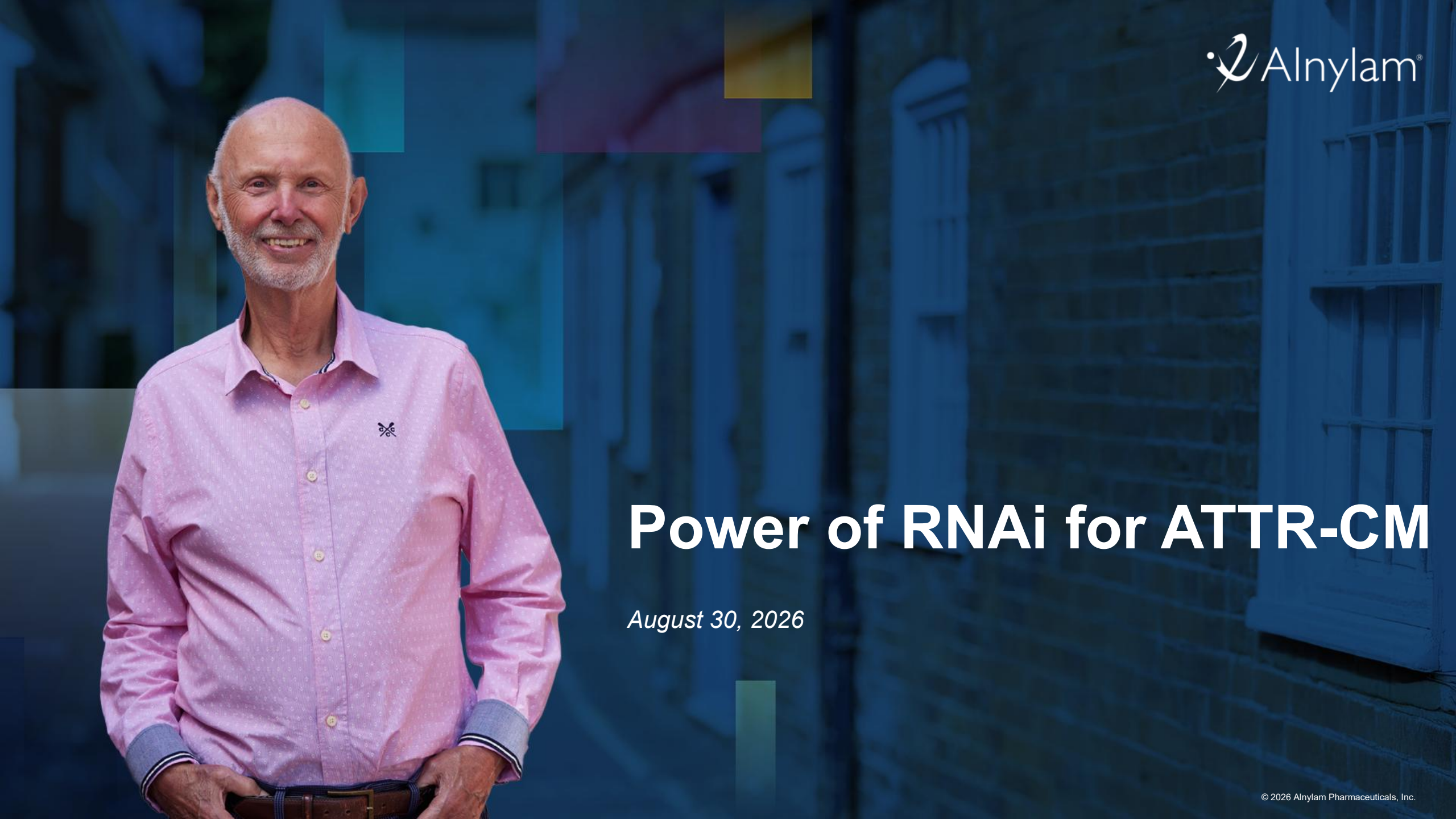


Power of RNAi for ATTR-CM

August 30, 2026

Agenda

01	Leadership in TTR	**Yvonne Greenstreet, M.D.** *Chief Executive Officer*
02	TRITON-CM: Designed for Success	**Pushkal Garg, M.D.** *Chief R&D Officer*
03	Q&A Session	

Alnylam Forward-Looking Statements

This presentation contains forward-looking statements. Forward looking statements include statements regarding Alnylam's expectations, beliefs, goals, plans or prospects including, without limitation, statements regarding: Alnylam's ability to achieve durable TTR leadership; the potential for AMVUTTRA to be a first-line treatment of choice, and a foundational treatment, in ATTR-CM; the potential for future growth in the ATTR-CM category, including potential growth in the number of diagnosed and treated ATTR-CM patents; Alnylam's ability to maintain broad access to AMVUTTRA in the future; the potential for AMVUTTRA to achieve future growth, including through growth in the breadth of prescribers who prescribe AMVUTTRA; Alnylam's ability to achieve the goals in its Alnylam 2030 strategy, including to achieve global TTR leadership, grow through sustainable innovation, and scale with discipline and agility; the potential for any of Alnylam's clinical trials to readout successfully and to unlock the next wave of transformative, RNAi-powered medicines; the potential for the TRITON-CM clinical trial of nucresiran in ATTR-CM to achieve positive results, including the potential for nucresiran to show a benefit on top of background stabilizer use; and the potential for Alnylam's TTR efficacy model to accurately predict the outcome of the TRITON-CM clinical trial or any other clinical trial.

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 2030 strategy; Alnylam's ability to successfully launch, market and sell Alnylam's approved products globally, including AMVUTTRA; Alnylam's ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of its product candidates; the pre-clinical and clinical results for Alnylam's product candidates; actions or advice of regulatory agencies and Alnylam's ability to obtain and maintain regulatory approval for its product candidates, as well as favorable pricing and reimbursement; delays, interruptions or failures in the manufacture and supply of Alnylam's marketed products or its product candidates; obtaining, maintaining and protecting intellectual property; Alnylam's ability to manage its growth and operating expenses through disciplined investment in operations; Alnylam's ability to maintain strategic business collaborations; Alnylam's dependence on third parties for the development and commercialization of certain products; the outcome of litigation and government investigations; the risk of future litigation and government investigations; and unexpected expenditures; as well as those risks and uncertainties more fully discussed in the "Risk Factors" filed with Alnylam's most recent periodic report (Quarterly Report on Form10-Q or Annual Report on Form 10-K) filed with the SEC and in its other SEC filings. Alnylam explicitly disclaims any obligation, except to the extent required by law, to update any forward-looking statements.

