# FDA Approval of AMVUTTRA® (vutrisiran) for ATTR Amyloidosis with Cardiomyopathy

***First RNAi Therapeutic Approved to Reduce Cardiovascular Death, Cardiovascular Hospitalizations and Urgent Heart Failure Visits in Adults with ATTR-CM***

March 20, 2025

See full Prescribing Information for additional information about AMVUTTRA

# Agenda

## Welcome

- **Christine Lindenboom**
  Chief Corporate Communications Officer

## An Inflection Point in the Treatment of ATTR-CM

- **Yvonne Greenstreet, MBChB, MBA**
  Chief Executive Officer

## AMVUTTRA® (vutrisiran) Label and Data

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

## Delivering AMVUTTRA to Patients

- **Tolga Tanguler**
  Chief Commercial Officer

## Q&A Session

# 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, statements regarding the potential for AMVUTTRA's FDA approval in ATTR-CM to represent an inflection point for ATTR-CM patients; Alnylam's expectations regarding the safety and efficacy of AMVUTTRA for the treatment of ATTR-CM, including the potential of AMVUTTRA to help patients live longer and better lives and the potential for AMVUTTRA to become a new standard of care and/or first-line treatment in ATTR-CM; the potential for Alnylam to achieve durable growth in its ATTR franchise and to demonstrate unmatched leadership and longevity in ATTR; Alnylam's planned achievement of its *"Alnylam P$^5$x25"* goals; the potential for vutrisiran to obtain regulatory approval for the treatment of ATTR-CM in any country outside the U.S. and the timing of any such regulatory approval(s); the potential for Alnylam to successfully launch AMVUTTRA in ATTR-CM and its ability to optimize access pathways, expand treatment sites, obtain health systems formulary approval and engage with payers; the potential for AMVUTTRA to have a differentiated value proposition and broad patient access in ATTR-CM; the potential for the net price of AMVUTTRA for ATTR-CM to decrease over time; Alnylam's continued investment in ATTR Amyloidosis and the potential for Alnylam to continue to advance innovation in ATTR Amyloidosis, including Alnylam's ability to advance nucresiran through clinical trials and to gain approval of nucresiran for the treatment of any manifestation of ATTR amyloidosis; and Alnylam's projected commercial and financial performance, including the expected range of combined TTR net product revenues for 2025, 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"* goals; Alnylam's ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of its product candidates; the pre-clinical and clinical results for Alnylam's product candidates; actions or advice of regulatory agencies and Alnylam's ability to obtain and maintain regulatory approval for its product candidates, as well as favorable pricing and reimbursement; successfully launching, marketing and selling Alnylam's approved products globally; delays, interruptions or failures in the manufacture and supply of Alnylam's product candidates or its marketed products; obtaining, maintaining and protecting intellectual property; Alnylam's ability to successfully expand the approved indications for AMVUTTRA; Alnylam's ability to manage its growth and operating expenses through disciplined investment in operations and its ability to achieve a self-sustainable financial profile in the future; Alnylam's ability to maintain strategic business collaborations; Alnylam's dependence on third parties for the development and commercialization of certain products; the outcome of litigation; the potential risk of future government investigations; and unexpected expenditures; as well as those risks more fully discussed in the "Risk Factors" filed with Alnylam's 2024 Annual Report on Form 10-K filed with the SEC, as may be updated from time to time in 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 the date of this presentation and should not be relied upon as representing Alnylam's views as of any subsequent date. Alnylam explicitly disclaims any obligation, except to the extent required by law, to update any forward-looking statements.

