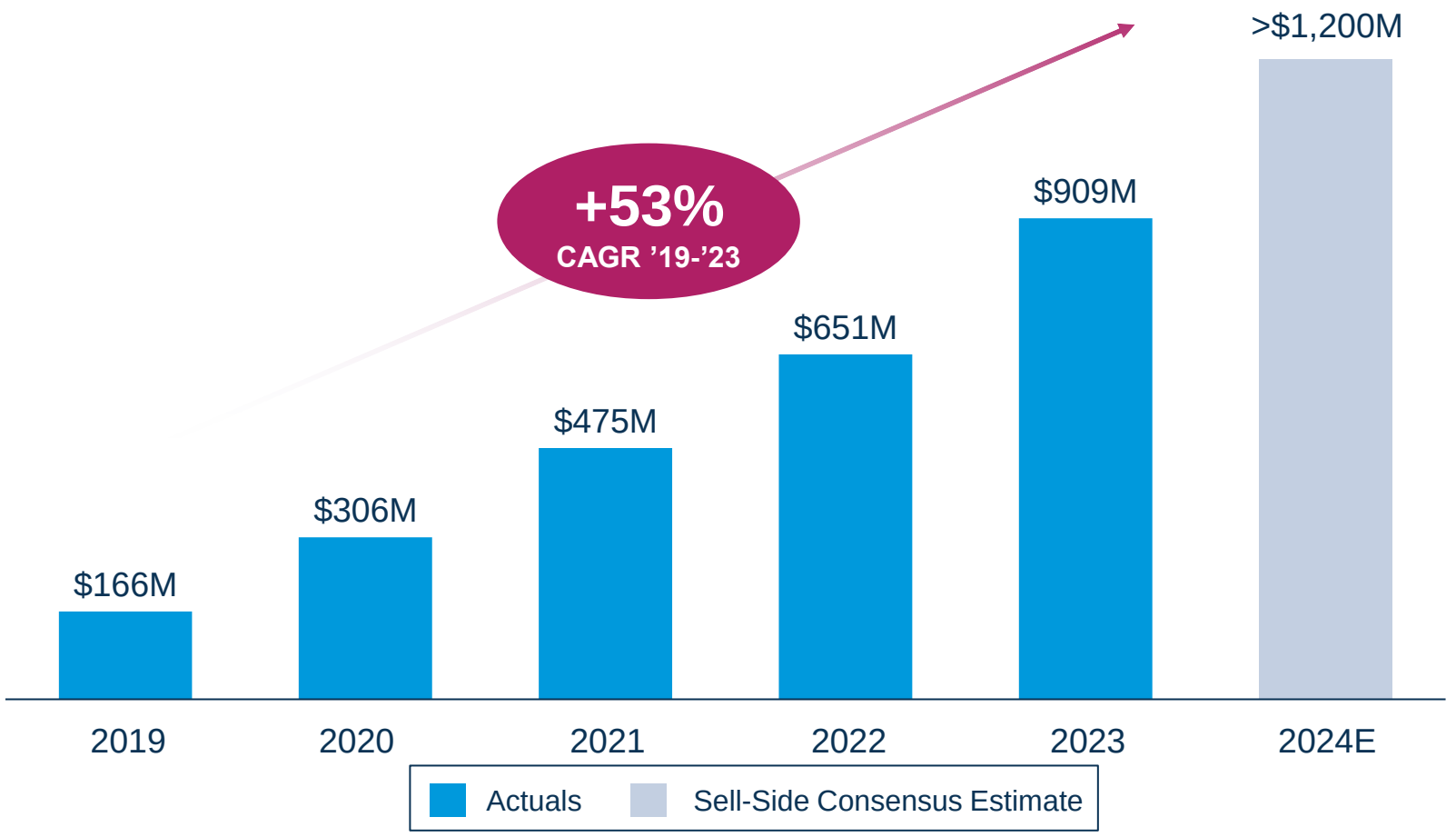


1. Alnylam internal market research, US specific diagnoses rate given data availability, 2. Analog Assessment 3. ATTR-CM, based on Alnylam modeling data,

Alnylam®

Demonstrated Market Leadership in hATTR-PN

Alnylam TTR Product Sales



Established hATTR-PN Category in U.S.

>45% YoY

CAGR between 2019-2023

Competed Effectively in EU & JP

>80%

Estimated share of the hATTR-PN market in Europe & Japan[1]

1. Internal data; top 5 EU markets and Japan

We Know What it Takes to Succeed

Market-Leading Profile

The Right Talent

Patient-Centric Approach

Organizational Focus and TTR Experience

$ Multi-Billion

Market Potential

Alnylam

We Have Built a World-Class Leadership Team

Joining us here today:

John Kennedy
TTR Franchise Commercialization Lead

Mark Soued
Head of U.S. & TTR Lead

Jason Gidelson
U.S. Market Access

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We Are On a Path to Leadership

Large, untapped and growing category with significant unmet need

AMVUTTRA is poised to become the standard of care for first line patients in ATTR-CM[1]

Our success and strong leadership in hATTR-PN position us to be highly competitive in ATTR-CM

We have a deep focus on ATTR and have scaled for a successful launch

1. Assuming regulatory approval

Driven by Patient Needs

John Kennedy
TTR Franchise
Commercialization Lead

Alnylam®

ATTR-CM Market is Large, Growing and Underserved with Unmet Needs Across Three Patient Segments

	New to Treatment	Stabilizer Progressors	Undiagnosed
Global Est. Size[1]	**~18K** New to Treatment, Annually (and Growing)	**~20K** Treatment Progressors	**~80%** Undiagnosed Patients (Diagnosis/Treatment Rate Improving)
Goal	**Establish AMVUTTRA as first-line choice**	**Capture switch / add-on opportunity**	**Drive earlier diagnosis across ATTR-CM patients**

We've Developed Robust Strategy to Grow our TTR Franchise Over Time

1. Global represents US + EU5 + Japan; Sizing estimates based on claims analyses & internal market research (2024), as well as Pfizer public statements

~40K patients are being actively treated (globally)1. Recent literature show a range of estimates for many patients experiencing suboptimal response to Tx. In an analysis of US claims/EHR data (Fontana M, et al. data presented at Heart failure Society of America Annual Scientific Meeting 2024) ~50% experienced cardiac worsening (n >800, over median ~ 1 year)

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Establish AMVUTTRA as First-Line Choice in ATTR-CM for Patients New to Treatment

New to Treatment

illustrative

~18K

New to Treatment, Annually (and Growing)

What We Know

- **>50% YoY growth** in volume of ATTR-CM patients treated with approved therapy today[1]
- **Largest & fastest growing** patient segment aligned with HELIOS-B profile (milder disease)[2]
- **~20-30% mixed phenotype** patients[3]

What It Will Take

- Drive brand awareness, access & preference

1. Internal analysis 2. Ioannou et al, Circulation 2022; 3. Polydefkis, ConTTRibute registry data, ISA 2023 abstract

HELIOS-B Delivers First-Line Potential for AMVUTTRA

Clinical Considerations

Compelling HELIOS-B Dataset

Patients with milder symptoms on substantial background therapy underscore **magnitude of treatment effect** and **relevance of data to real world**

Magnitude & consistency of impact on **cardiovascular events and mortality outcomes**

Disrupted disease progression as assessed by biomarkers, imaging, function and QoL

Impact **optimized when vutrisiran treatment started early**

Practical Considerations

Patient Experience

4x **dosing** per year › **~95%** **adherence** as demonstrated in hATTR-PN[1]

Access & Affordability

>99% of U.S. insured lives have confirmed coverage[2] › **~70%** of patients have **$0 copay***