Leadership in TTR

Yvonne Greenstreet, M.D.

Chief Executive Officer

Strongly Positioned for Durable TTR Leadership

AMVUTTRA

HELIOS-B Data Support AMVUTTRA as the First-Line Treatment of Choice in ATTR-CM

Consistency in effect across endpoints and subgroups reinforces our conviction in AMVUTTRA as a foundational treatment in ATTR-CM.

NUCRESIRAN

Learnings from CARDIO-TTRansform Strengthen Our Conviction in TRITON-CM

TRITON-CM combines the depth of TTR knockdown, patient population and study design required to maximize the probability of success.

AMVUTTRA's Differentiated Clinical Profile Supports its Role as a Foundational, First-Line Therapy in ATTR-CM

	amvuttra (vutrisiran) injection 25 mg/0.5 mL	tafamidis	acoramidis	eplontersen
Approved for the treatment of ATTR-CM in adults in the U.S.	✓	✓	✓	
Approved for the treatment of hATTR-PN in adults in the U.S.	✓			✓
Consistency in treatment effect with or without background stabilizer	✓			
Dosing frequency	**Quarterly (HCP–administered prefilled syringe)**	Daily (1 capsule)	Daily (2 capsules, twice a day)	Monthly (self-administered autoinjector)

Compelling profile driving >50% share of new starts amongst AMVUTTRA-experienced HCPs

Strong U.S. Fundamentals to Drive Future Growth of AMVUTTRA

Robust Category Growth

~80%
ATTR-CM patients remain untreated

~15K+
New to treatment ATTR-CM patients annually

~75K
Anticipated treated ATTR-CM patients by 2030

Emerging HCP Preference with Experience

>1,700
New AMVUTTRA prescribers since ATTR-CM launch

>50%
New patient starts among AMVUTTRA-experienced prescribers

~1/3
Active ATTR-CM treaters prescribing AMVUTTRA

Continued Broad Access

~99%
Overall coverage

>90%
first-line access with no step

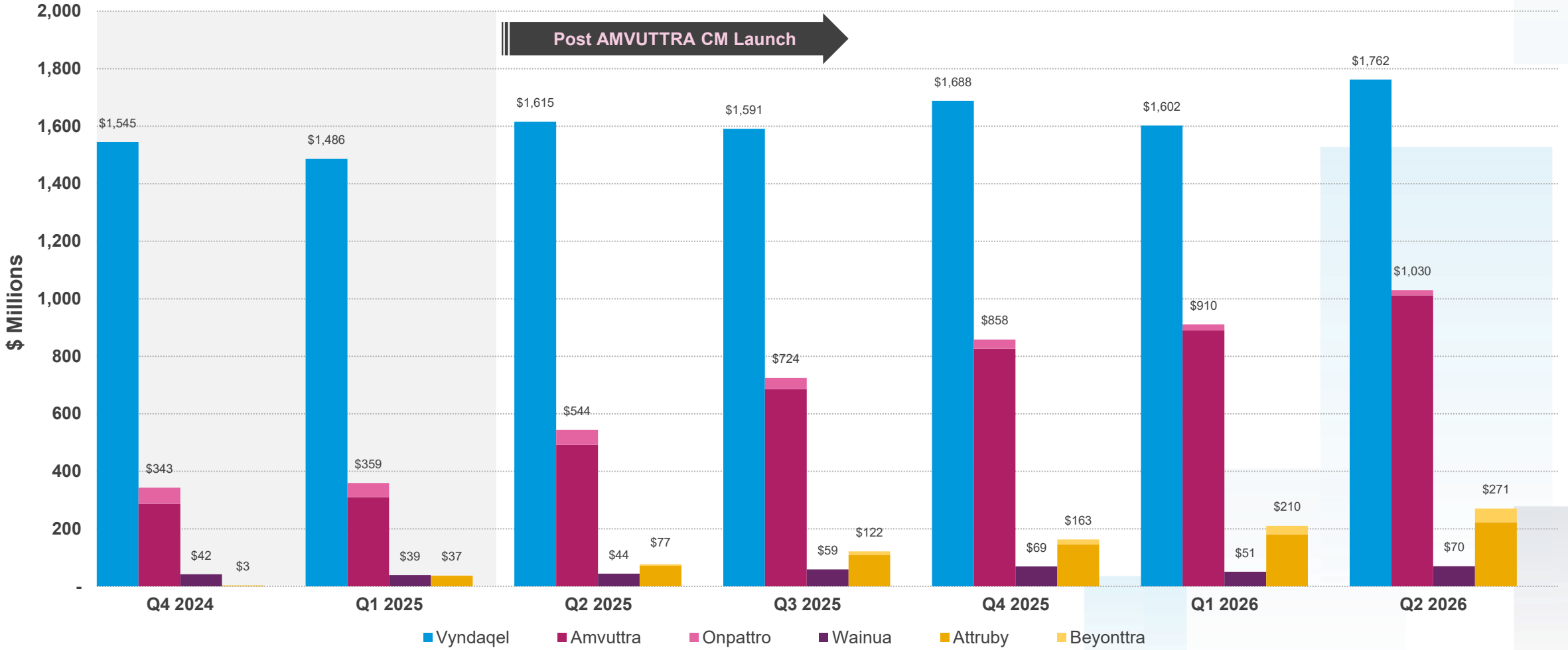
$0
Out-of-pocket cost for most patients

Driving breadth of prescribers is key to unlocking AMVUTTRA's next wave of growth

Progressing Toward TTR Leadership

On the Path to Realizing *Alnylam 2030* Ambitions

Quarterly Sales by Product



Source: Evaluate. ATTRUBY+BEYONTTRA Revenues = ATTRUBY US reported revenues + BBIO royalty revenue/32%. PFE Q2 2026 earnings PR for VYNDA Q2'26 data. ATTRUBY Q2'26 revenues are estimated using visible alpha consensus as of 8.6.26 for ACO and BBIO consensus royalty revenue/32%.for Beyonttra

2H26 Readouts Unlocking the Next Wave of Transformative, RNAi-Powered Medicines

ALN-HTT02

Huntington's Disease

Phase 1 Data

EHDN
October 23
Krakow, Poland

ALN-6400

Bleeding Disorders

Ph 1 Data in Healthy Volunteers

Ph 2 HHT Results

ALN-2232

Obesity & Weight Management

Phase 1 Data

Alnylam 2030

Accelerating Innovation. Scaling Impact.