# An Inflection Point in the Treatment of ATTR-CM

**Yvonne Greenstreet, MBChB, MBA**
Chief Executive Officer

Alnylam®

amvuttra® (vutrisiran) injection 25 mg/0.5 mL

# Now Approved for the Treatment of the Cardiomyopathy of Wild-Type or Hereditary ATTR Amyloidosis

**Only**
FDA-approved product for the treatment of
**Both:**

**POLYNEUROPATHY**
of Hereditary
ATTR Amyloidosis

**CARDIOMYOPATHY**
of Wild-Type or Hereditary
ATTR Amyloidosis

# AMVUTTRA: Potential to Become New Standard of Care in ATTR-CM

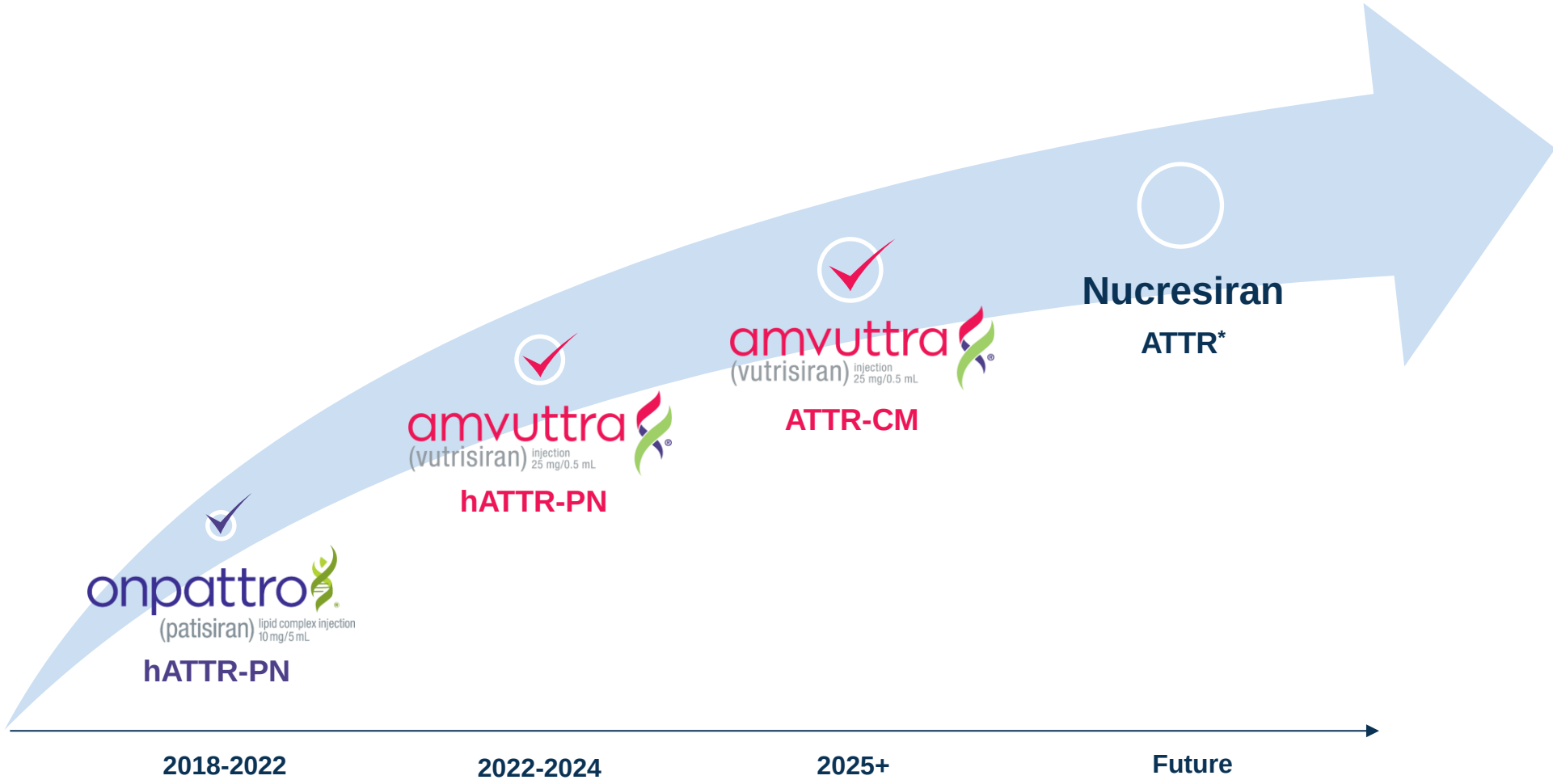
Results demonstrated in population reflective of today's ATTR-CM patients: **earlier in disease** and on **substantial background therapy**

- Rapid knockdown of TTR works upstream, addressing disease at its source
- Profound benefit on CV outcomes, including 36% reduction in all-cause mortality*
- Early clinical impact and preservation of functional capacity, health status & quality of life
- **4x** Convenience of only four doses per year

** Relative risk reduction vs. placebo; prespecified secondary endpoint*

# Alnylam TTR Franchise Poised for Durable Growth

## Built for Unmatched Leadership and Longevity




** Nucresiran is an investigational drug and not approved by any health agency; its safety & effectiveness have not been established*

# AMVUTTRA Approval Represents a Critical Step Toward Achieving Five-Year Goals

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; 10+ in late stages; 4+ INDs per year