* Based on experience in hATTR-PN. Similar access dynamics expected in ATTR-CM

1. Internal data 2. Based on DKP PayerScope® data as of August 2024

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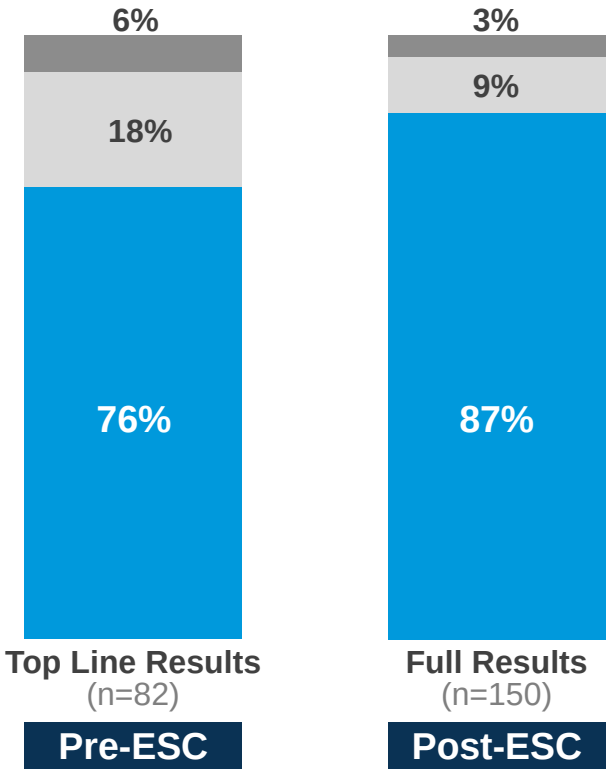
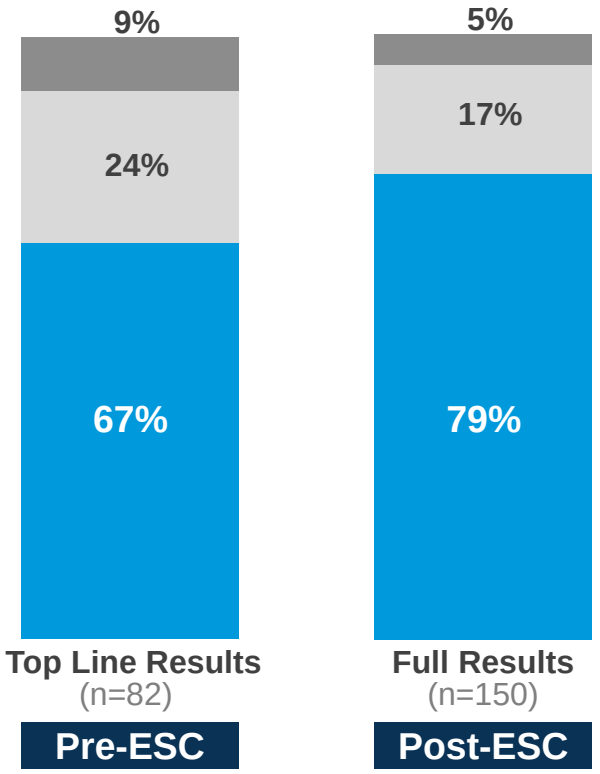
Encouraging Cardiologist Response to HELIOS-B

In an Independent Poll of ATTR-CM Treating Cardiologists Across U.S. & EU Based on the HELIOS-B Data Released...

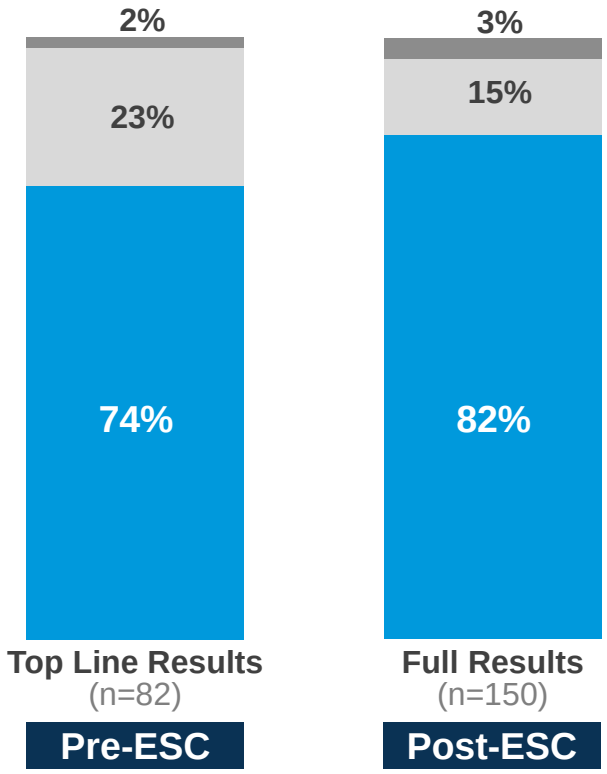
Likelihood to Prescribe AMVUTTRA for ATTR-CM Patients

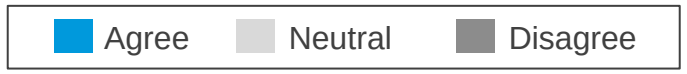


Likelihood to Prescribe AMVUTTRA as 1L Monotherapy for ATTR-CM



Data Support AMVUTTRA Becoming SOC Therapy for ATTR-CM





Medefield Medepoll survey conducted on behalf of IPSOS: Online short-form questionnaire collected during July 2024 and Sept 2024 consisting of cardiologists across US, France, Germany, Italy, Spain and UK. Data copyright by Medefield, and analysis/interpretation attributed to Ipsos.
Top Line Results = Survey initiated independently by Ipsos following initial top-line results announcement (July 2024, n = 82); Full Results = Survey repeated following full results presentation at ESC & simultaneous publication in NEJM (September 2024, n = 150); Base = All cardiologists that personally managed ATTR-CM patients in the past 3 months

Encouraging Cardiologist Response to HELIOS-B

In an Independent Poll of ATTR-CM Treating Cardiologists Across U.S. & EU Based on the HELIOS-B Data Released...

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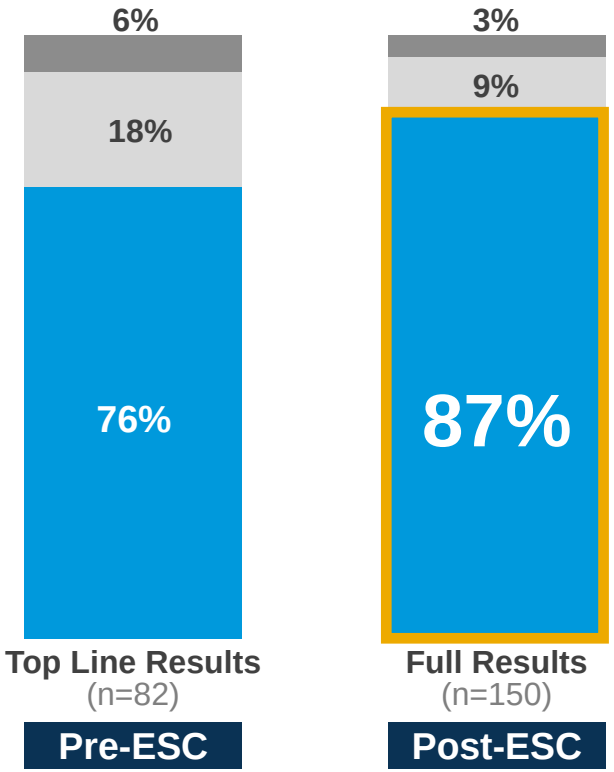