Achieve Global TTR Leadership

BUILD A DURABLE TTR FRANCHISE

- Lead TTR market in revenue by 2030 and cumulatively across 5-year period
- Launch best-in-class, next-gen silencer, nucresiran, in PN by 2028 and CM by 2030

Grow Through Sustainable Innovation

DELIVER THERAPIES THAT PREVENT, HALT, OR REVERSE DISEASE

- Deliver 2+ new transformative medicines beyond TTR with blockbuster potential
- Expand to 10 tissue types and > 40 clinical programs
- Invest ~30% of revenues in non-GAAP R&D, including select external innovation

Scale with Discipline & Agility

DRIVE SUSTAINED, PROFITABLE GROWTH

- Achieve 25%+ total revenue CAGR through YE 2030
- Deliver ~30% non-GAAP operating margin

TRITON-CM: Designed for Success

Pushkal Garg, M.D.

Chief Research & Development Officer

Overview

- Data from a variety of amyloidotic diseases – AL, AA and hATTR-PN – all demonstrate that **deep lowering** of the pathogenic protein is **essential to improving patient outcomes**

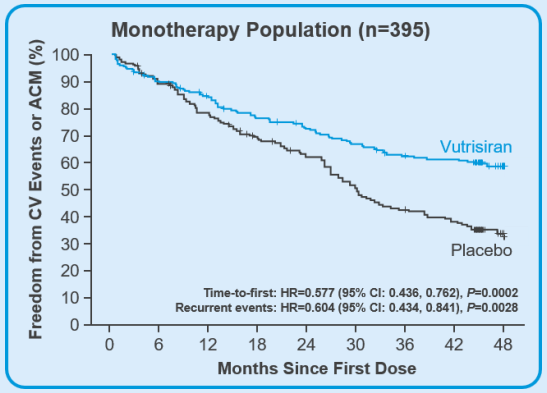
- Similarly, outcomes in these diseases further improve if therapies to reduce protein production are **initiated early in disease** before irreversible organ damage occurs

- Analyses of HELIOS-B, **now corroborated by learnings** from CARDIO-TTRansform, highlight that these principles are likewise critical to delivering an effective therapy for ATTR-CM

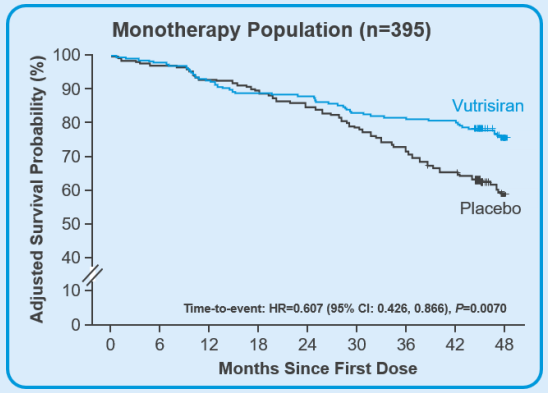
- TRITON-CM was designed with these insights in mind to **maximize clinical benefit and the probability of success**
  - Treatment with nucresiran, which provides the deepest knockdown ever evaluated
  - Focus on patients early in disease course
  - Event-driven design with an endpoint that captures overall disease burden

AMVUTTRA: Powerful Efficacy from HELIOS-B Supports First-Line Use

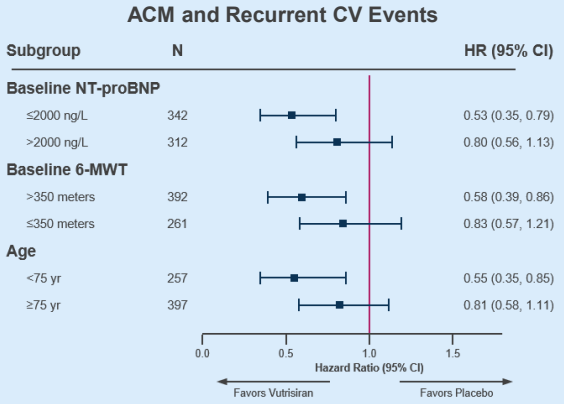
Time-to-First CV Event or ACM[1]



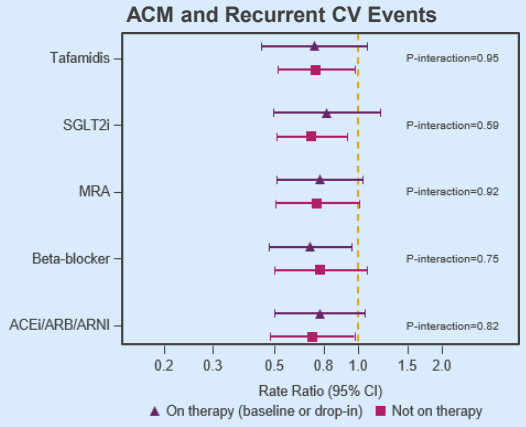
Time to ACM[1]



Early Patients Realize Greatest Benefit[2]



Consistent Effect Across Background Meds[2]



- **Large reductions in all-cause mortality and cardiovascular events**
- **Benefits greatest when initiated early in disease**
- **Consistent effect on top of background medications, including stabilizers**
- **Quarterly dosing that supports adherence**

[1] Garcia-Pavia, et al. ESC 2025; [2] NEJM 2024 (BNP and Age)/Data on file (6-MWT); [3] Abovich, et al. ESC Heart Failure 2026.
All-cause mortality (ACM) includes heart transplantation and left ventricular assist device placement, and CV events include CV-related hospitalizations and urgent heart failure visits.