**PERFORMANCE:** ≥40% revenue CAGR through YE 2025

**PROFITABILITY:** Achieve sustainable non-GAAP profitability within period



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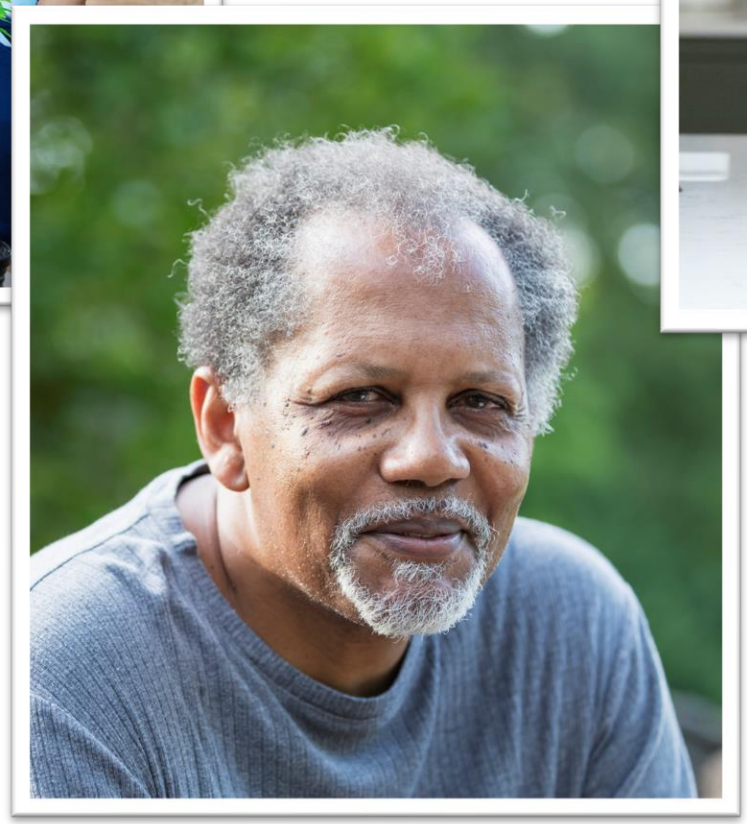
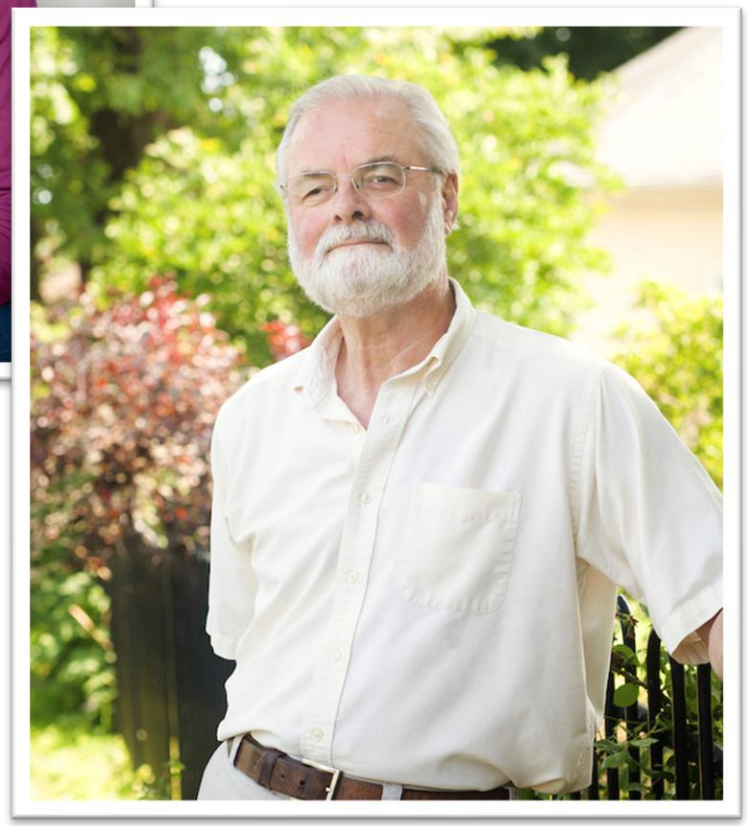




# AMVUTTRA® (vutrisiran) Label & Data

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

Alnylam®

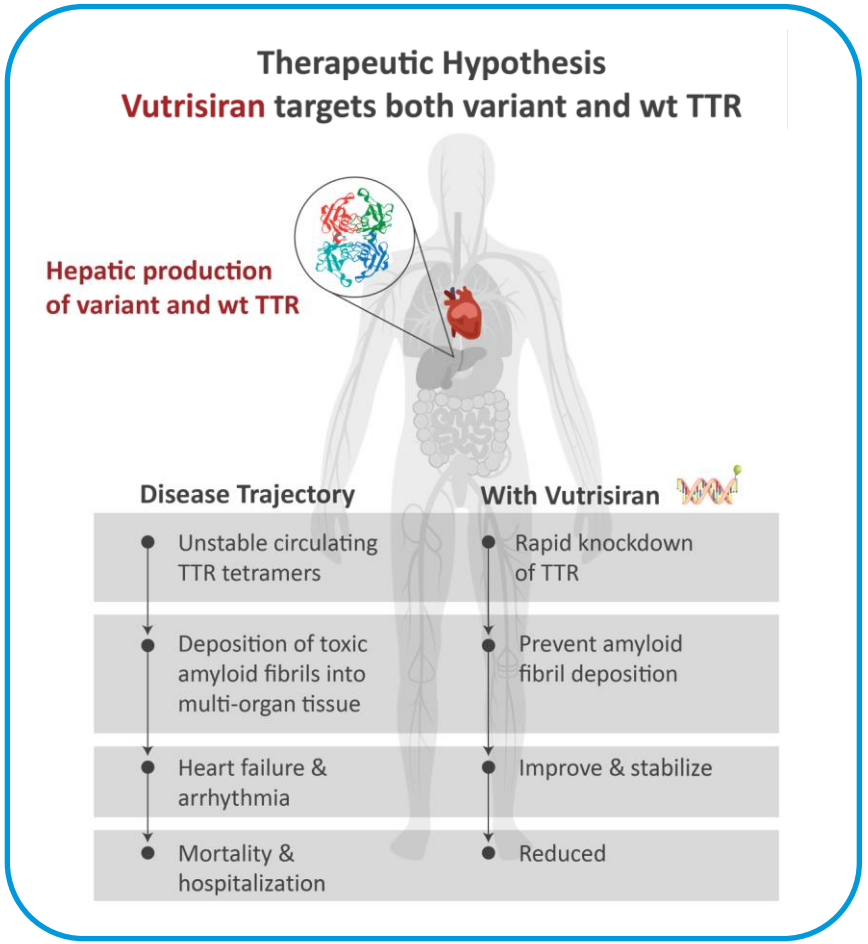
# ATTR-CM: A Progressive, Debilitating, and Fatal Disease