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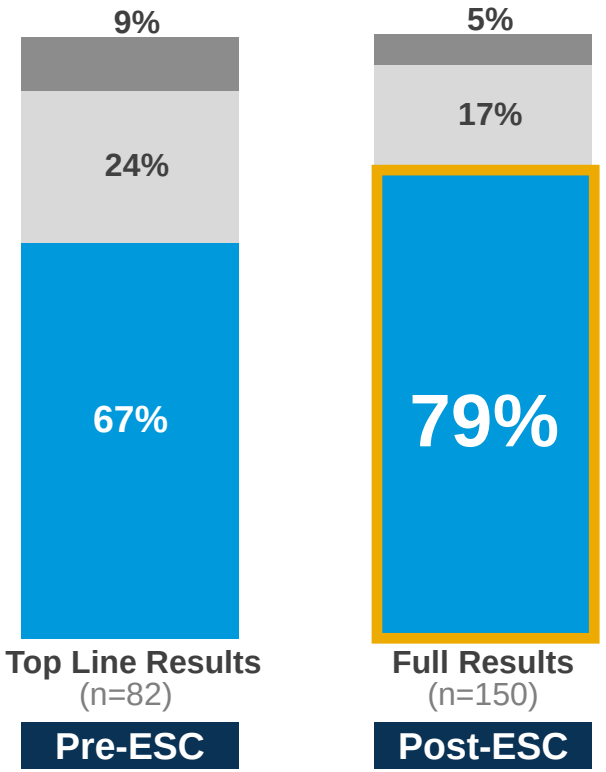
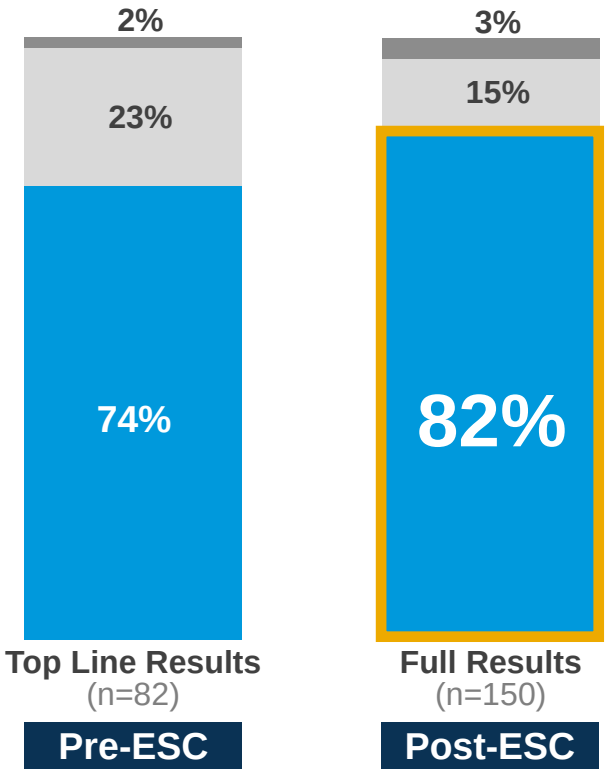
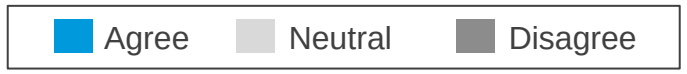


Data Support AMVUTTRA Becoming SOC Therapy for ATTR-CM





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Capture Stabilizer Progressors for Switch / Add-On Opportunity

Stabilizer Progressors

illustrative

~20K

Stabilizer Progressors

What We Know

- **~50% of stabilizer treated patients** experienced cardiac worsening* over ~12 mos (median), in recent US claims/EHR analysis (n > 800)[1]
- **Progressor enrollment** in APOLLO-B / Patisiran EAP illustrate the unmet need
- **Treatment persistence gaps with daily oral Rx's** evident in claims data, in ATTR-CM[2] & analogous therapeutic areas[3,4]

What It Will Take

- Urgency to optimize (what's lost cannot be regained)
- Clinical decision-support (e.g., progression red flags)

*Cardiac worsening is defined as the occurrence of any of the following events: myocardial infarction (MI), deep venous thrombosis (DVT), pulmonary embolism (PE), stroke, New York Heart Association (NYHA) Class change to a more severe class, CVD-related hospitalization, aortic valve replacement, aortic stenosis, revascularization, arrhythmia, or progression in ATTR staging

1. Fontana M, et al. Presented at: Heart failure Society of America Annual Scientific Meeting 2024, Atlanta, GA, USA; September 27-30, 2024; 2. Internal data based on claims data, 3. Prostate Cancer (Higano et al, Journal of Urology, March 2023); 4. MS (Nicholas et al, BMC Neurology, July 2020)

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Drive Earlier Diagnosis Across All Addressable ATTR-CM Patients

Undiagnosed

illustrative

~80%

Undiagnosed Patients (Diagnosis/Treatment Rates Improving)

What We Know

- **~ 10x growth in Diagnosis in US**, 2019 – 2023[1]
- **Competition accelerates category growth** as seen in analogous, under-served specialty treatment categories[2]
- **Alnylam track record** driving sustained growth 53% CAGR (2019-2023) in hATTR-PN[3]

What It Will Take

- Advanced analytics / AI-assisted diagnosis
- Broad community (HCP/Patient) activation

1. Based on internal market research+ Pfizer public statements; 2. (e.g.,MS, RA and gMG) per ZS analogue assessments, 2023, 2024; 3. Actuals

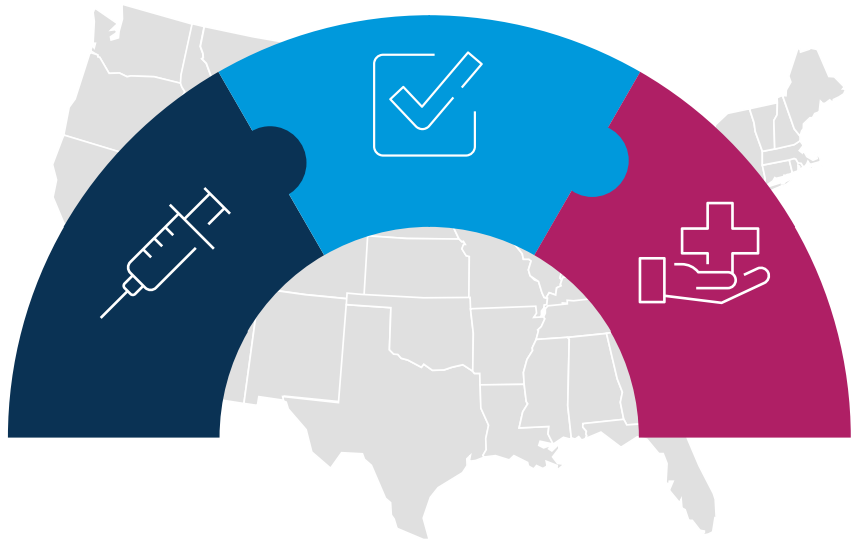
To Achieve Our Goals, We Must Be Ready to Scale

Opportunity

- **Establish AMVUTTRA as first-line choice**
- **Capture switch / add-on opportunity**
- **Drive earlier diagnosis across ATTR-CM patients**

How We'll Get There

Successful first launch in U.S. is key enabler of early momentum



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Unlocking the U.S. Opportunity in ATTR-CM

Mark Soued
SVP, Head of U.S. & TTR Lead

Jason Gidelson
VP, U.S. Market Access

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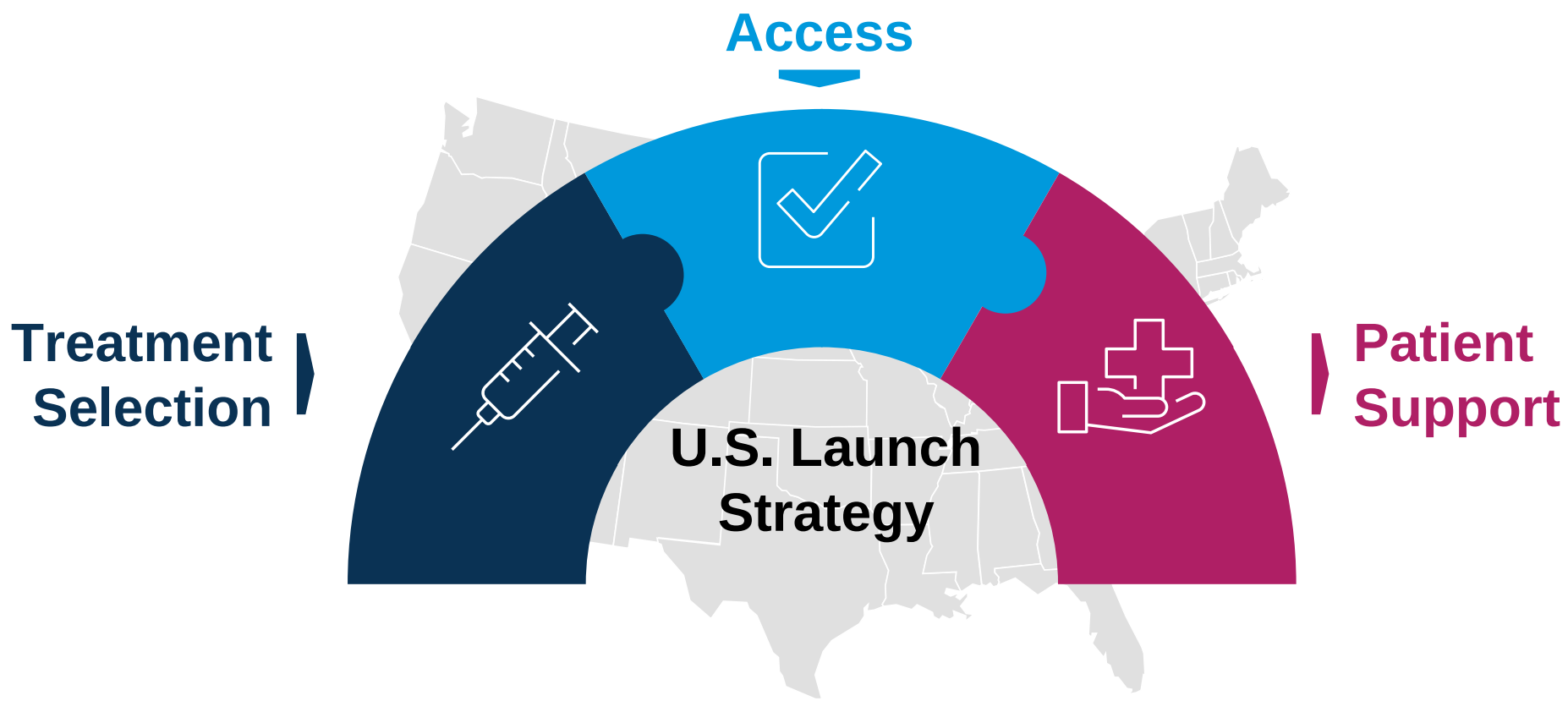
Three Foundations For a Successful Launch In ATTR-CM