TRITON-CM: Optimized for Success & Broad Patient Impact

TRITON-CM
ATTR-CM CLINICAL STUDY

Targeting Launch by 2030

- Randomized, double-blind, event-driven outcomes study of nucresiran versus placebo
- N ~1,750
- Includes patients on monotherapy and background stabilizer
- Primary endpoint of all-cause mortality and recurrent CV events

Largest Study in ATTR-CM

Enriched Patient Population for Greatest Benefit

Rapid and Deep TTR knockdown

Event Driven Endpoint of All-Cause Mortality & Recurrent CV Events

Nucresiran is an investigational therapeutic in development for the treatment of ATTR amyloidosis. The safety and efficacy of nucresiran have not been established or approved by the FDA, EMA or any other health authority.

Key Cardio-TTRansform Questions Going Into ESC

Patient characteristics
disease severity across subgroups; background meds

TTR knockdown
depth and time to achieve; variability

Safety & tolerability
adherence to study drug; competing risks

Study execution
completeness of follow-up

Outcomes
impact on endpoint components (CVM, CV events) as well as ACM; accrual of events over time; treatment effect over time; across subgroups (e.g., disease severity)

What Have We Learned at ESC?

Potential Explanations for CARDIO-TTRansform Failure

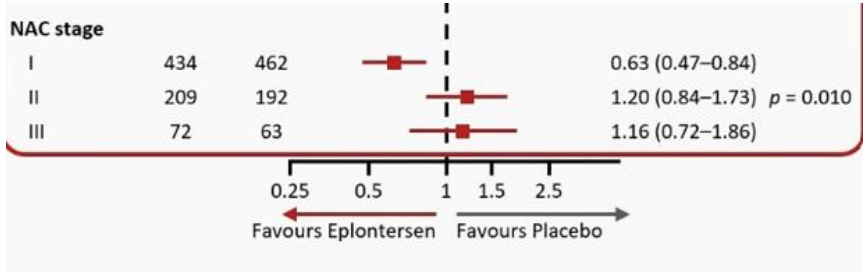
LESS TTR KNOCKDOWN

	Eplontersen[1]	Vutrisiran[2]	Δ
Mean	69.7%	81.0%	~11%
Median	76.2%	86.8%	~11%

MORE ADVANCED POPULATION

Baseline characteristic	CARDIO-TTRansform	HELIOS-B
NYHA class III	17%	9%
NAC stage 3	9%	5%
NT-proBNP, median pg/mL	2,025	1,920
BNP >8500 pg/mL	4.5%	0.5%
eGFR <45	16%	11%

CARDIO-TTRansform primary composite endpoint by NAC stage



ENDPOINT SELECTION

Cardiovascular mortality

↔

No clear mortality signal

Up to 140 wks: HR 0.88 (95% CI 0.65–1.18), P=0.39
Up to 160 wks: HR 0.86 (95% CI 0.65–1.14), P=0.29

All-cause mortality

↓

Apparent survival benefit

Up to 140 wks: HR 0.77 (95% CI 0.60–0.99), P=0.043
Up to 160 wks: HR 0.78 (95% CI 0.61–0.99), P=0.039

[1] CARDIO-TTRansform; [2] HELIOS-B (steady state values)

Note: For illustrative purposes only. Data are derived from different clinical trials conducted at different times, with differences in trial design and patient populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted

Continued High Confidence in TRITON-CM Based on Data & Experience

Our Molecule

- ✓ *RNAi*
- ✓ *>95% TTR knockdown[2]*
- ✓ *2 prior studies showing effect on top of stabilizers[1]*

Our Study

- ✓ *~1,750 patients*
- ✓ *Event driven*
- ✓ *Enriched for patients most likely to benefit*

Our Track Record

- ✓ *>15 years in TTR drug development*
- ✓ *Deep patient-level insights from prior studies*
- ✓ *Meticulous study execution driving successful results (e.g., HELIOS-B)*

[1] HELIOS-B and APOLLO-B [2] Phase 1 data (300 mg Q6M).

Recent Datasets Suggest Advantages of RNAi Silencing

Target & Molecule	Mechanism	Dosing Regimen	Target KD	Key Trial Result	
AGT				**SBP**	ASO development shifted to a follow-on asset, currently in development for a narrower, more severe population
Zilebesiran[1] (monotherapy)	RNAi	300 mg Q6M	-93% @M6	-14.5 mmHg @M6	
IONIS-AGT-L_{RX}[2] (monotherapy)	ASO	80 mg QW x 6	-54% @D43	-8 mmHg @D43	
APOC3				**TG**	ASO has Warnings & Precautions for hypersensitivity and liver enzyme elevations
Plozasiran[3]	RNAi	25 mg Q3M	-91% @M10	-80% @M10	
Olezarsen[4]	ASO	80 mg QM	-72% @M6	-30% @M6	
PCSK9				**LDL-C**	ASO development discontinued due to failure to meet prespecified efficacy criteria
Inclisiran[5]	RNAi	284 mg Q6M	-69% @M6	-53% @M6	
ION449 (AZD8233)[6]	ASO	60 mg QM	-78% @W28	-57% @ W28	

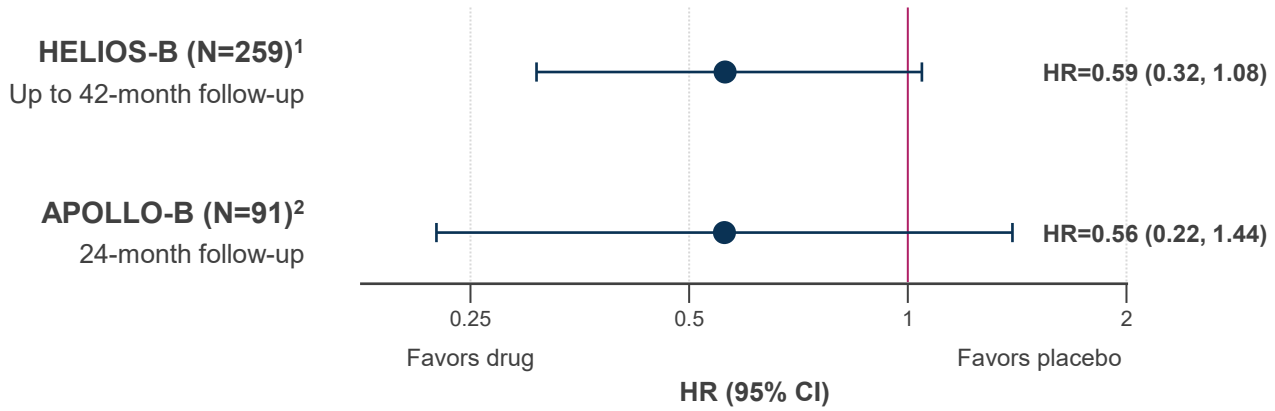
Note: For illustrative purposes only. Data are derived from different clinical trials conducted at different times, with differences in trial design and patient populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted

[1] KARDIA-1, AHA 2023; [2] Morgan, et al. JACC 2021; [3] REDEMPLO U.S. Prescribing Information; [4] TRYNGOLZA U.S. Prescribing Information; [5] LEQVIO U.S. Prescribing Information; [6] Koren, et al. JACC 2022

RNAi Benefit on Top of Stabilizers Supported by Strong Clinical Data

ATTR Cardiomyopathy

All-Cause Mortality in Patients on Background Stabilizer



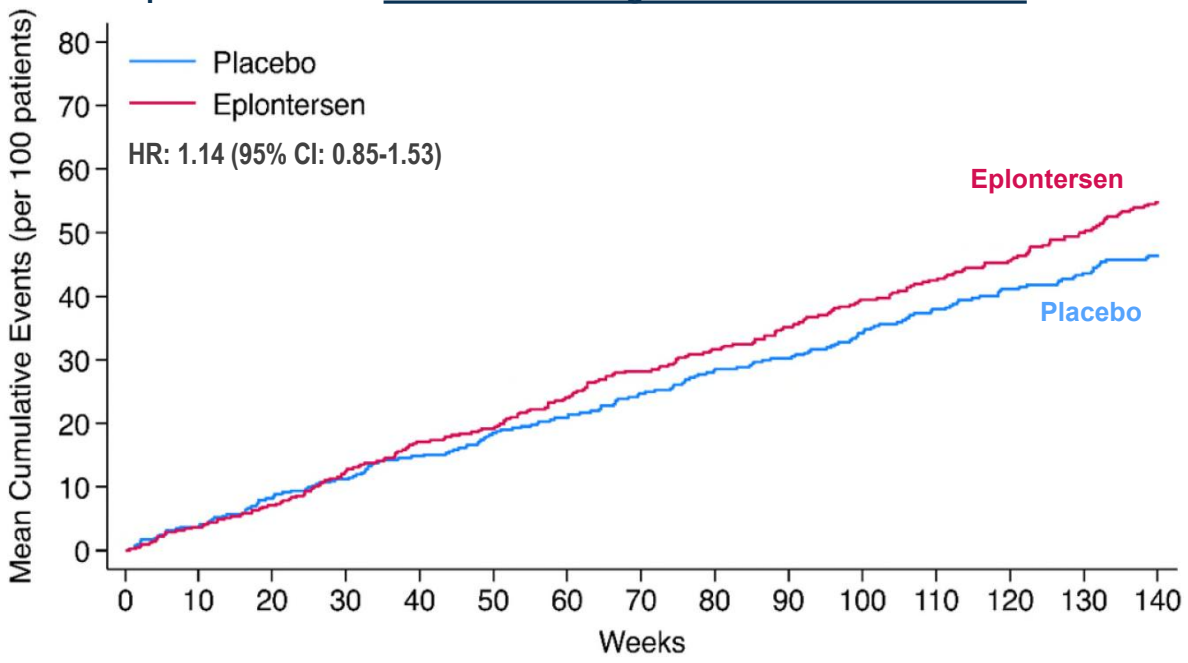
Two independent studies with different RNAi therapeutics demonstrated reduction of ACM on top of background stabilizers

[1] *Pre-specified subgroup analysis of secondary endpoint; includes OLE.* [2] *Pre-specified analysis of component of composite endpoint (exploratory endpoint); includes OLE.*

HELIOS-B Demonstrated Additive Benefit of Vutrisiran on Top of Stabilizer Therapy Using CARDIO-TTRansform Primary Endpoint

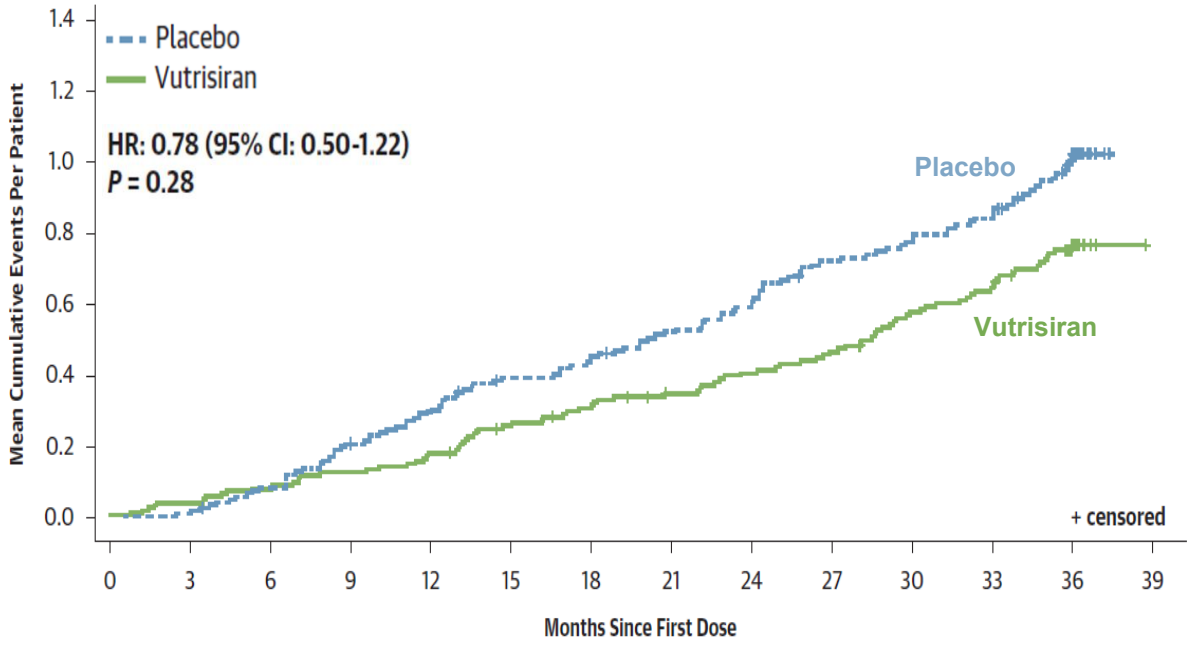
CARDIO-TTRansform[1]