## ATTR Cardiomyopathy

- Results from accumulation of wild type or variant TTR amyloid fibrils in the heart[1-5]
- Leads to progressive heart failure, arrhythmias, declines in functional status and QOL, increased hospitalizations and reduced survival[6–10]
- Evolution toward earlier diagnosis and improved HF management; contemporary patients have less advanced disease, and are managed with tafamidis, SGLT2 inhibitors, and diuretics

## HELIOS-B study

- Evaluated vutrisiran, a SC administered RNAi therapeutic, with four doses per year
- Objective: Establish efficacy and safety in a population reflective of today's ATTR-CM patients




*References: 1. Hawkins et al. Ann Med 2015;47:625–38; 2. Ruberg et al. J Am Coll Cardiol 2019;73:2872–92; 3. Maurer et al. J Am Coll Cardiol 2016;68:161–72; 4. Živković et al. Amyloid 2020;27:142–3; 5. Sipe et al. Amyloid 2014;21:221–4; 6. Castano et al. Heart Fail Rev 2015;20:163–78; 7. Swiecicki et al. Amyloid 2015;22:123–31; 8. Ruberg et al. Am Heart J 2012;164:222–8.e1; 9. Sattianayagam et al. Eur Heart J 2012;33:1120–7; 10. Gertz et al. Mayo Clin Proc 1992;67:428–40.* *Abbreviations: ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; HF, heart failure; QOL, quality of life; RNAi, RNA interference; SC, subcutaneous; SGLT2, sodium/glutamate cotransporter 2; TTR, transthyretin; wt TTR, wild-type transthyretin.*



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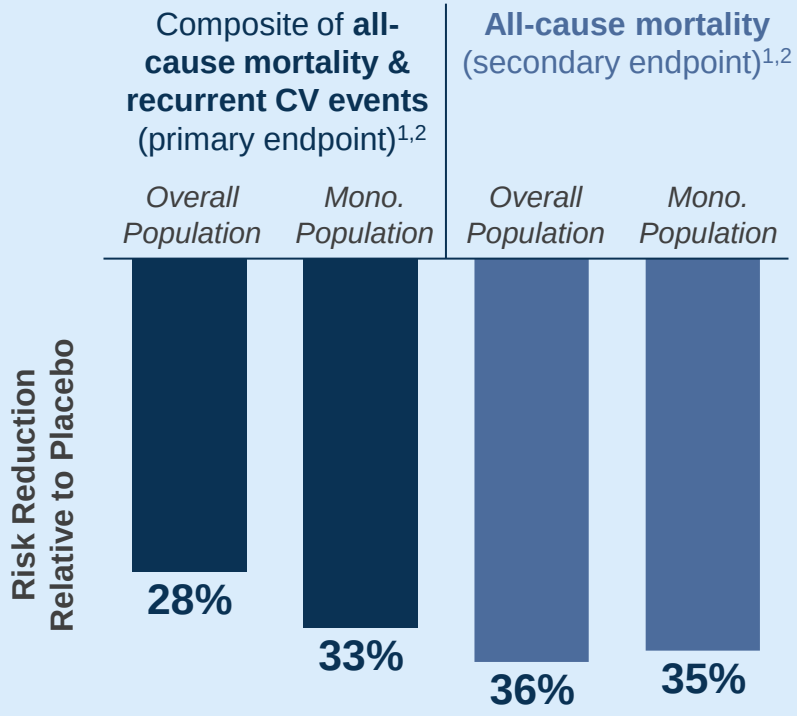
# AMVUTTRA Therapeutic Profile Supports First-Line Potential

**Population Representative of Today's Patients**

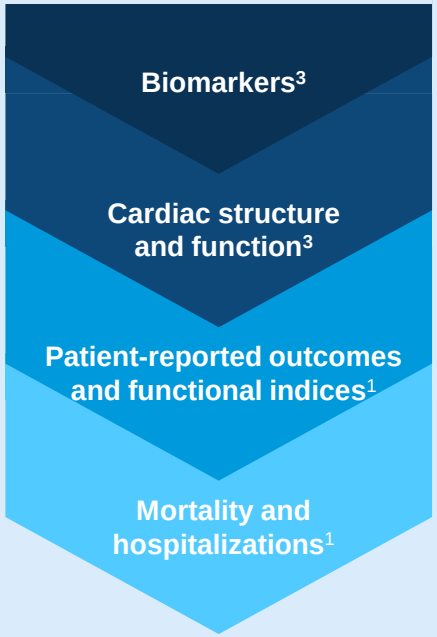
**~50%**
of patients were on **tafamidis** at baseline or during DB period