Entering ATTR-CM represents a step-up, NOT a giant leap

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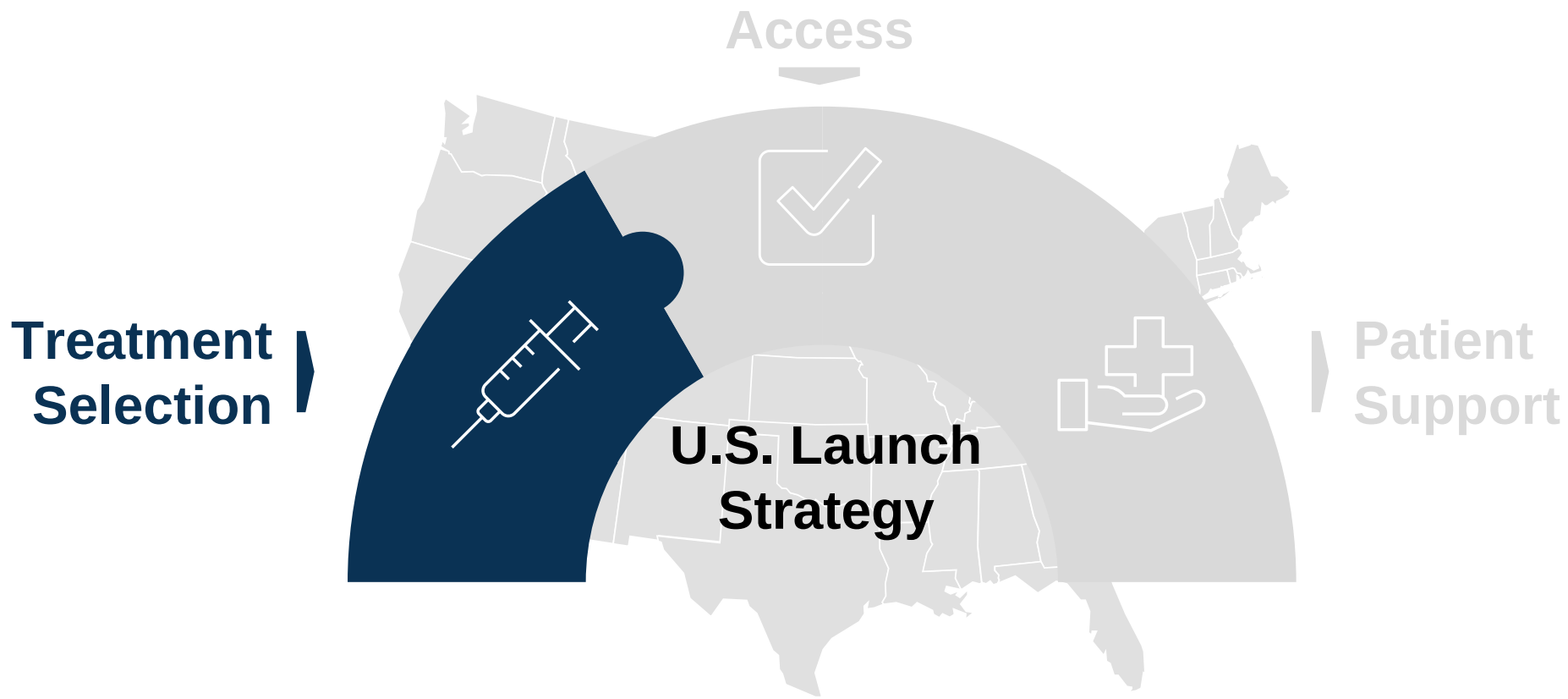
Expanded Field Teams Ready to Establish AMVUTTRA as Preferred 1L Treatment Across Three Patient Segments



AMVUTTRA Opportunity Spans Three Key Segments

~150K Prevalent Patients in the U.S.

1 New To Treatment

- **~5-10K** ATTR-CM patients initiating treatment annually at increasing rate
- AMVUTTRA well positioned to compete as 1L choice
- Fastest segment to unlock

2 Stabilizer Progressor

- **~15-25K** patients currently on stabilizers
- **~8-13K** patients who may benefit from add-on or switching
- Add-on will be more common after tafamidis LOE
- Establishing AMVUTTRA in 1L will help facilitate switching

3 Undiagnosed

- **~75-95K** patients currently undiagnosed
- With increased disease awareness/education, diagnosis rate expected to accelerate

Note: Internal data, 2024

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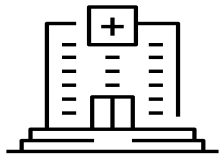
Field Teams Expanded to Deliver 100% Coverage At Launch

	FROM Today (PN)	**TO** At Launch
 **~3,700** HCPs treating ~95% of patient population	**~65%** **ALNY Coverage** (due to hATTR-PN diagnostic pathways)	**100%** **ALNY Coverage**
 **~170** Health systems accounting for ~80% of potential Rx volume *(e.g., Ascension, Mayo Clinic, Stanford)*	**~45%** **ALNY Coverage**	**100%** **ALNY Coverage**