Composite of Cardiovascular Death and Recurrent Cardiovascular Events up to Week 140 in Patients Receiving TTR Stabilizers at Baseline



HELIOS-B[2]

Mean Cumulative Cardiovascular Mortality and Cardiovascular Events by Treatment During the Double-Blind Period in the Baseline Tafamidis Subgroup

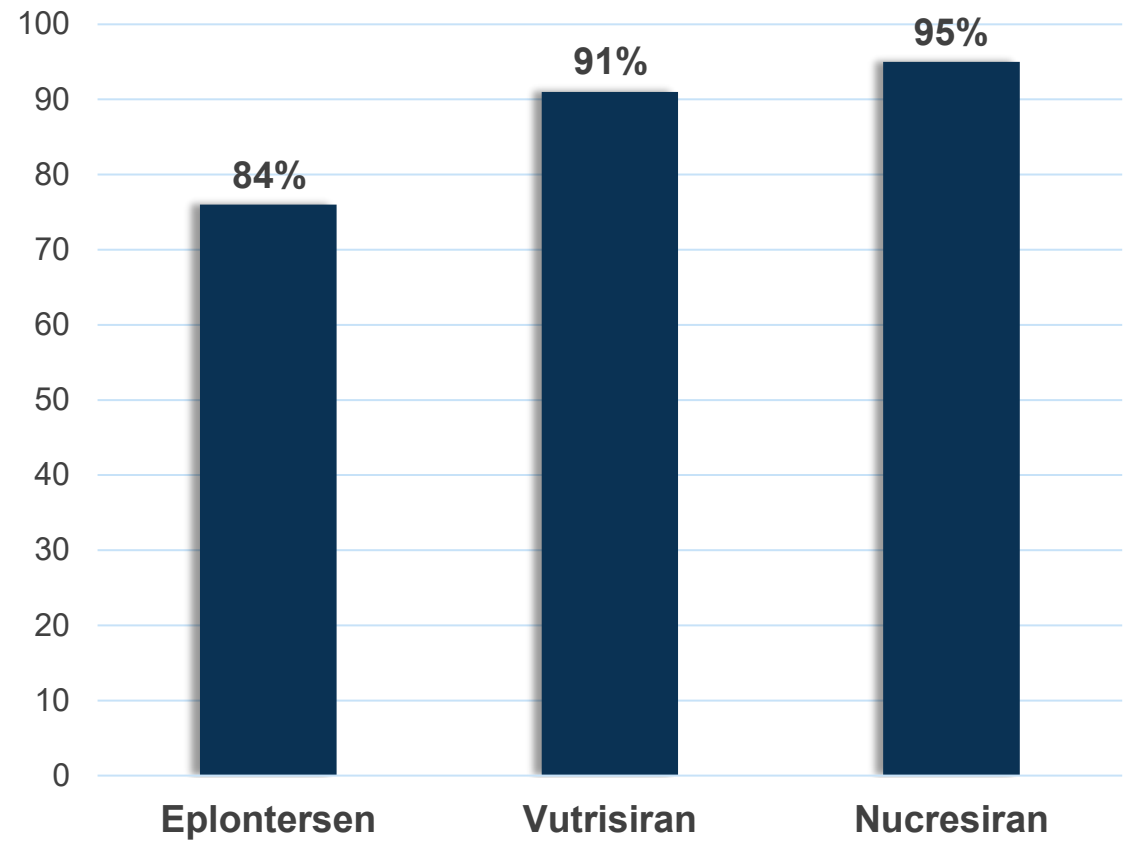