**~30%**
of patients started **SGLT2** inhibitors during DB period

**~80%**
of patients were on **diuretics** at baseline and ~50% had intensification or initiation of diuretics after 1st dose




**Broad Impact on ATTR-CM Parameters with Substantial Improvement of CV Outcomes**




**4 subcutaneous doses per year**

*Primary composite endpoint assessed over 33-36 months. Secondary all-cause mortality endpoint assessed over 33-42 months.*

*References: 1. Fontana et al. N Engl J Med. 2025;392(1):33-44; 2. Fontana et al. ESC Congress 2024. London, UK; 3. Fontana et al. N Engl J Med. 2025;392(1):33-44 (supplement).*

# Highlights of AMVUTTRA® (vutrisiran) U.S. Prescribing Information

## Only FDA-Approved Treatment for Both PN and CM Manifestations of ATTR Amyloidosis

**INDICATIONS AND USAGE**

**Polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis**

AMVUTTRA is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN) in adults.

**Cardiomyopathy of Wild-type or Hereditary Transthyretin-mediated Amyloidosis**

AMVUTTRA is indicated for the treatment of the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality, cardiovascular hospitalizations, and urgent heart failure visits.

**DOSAGE**

The recommended dosage of AMVUTTRA is 25 mg administered by subcutaneous injection once every 3 months (quarterly).

**WARNINGS AND PRECAUTIONS**

AMVUTTRA treatment leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance of vitamin A is advised for patients taking AMVUTTRA. Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency.




*These highlights do not include all the information needed to use AMVUTTRA safely and effectively. See full prescribing information for AMVUTTRA.*

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# Significant Reduction in Risk of All-Cause Mortality and Recurrent CV Events

**Primary Composite Endpoint and its Individual Components in HELIOS-B**

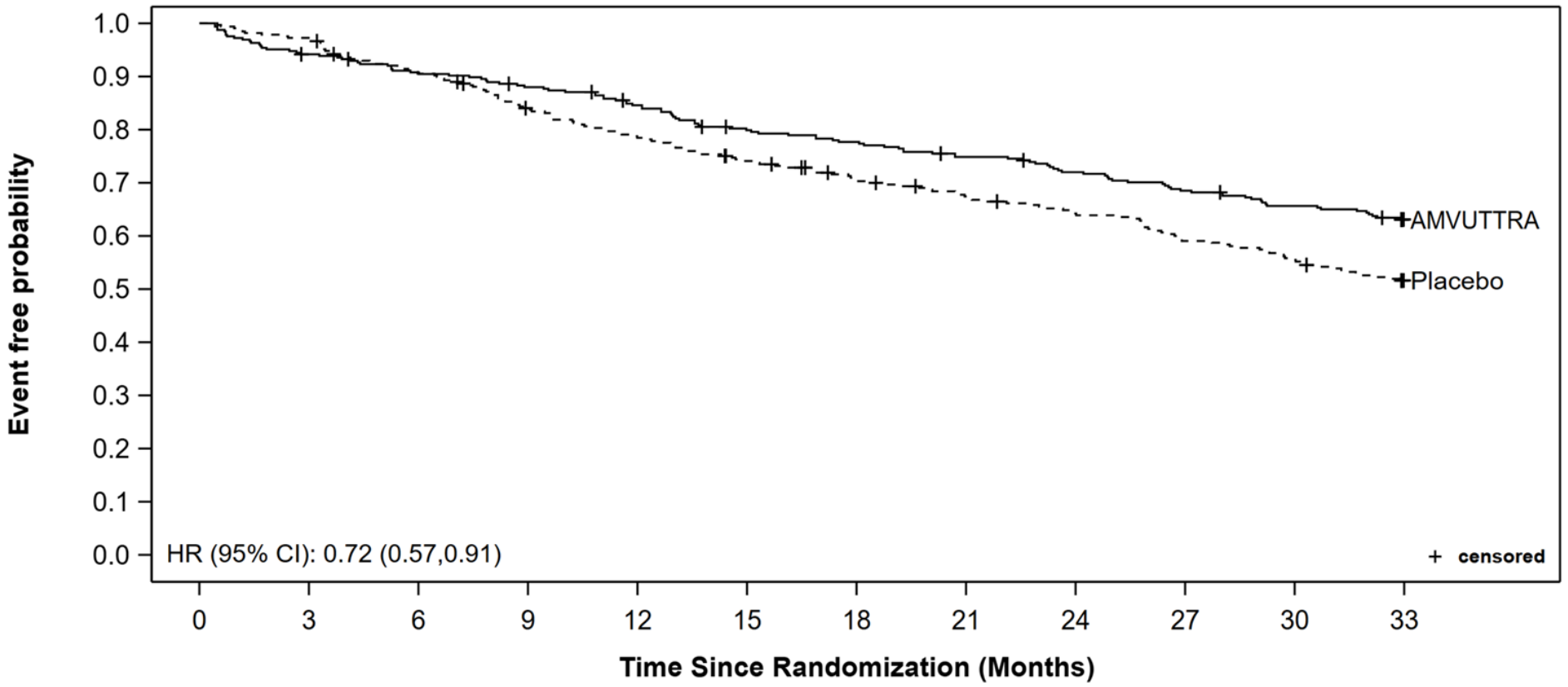
| Endpoint | | Overall population | | Monotherapy population | |
|---|---|---|---|---|---|
| | | AMVUTTRA (N=326) | Placebo (N=328) | AMVUTTRA (N=196) | Placebo (N=199) |
| **Primary composite endpoint*** | Hazard Ratio (95% CI)†<br>*p*-value† | 0.72 (0.55, 0.93)<br>0.01 | | 0.67 (0.49, 0.93)<br>0.02 | |
| **Components of the Primary Composite Endpoint** | | | | | |
| **All-cause mortality** | Hazard Ratio (95% CI)‡ | 0.69 (0.49, 0.98) | | 0.71 (0.47, 1.06) | |
| **CV hospitalizations and UHF visits** | Hazard Ratio (95% CI)† | 0.73 (0.55, 0.96) | | 0.67 (0.47, 0.96) | |