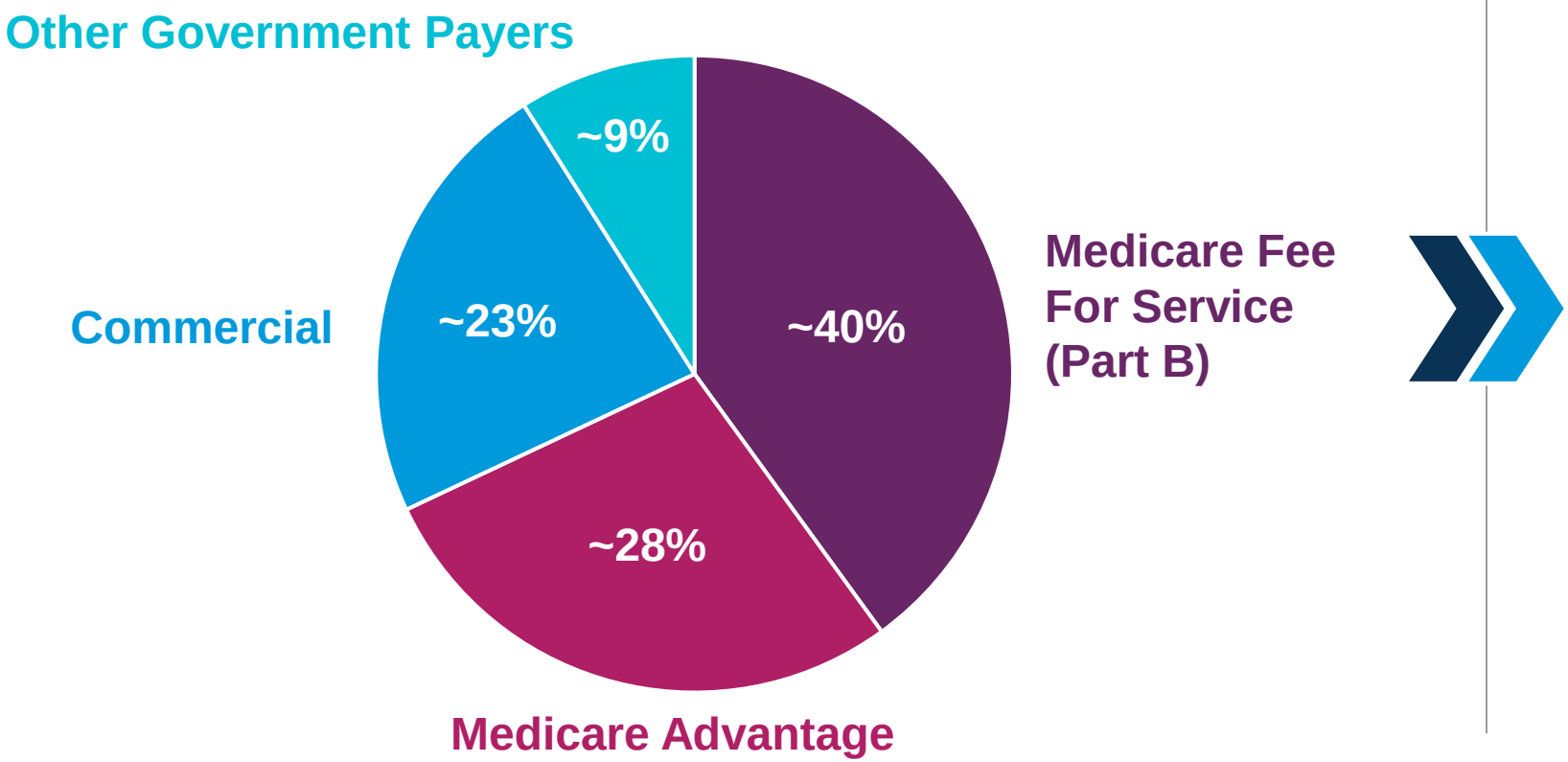
Entering ATTR-CM represents a step-up, NOT a giant leap

Sources (non-exhaustive): Komodo, IQVIA, and Alnylam internal analysis as of Q2 2024

We Expect to Maintain Favorable Access in ATTR-CM

In hATTR-PN, AMVUTTRA Maintains Broad Access

AMVUTTRA Has >99% Coverage[1,2]



AMVUTTRA has maintained favorable coverage since launch

~70% of AMVUTTRA patients today pay $0 OOP

1. Based on DKP PayerScope® data as of August 2024; 2. Payer mix based on Alnylam Assist data

In ATTR-CM, HELIOS-B Provides Compelling Clinical Data

Payers First Consider Clinical Data and Then Cost in Coverage Policies[1]

- Clinical Efficacy
- Safety
- Net Price
- Unmet Need
- Treatment Cost vs. Standard of Care
- Total Direct Treatment Cost Offset
- Therapeutic Area Treatment Algorithm
- Durability
- Indirect Treatment Cost Offset

HELIOS-B Clinical Benefits

There is an unmet need in ATTR-CM given limited treatment options

HELIOS-B demonstrated that treatment can be optimized by delivering:

- Robust cardiovascular outcomes including mortality benefit
- Reduction in hospitalizations
- Preservation of function and quality of life

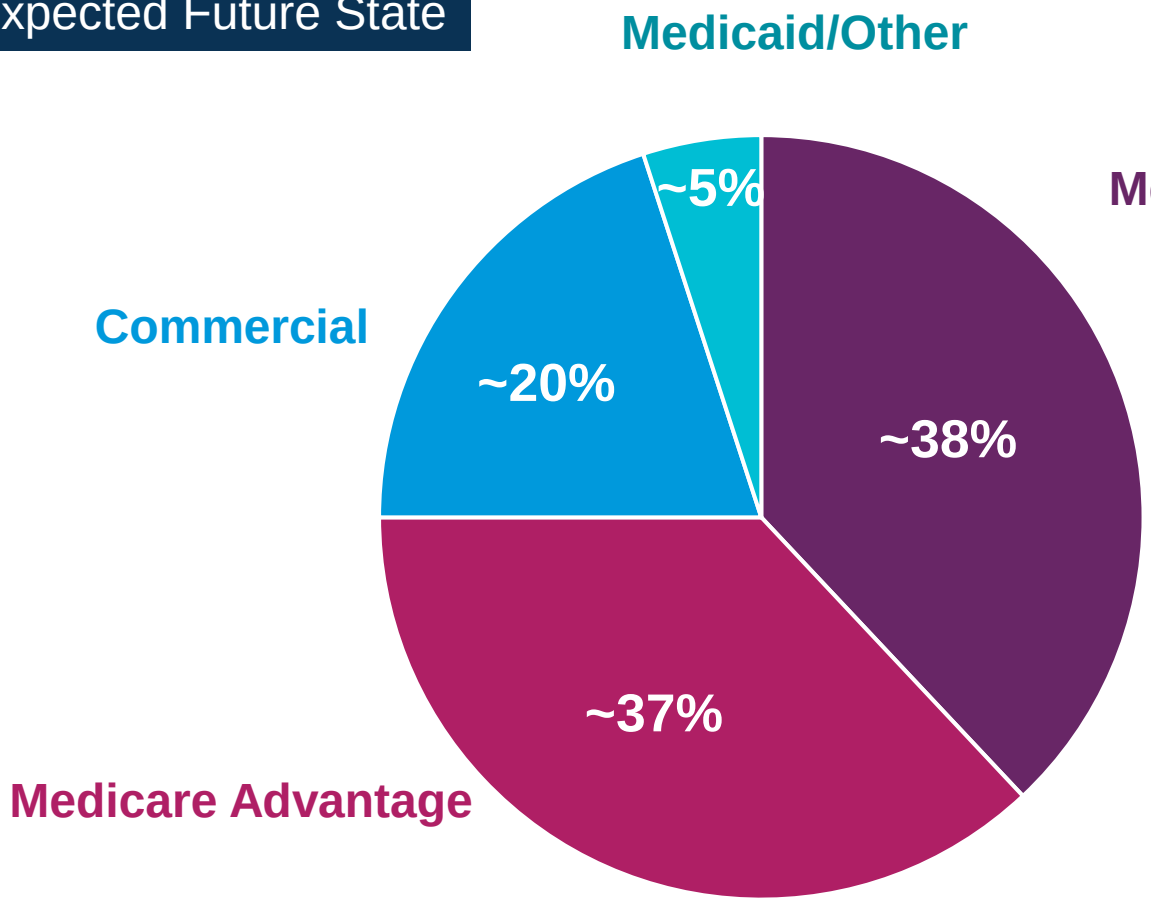
…in today's patient population

AMVUTTRA delivered consistent benefit even on backdrop of substantial background therapies (including tafamidis)

1. 2023 Rare and Specialty Trend Report, Perspective from Healthcare Payers Sponsored by Alnylam

In ATTR-CM, AMVUTTRA Expected to Have Widespread Coverage

Expected Future State



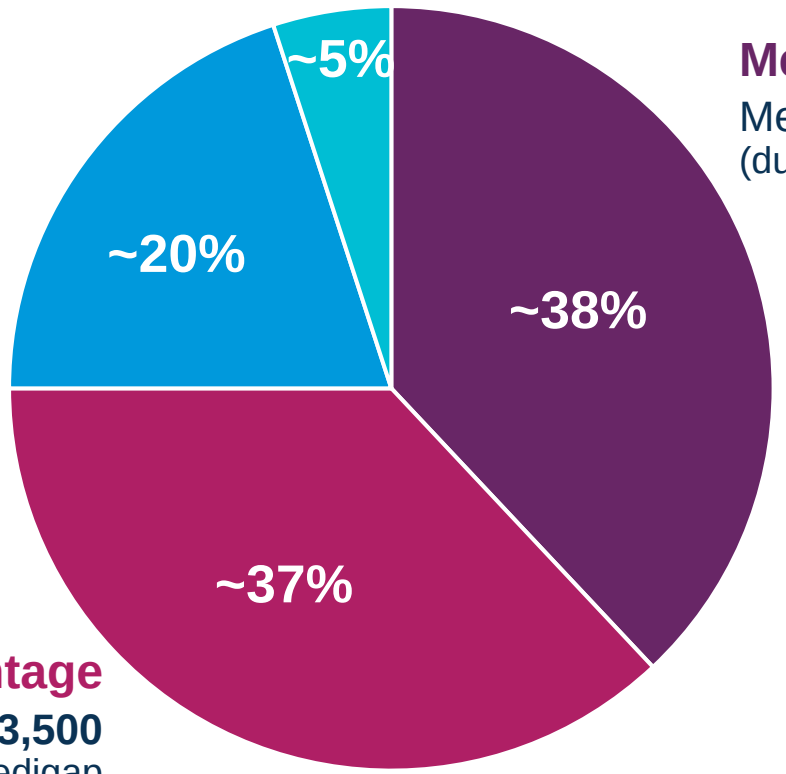
Payer mix in ATTR-CM expected to be similar to hATTR-PN, and consistent with current ATTR-CM dynamics

Sources (non-exhaustive): Komodo and Alnylam internal analysis as of Q2 2024.