[1] Fontana et al., NEJM, 2026; [2] Witteles et al., JACC, 2025

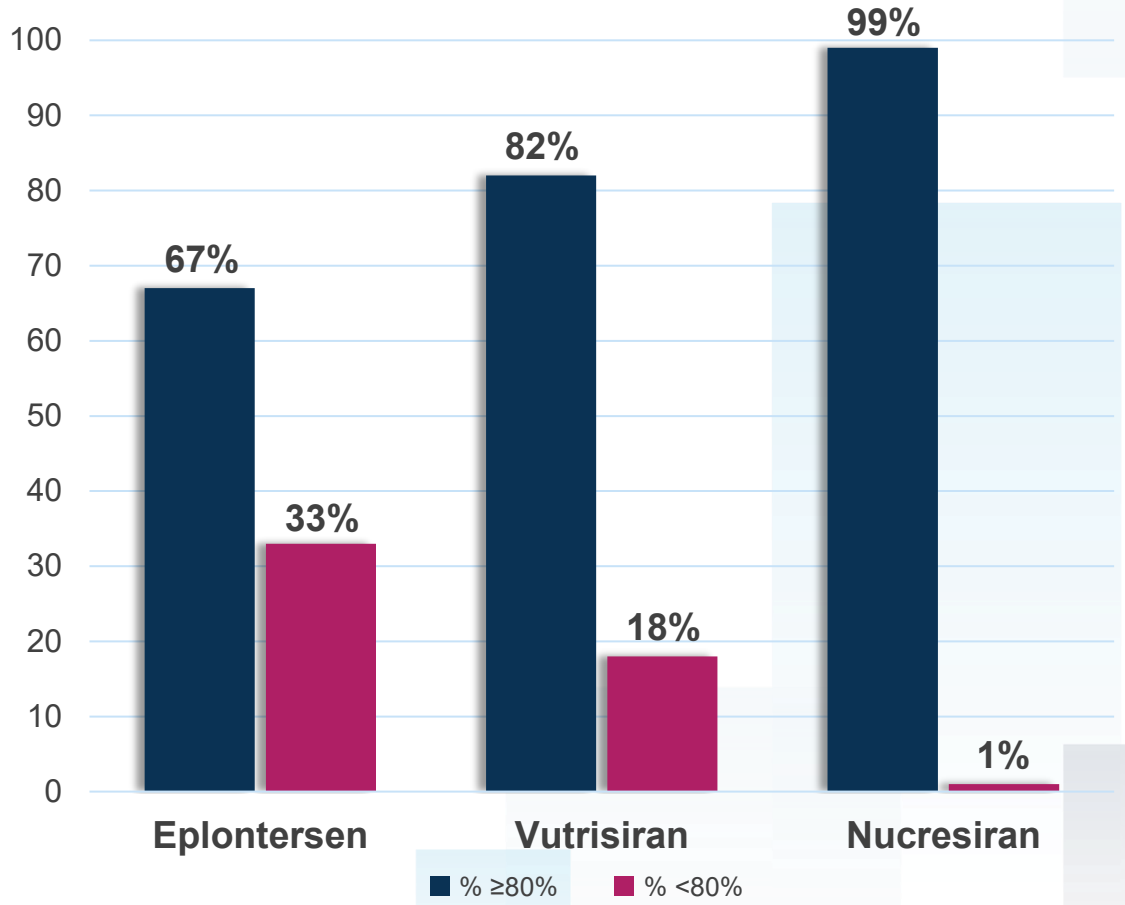
RNAi Drives Deep, Consistent Knockdown of TTR

Vutrisiran and Eplontersen Values Derived from hATTR-PN Studies

Median TTR KD (%)

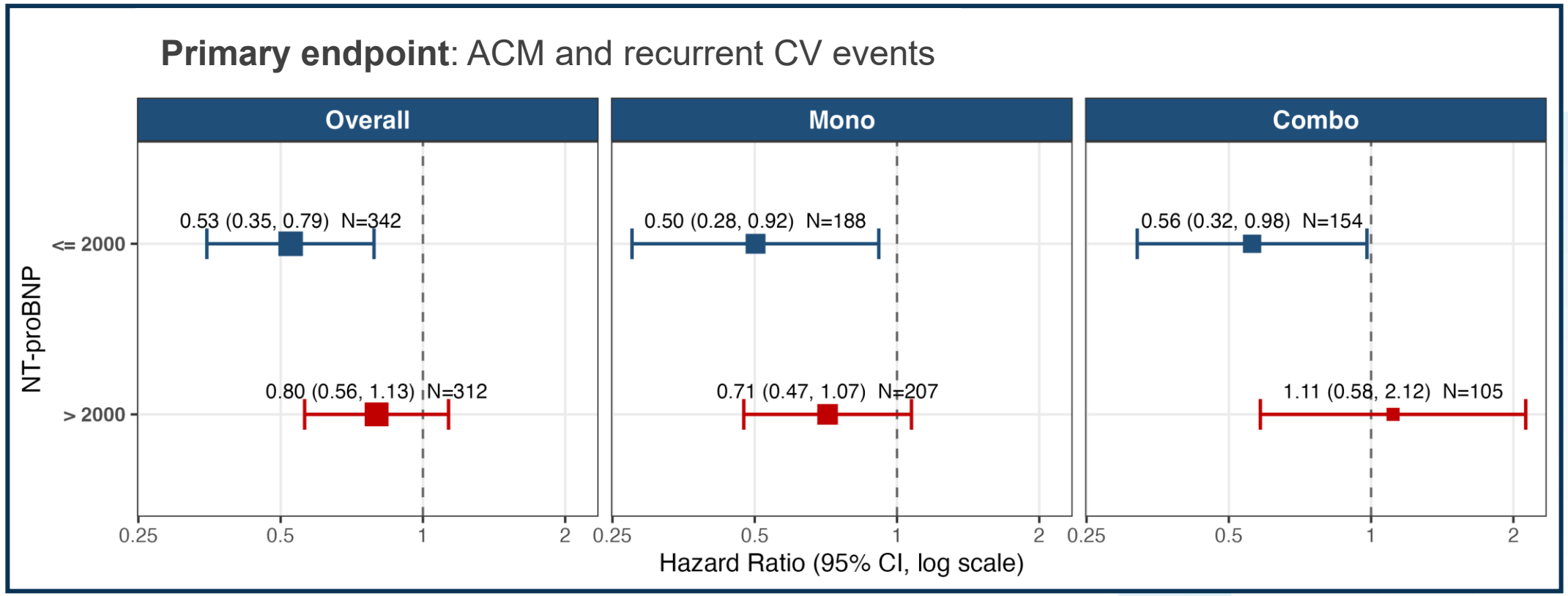


Estimated Percent Above or Below Threshold[1]