Abbreviations: CI=confidence interval; CV=cardiovascular; UHF=urgent heart failure.
Heart transplantation and left ventricular assist device placement are treated as death. Deaths after study discontinuation are included in the all-cause mortality component analysis.
* Primary composite endpoint defined as: composite outcome of all-cause mortality and recurrent CV events. Primary analysis included at least 33 months (and up to 36 months) follow-up on all patients.
† Hazard Ratio (95% CI) and *p*-value are based on a modified Andersen-Gill model.
‡ Hazard Ratio (95% CI) is based on a Cox proportional hazard model.

# Early and Growing Benefit on Outcomes

## Demonstrated in Patient Population on Substantial Background Therapy

**Time to All-Cause Mortality or First CV Event (Overall Population)**



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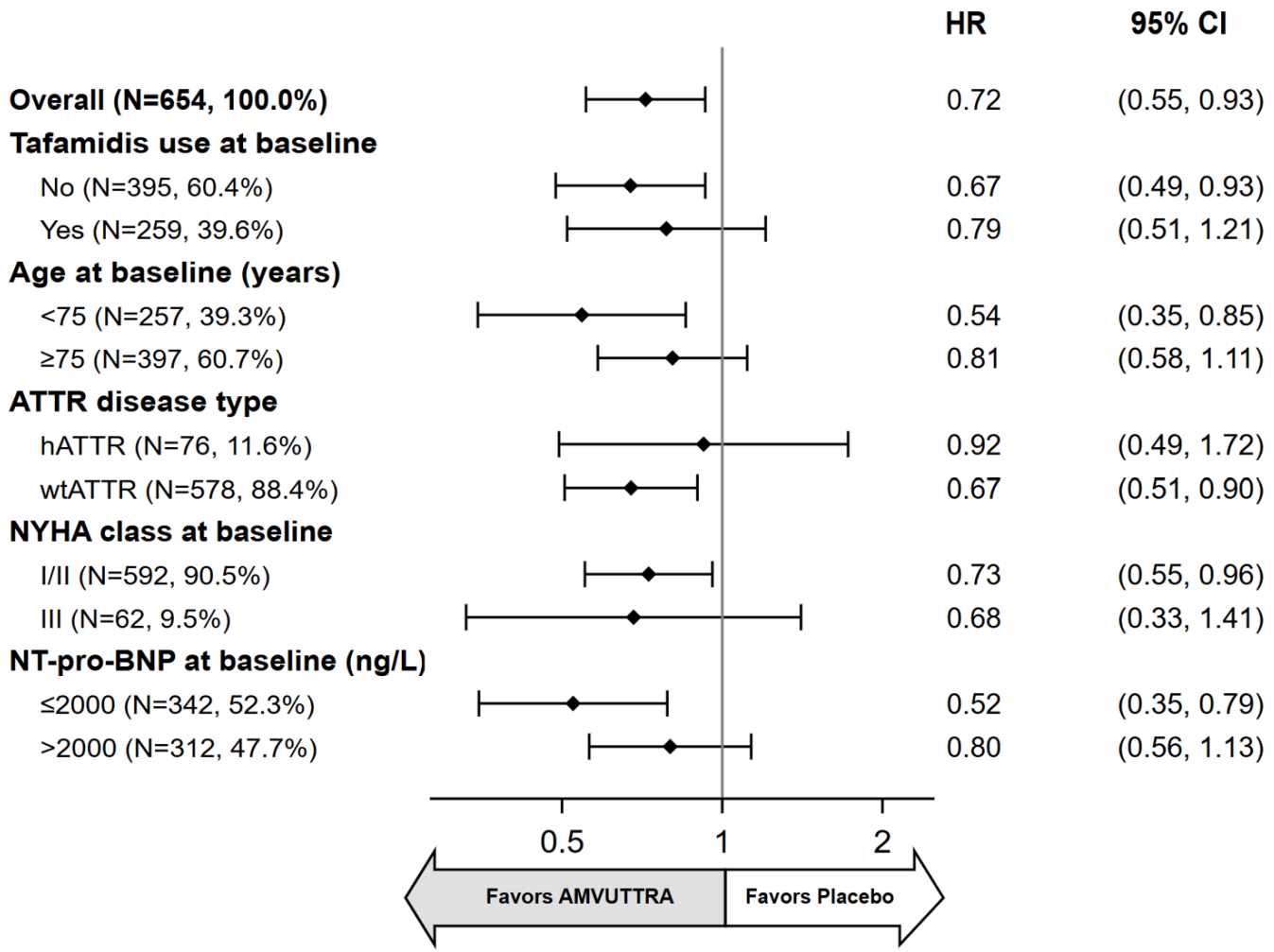
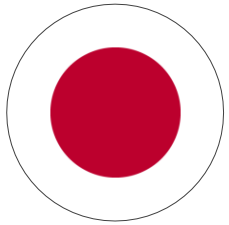
# AMVUTTRA Favored Across All Prespecified Subgroups