AMVUTTRA is assumed to have a similar payer mix with a majority of coverage under the Medical benefit (i.e. Part B) if approved in ATTR-CM.

In ATTR-CM, Most AMVUTTRA Patients Expected to Pay $0 Out of Pocket[1,2]

Expected Future State



Medicaid/Other
Median OOP **$0**

Medicare FFS
Median OOP **$0**
(due to Medigap)

Commercial
Median OOP **$0**
(due to copay card)

Medicare Advantage
Median OOP ~**$3,500**
(ineligible for Medigap or copay assistance)

Sources (non-exhaustive): Komodo, Alnylam Assist data, Alnylam internal analysis as of Q2 2024.

1. AMVUTTRA is assumed to have a similar payer mix with a majority of coverage under the Medical benefit (i.e. Part B) if approved in ATTR-CM; 2. Assumes AMVUTTRA ATTR-CM patients have similar out-of-pocket costs to AMVUTTRA hATTR-PN patients.

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Inflation Reduction Act Has Important Implications For Part D

Part D

Patient Copay	**$2,000** per year max
Payer Liability	**4X** Increase[1]

Part B

Patient Copay	**No change**[2]
Payer Liability	**No change**

1. The IRA increases health plan liability in the catastrophic coverage phase from 15% to 60% of the drug cost in 2025; 2. Medicare Part B beneficiaries may have a lower coinsurance for some drugs if the drug's price increases faster than the rate of inflation.

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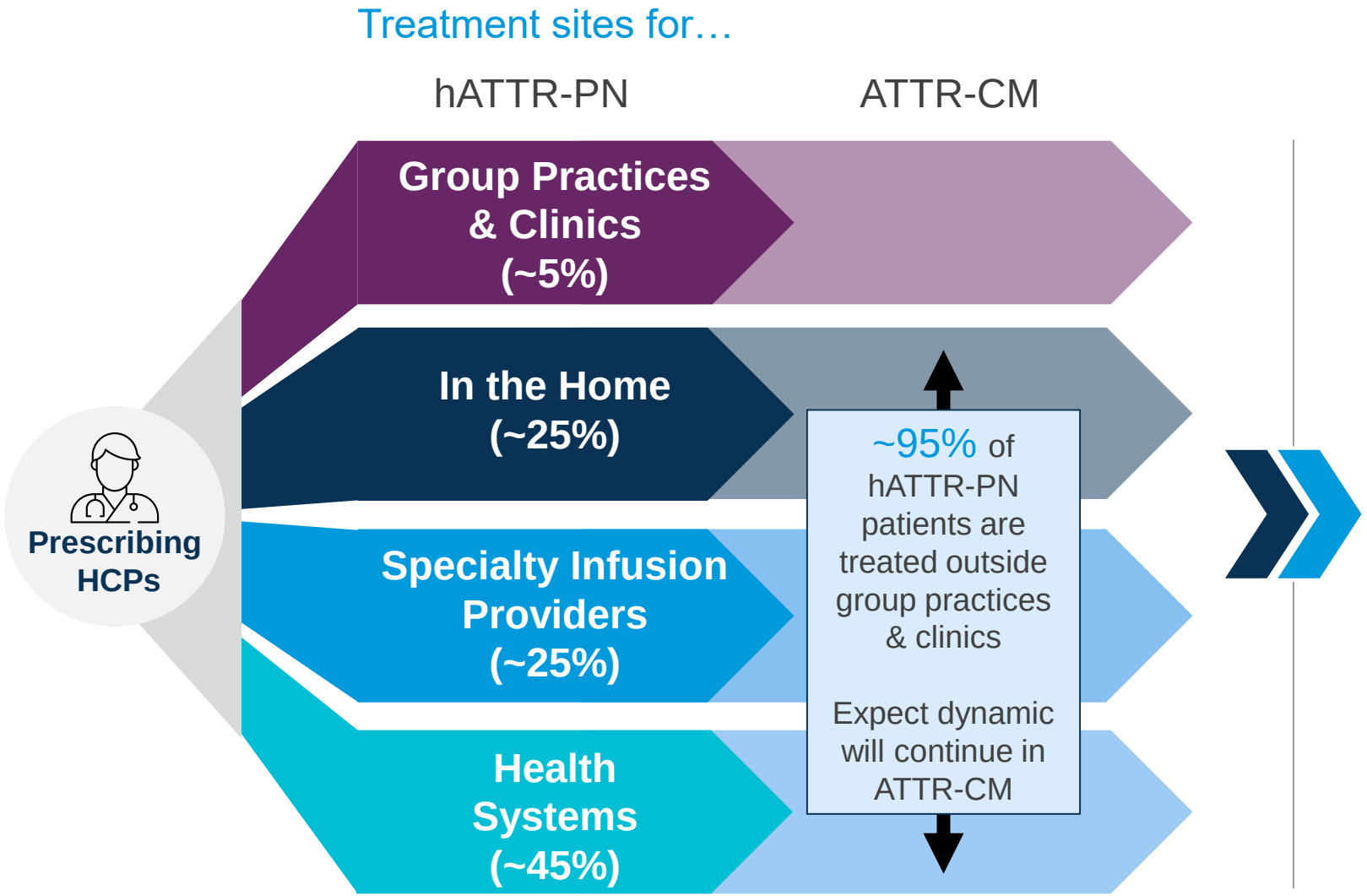
Existing Buy & Bill Network For AMVUTTRA in hATTR-PN Will Be Leveraged to Scale In ATTR-CM[1]



Most prescribers are affiliated with, or referring to, treatment sites that buy and bill AMVUTTRA