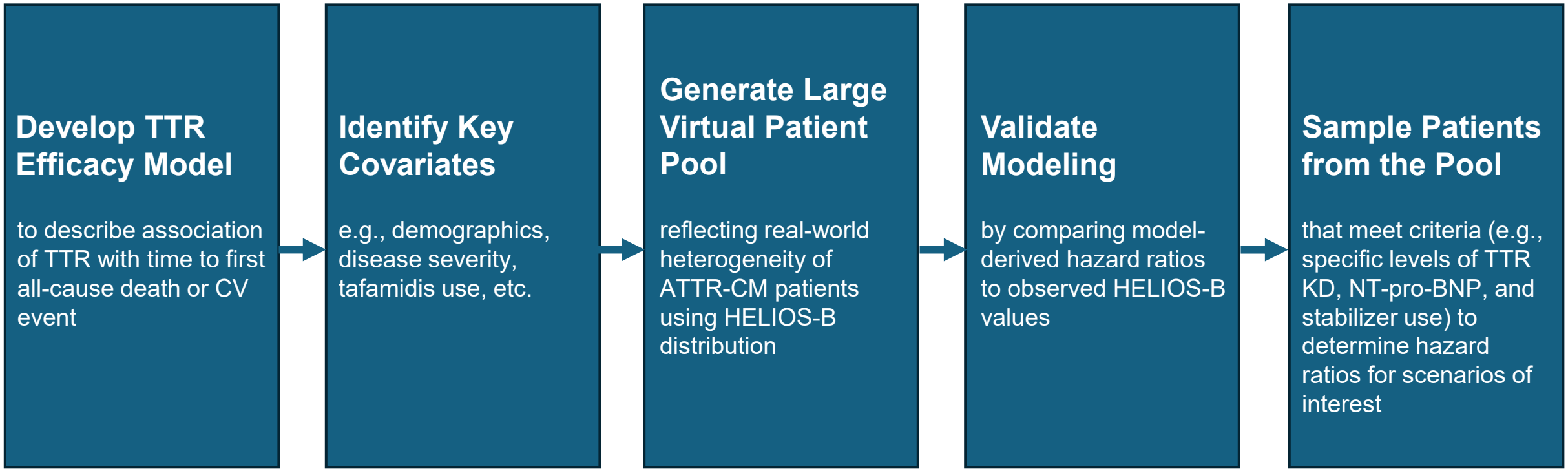


Eplontersen data: NEURO-TTRansform; Vutrisiran data: HELIOS-A; Nucresiran data: model predicted using Phase 1 data (300 mg Q6M).
Steady state KD numbers are based on week 35 data for eplontersen and M18 data for vutrisiran and nucresiran; The proportion of patients are model-based approximate estimates and calculated using observed (eplontersen and vutrisiran) or predicted (nucresiran) median & IQR and lognormal distribution assumption. [1] Polydefkis, et al. ISA 2018

HELIOS-B Demonstrated Silencing Early Drives Greatest Benefit, Irrespective of Background Stabilizer Use



Modeling Relationship Between TTR and Outcomes in ATTR-CM Using HELIOS-B Data

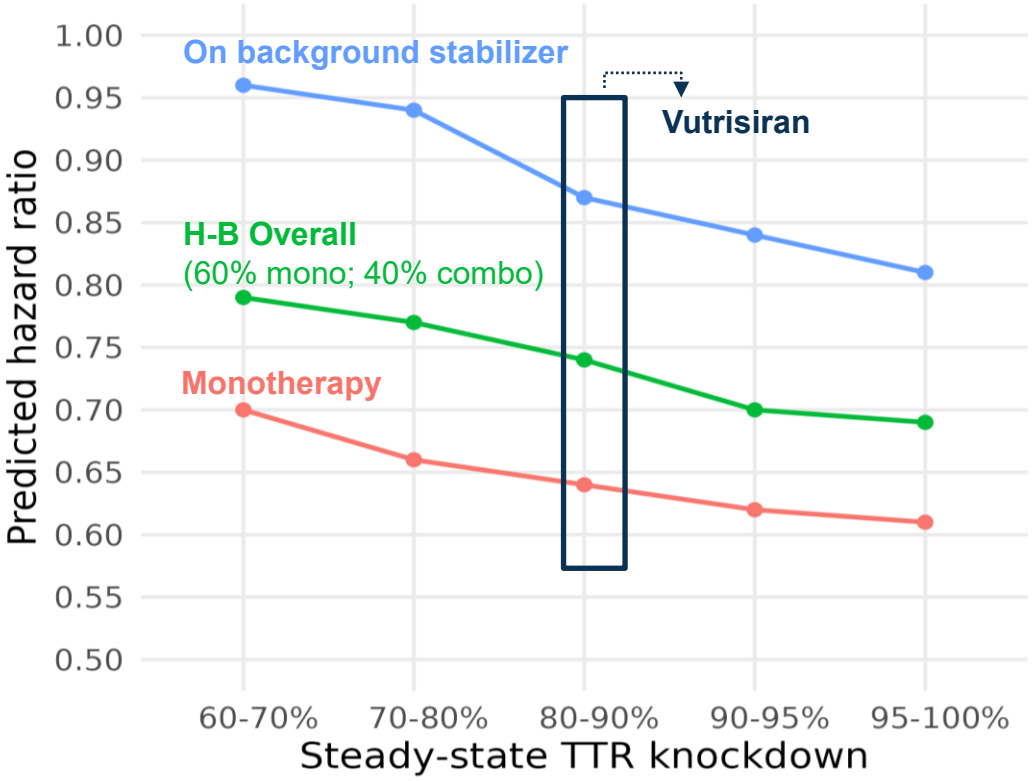


Key limitation: *Model built on individual patient-level data from HELIOS-B and assumes covariate relationships observed in that study can be appropriately extrapolated to other ATTR-CM patient populations and settings*

Model Illustrates Deeper TTR Knockdown Associated with Better Outcomes in ATTR-CM

Modeling Time to ACM or First CV Event

Model-Predicted Relationship Between TTR KD and Hazard Ratio in HELIOS-B Population



Steady State TTR KD (Median)

Vutrisiran HELIOS-B	Eplontersen CARDIO-TTRansform	Nucresiran[1]
87%	76%	95%

- Deep TTR KD drove HELIOS-B success
- Lower TTR KD and more advanced patient population may offer explanations for CARDIO-TTRansform failure
- Even deeper TTR KD and earlier patient population suggest nucresiran is positioned for success in TRITON-CM

[1] *Model predicted using Phase 1 data*

Nucresiran Designed for Success in TRITON-CM

Deep TTR knockdown, early treatment and endpoint selection are critical to demonstrating outcomes benefits of TTR silencing in ATTR-CM, and point to potential reasons for CARDIO-TTRansform failure

TRITON-CM optimized to demonstrate outcomes benefit

- Built upon learnings from two successful RNAi therapeutics that have already shown efficacy in monotherapy setting and on top of stabilizers
- Highest-ever knockdown; associated with greatest potential for efficacy
- Study enriched for less advanced patients who accrue greatest benefit
- Event-driven design with an endpoint that captures overall disease burden

Will continue to review CARDIO-TTRansform data and assess any implications for TRITON-CM

Q&A Session


Silence disease
Amplify life™
Alnylam®