## Subgroup Analyses of Primary Composite Endpoint (Overall Population)



# Anticipated Regulatory Approvals



**Japan**
*expected Q2 2025*

**European Union**
*expected Q3 2025*

**United Kingdom**
*expected Q3 2025*

**Brazil**
*expected Q4 2025*

**Canada**
*expected Q4 2025*

**Additional countries**
*expected 2026-2027*

# Additional Data to be Presented at ACC 2025 Further Support Vutrisiran's Compelling Profile

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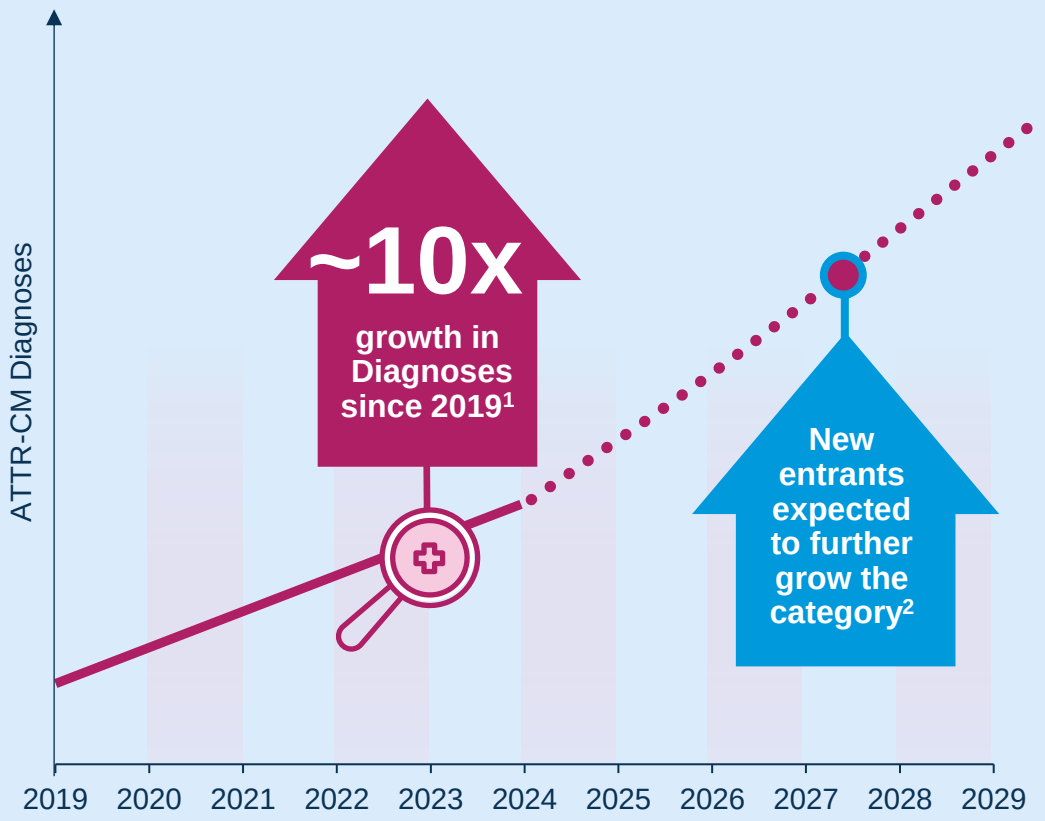
# Delivering AMVUTTRA to Patients