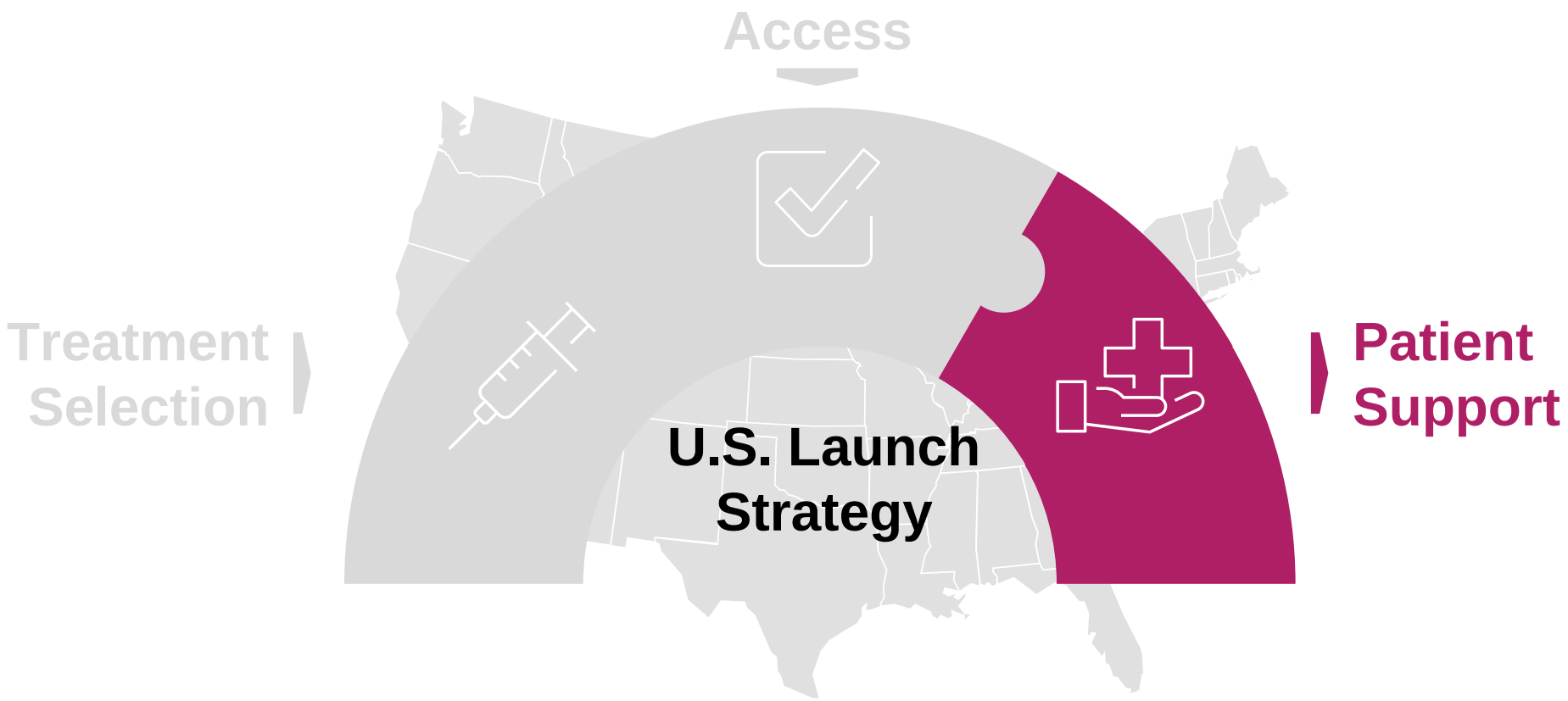
~900 Specialty Infusion Provider sites

~90% of Treated Patients live within 20 miles of a treatment site

Existing AMVUTTRA J-Code will continue to be used for reimbursement

1. Internal data

Our Robust Patient Support Is Essential to Ensure Patients Can Access Therapy and Stay on It



Entering ATTR-CM represents a step-up, NOT a giant leap

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Robust Patient Services Capabilities and Quarterly Dosing Will Support Strong Adherence in ATTR-CM

Benefit Verification

Financial Assistance

Disease & Product Education

Caregiver Guides

Provided by our dedicated Alnylam patient support team

Serving ~2,000 U.S. patients today

Alnylam ASSIST

~95% adherence today[1]

(supported by quarterly dosing)

Continuously optimizing our support for patients

Entering ATTR-CM represents a step-up, NOT a giant leap

1. Internal data

Alnylam

We Are On a Path to Leadership

Large, untapped and growing category with significant unmet need

AMVUTTRA is poised to become the standard of care for first line patients in ATTR-CM[1]

Our success and strong leadership in hATTR-PN position us to be highly competitive in ATTR-CM

We have a deep focus on ATTR and have scaled for a successful launch

1. Assuming regulatory approval

Q&A Chat With Our Commercial Leadership

Tolga Tanguler
Executive Vice President,
Chief Commercial Officer

MODERATOR

John P. Kennedy
TTR Franchise
Commercialization Lead

Mark Soued
Senior Vice President,
Head Of U.S. & TTR Lead

Jason Gidelson
Vice President,
U.S. Market Access

Alnylam®

Our Innovative Pipeline in TTR and Beyond

Yvonne Greenstreet, MBChB
Chief Executive Officer

Alnylam®

We Are Uniquely Positioned for Long-Term TTR Leadership

AMVUTTRA offers a market leading profile, well-positioned as a 1L treatment[1]

Strong commercial performance with proven successful track record in hATTR-PN

Positioned to win in ATTR-CM

TTR franchise is built for longevity

1. Assuming regulatory approval

ALN-TTRsc04 Reinforces Alnylam's Continuous Innovation in TTR

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

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

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

amvuttra® (vutrisiran) injection 25 mg/0.5 mL

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

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

ALN-TTRsc04

An Investigational RNAi Therapeutic for Potential Treatment of ATTR Amyloidosis

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

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

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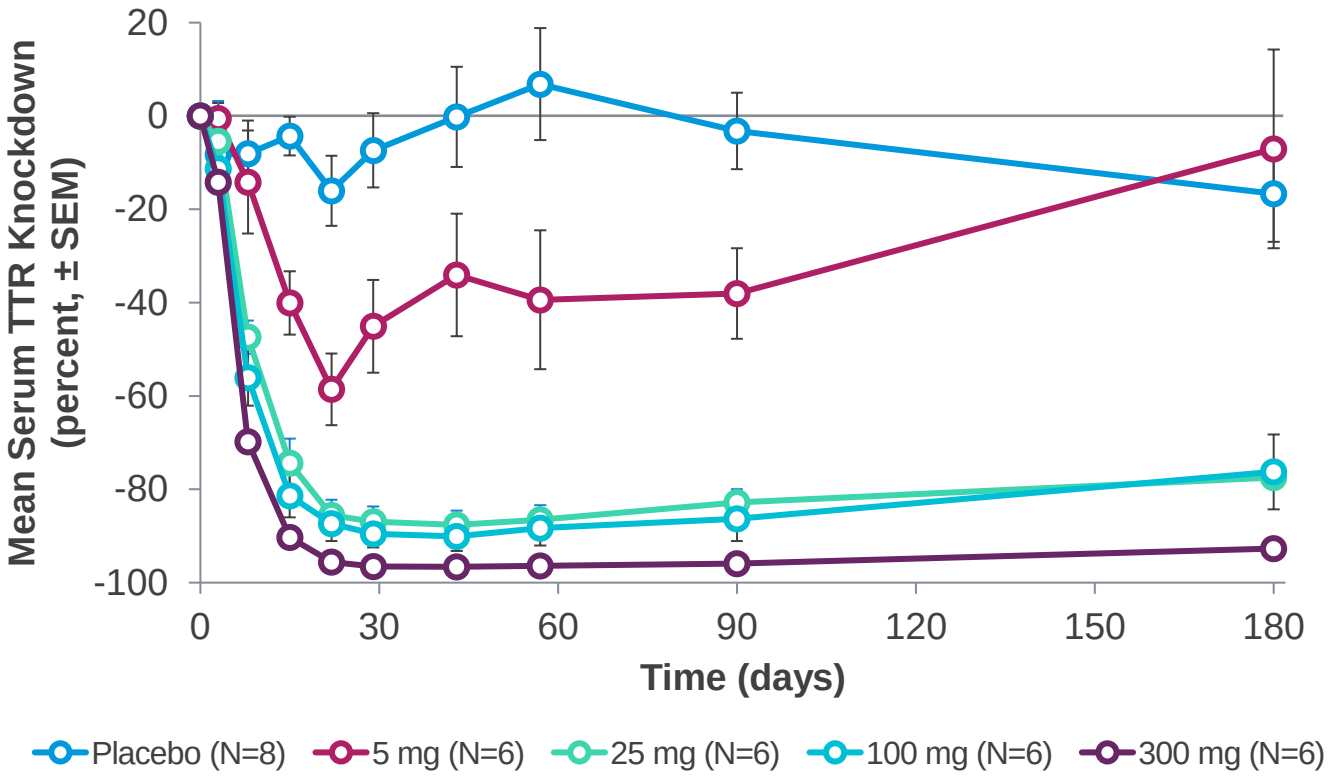
Expanding TTR Leadership with ALN-TTRsc04

Initial Phase 1 Results Support Best-in-Class Profile



- Single 300 mg dose resulted in **rapid, deep, and durable knockdown** of serum TTR:
  - **>90%** at Day 15
  - **97%** at Day 29
  - **93%** at Day 180
- All doses of ALN-TTRsc04 **well tolerated** to date; no adverse events considered related to study drug by investigator
- Data support **potential for annual or biannual subcutaneous dosing**