**Tolga Tanguler**
Chief Commercial Officer

Alnylam®

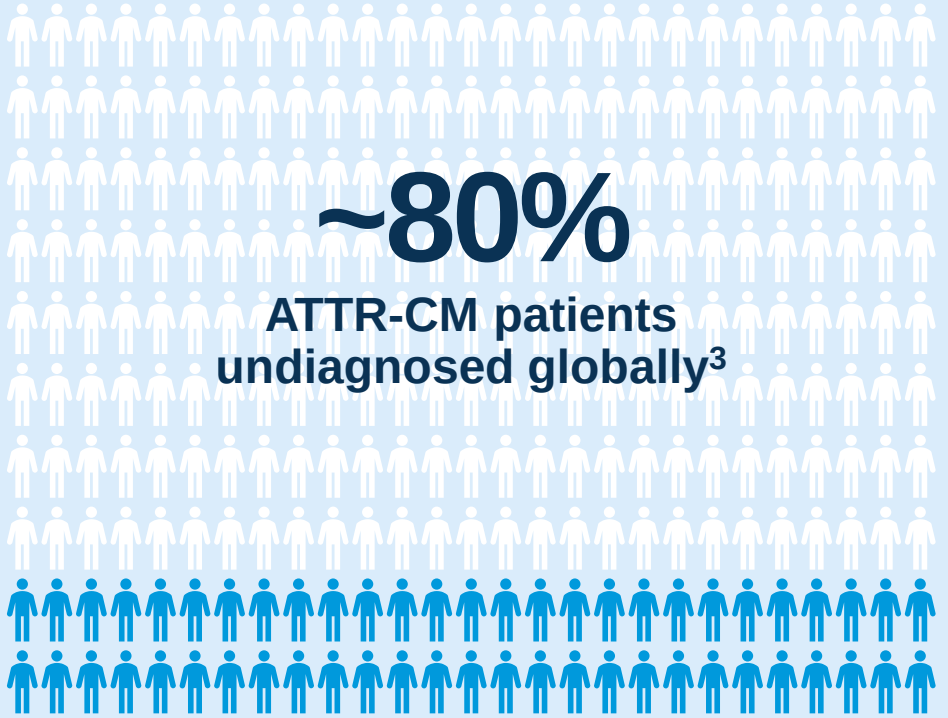
# Significant Opportunity for New Treatments in ATTR-CM

## Growing Category with Rapidly Improving Diagnosis Rate




## Significant Unmet Patient Need

**>300K patients globally[3]**




1. *Alnylam internal market research, U.S.-specific diagnosis rate given data availability; 2. Analog assessment; 3. Information based on Alnylam modeling data*

# Delivering Innovation and Broad Patient Access

## Differentiated Value Proposition

amvuttra (vutrisiran) injection 25 mg/0.5 mL

- First RNAi Therapeutic for ATTR-CM
- Efficacy & Outcomes
- Only Therapy FDA-Approved for hATTR-PN & ATTR-CM
- Studied in Today's Patients

## Broad Patient Access

- Maintain current AMVUTTRA list price
- Will decrease net price over time as patient uptake increases
- Expect broad access in ATTR-CM
  - ~99% coverage today in hATTR-PN
  - ~70% of patients pay $0 copay today in hATTR-PN

## Continued Investment in ATTR Amyloidosis

- Advancing next-generation RNAi therapeutic, nucresiran
- Ongoing evidence generation (e.g., RWE, research collaborations)
- Global compassionate use & extended drug provisions



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# Alnylam Offers Award-Winning In-House Patient Services

Alnylam ASSIST®

**Patient Assistance Program**

*Medicine for patients who are either not insured or underinsured at no cost*

**Quick Start Program**

*Initial dose for patients with coverage delays at no cost*

**Copay Assistance**

*Copay coverage for eligible patients*

**Continuity Program**

*Medicine for eligible patients to ensure no interruption to therapy at no cost*

**Insurance Counseling**

*Service to help patients understand insurance options*

**Patient Education**

*Service to educate patients & families about the disease*

*In 2024, Alnylam Assist® was recognized by Two Labs – a leading pharmaceutical services company – as the overall winner in the Provider Services category*

# Strong Foundation Enables Momentum in Second Half of 2025


- **Optimizing access pathways** at ~170 priority health systems
- **Treatment site expansion** (2x increase since Q4'24, achieving ~2,000 sites[1])
- **Continued payer engagements** (e.g., VBA expansion into ATTR-CM)
- **Health systems formulary approval** (via Pharmacy & Therapeutics Committees)

1. *Represents alternate sites of care*

# Committed to Advancing Innovation in ATTR Amyloidosis

## Continuous ATTR Evidence Generation

**Ongoing research on vutrisiran**

- >30 studies (real world, investigator led studies, and research collaborations)
- HELIOS-B post-hoc analyses

## New ATTR Studies

**Advancing next-generation RNAi therapeutic, nucresiran**

- TRITON-CM Phase 3 CVOT
- TRITON-PN Phase 3 study

## Clinical & Patient Community Support

- ATTR-relevant sponsorships & charitable contributions
- Fellowship programs
- Global hATTR genetic testing
- Compassionate use & extended drug provision

# Communicating Progress

✓

**PDUFA, US Launch**

Final Label & Launch Readiness Indicators

**Q1'25 Earnings**

Initial Customer Feedback

**Q2'25 Earnings**

Early Launch Indicators

**Q3'25 Earnings**

Customer Utilization

## 2025 Guidance

**$1,600 to $1,725 Million**

**Total TTR Net Product Revenues**

# Q&A Session

## FDA Approval of AMVUTTRA for ATTR Cardiomyopathy

Alnylam®


Silence disease
Amplify life™
Alnylam®