Q4 2024: Share additional findings from ongoing Phase 1 study

Q1 2025: Share Phase 3 Development Plan in ATTR-CM

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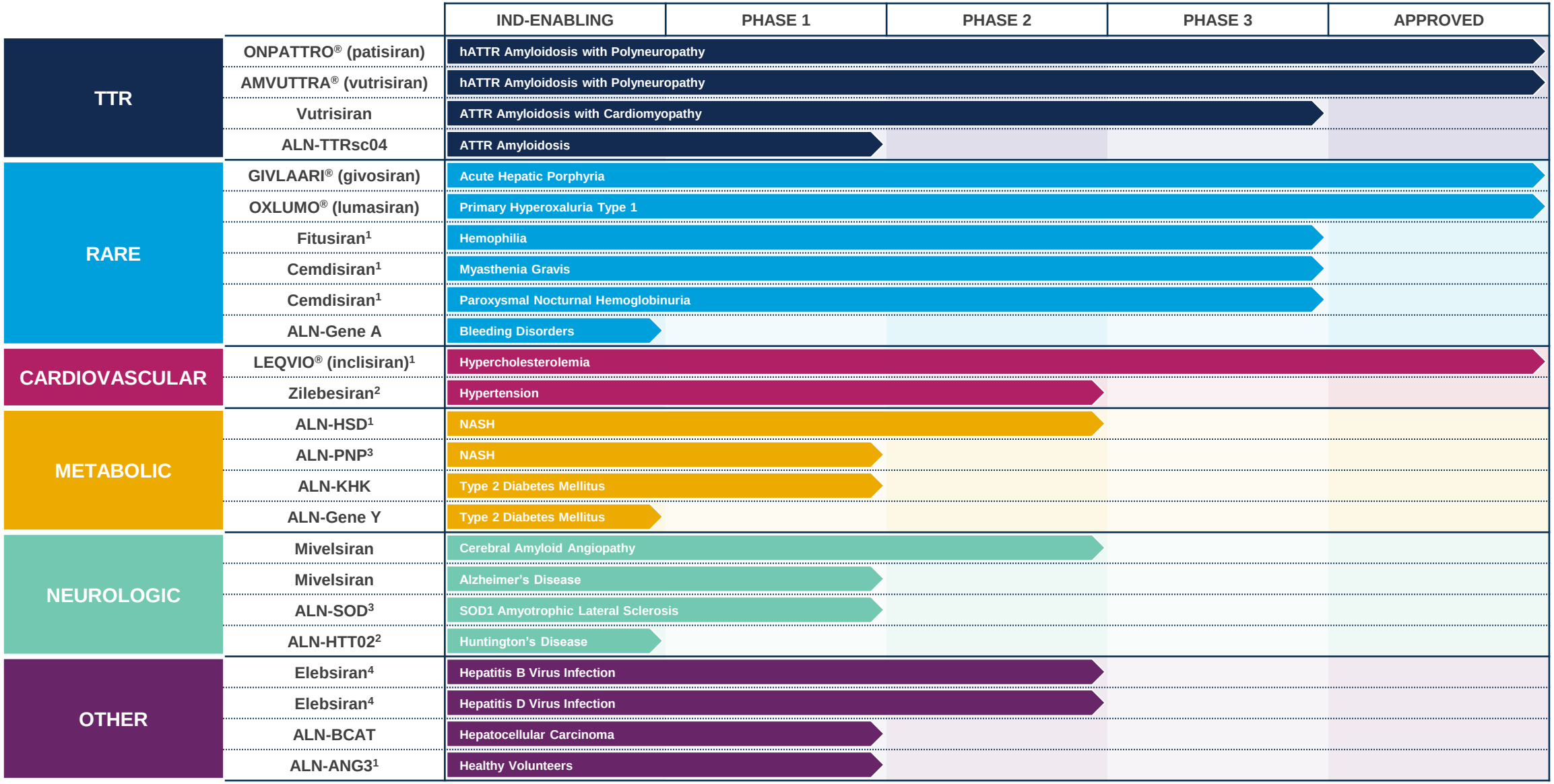
Advancing a Robust and High-Yielding Pipeline of RNAi Therapeutics

Positioned to Deliver Strong Growth and Innovation Across Multiple Disease Areas and Indications



[1] Out-licensed with milestones and/or royalties; [2] Partnered, Alnylam-led development with U.S. profit split and milestones/royalties; [3] Partner-led with profit split; [4] Partner-led with Alnylam option for profit split

Driving a Large Multi-Organ Pipeline to Clinic by End of 2025

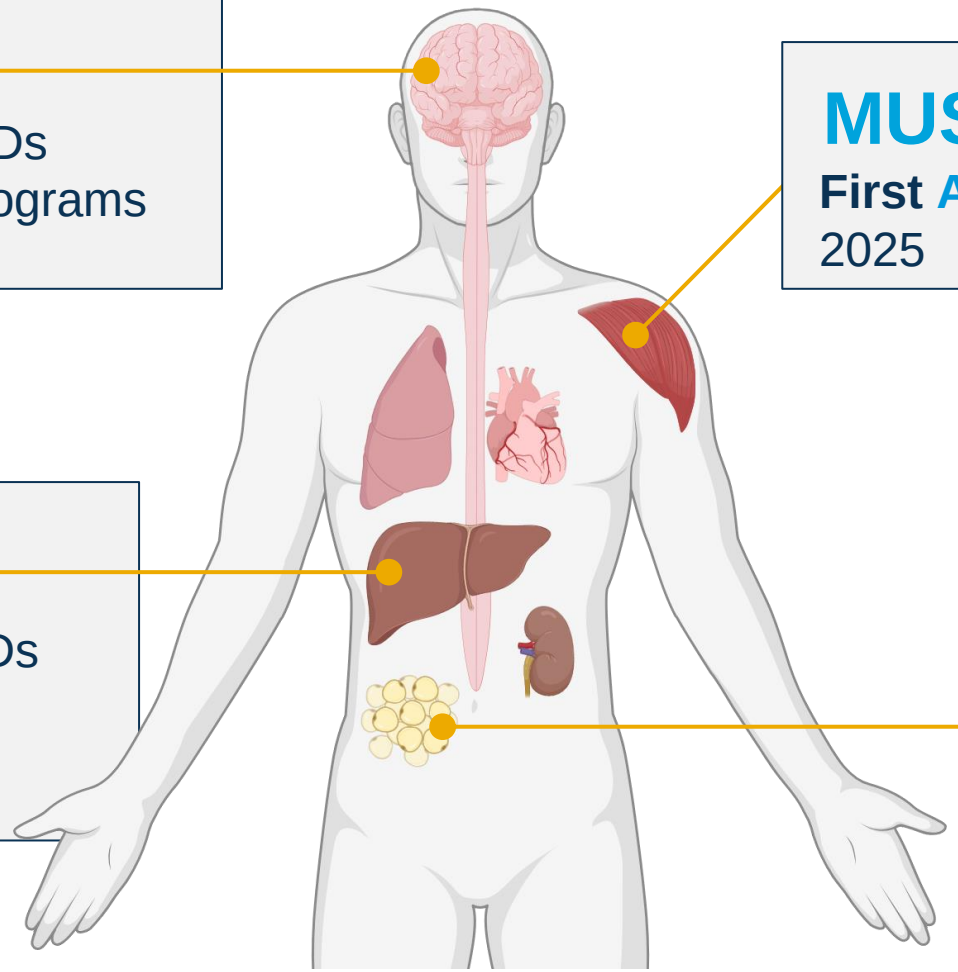
From Liver Delivery to CNS Human PoC; Now Advancing to Adipose, Muscle, and More

CNS

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

LIVER

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



MUSCLE

First ALNY IND by end of 2025

ADIPOSE

First ALNY IND by end of 2025

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We Have the Key Components for Success

Established Leadership in hATTR-PN

- **>80% share** in markets with an approved competitor
- **$307M** global TTR net product revenue in 2Q24

Durable Flagship Franchise

- Growing ATTR-CM market
- Focused TTR team built for execution and agility
- Next-gen candidate with potential best-in-class profile

Best-in-Class Team

- Demonstrated success delivering global blockbuster products to patients
- Deep experience and dedicated focus
- Pioneers in RNAi

Track Record of Commercial Excellence

- Delivered **$410M** in global net product revenue in 2Q24
- Global footprint, with presence in **>60 countries**

Robust Clinical Pipeline

- Up to **30 clinical programs** anticipated by end of 2025
- **5 approved** medicines

Sustainable Innovation Engine

- Novel extrahepatic delivery systems
- Fueling pipeline of novel RNAi therapeutics

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