Phase 3 HELIOS-B Study Rationale

MED-US-TTRSC02-2400015

Phase 3 HELIOS-B Study Rationale

- This resource is intended to support scientific exchange and may contain information that is not in the approved Prescribing Information for AMVUTTRA® (vutrisiran). The information provided is not intended to serve as recommendations for clinical practice.
- Alnylam does not recommend or suggest the use of its products in any manner that is inconsistent with the approved Prescribing Information.
- Please see the AMVUTTRA full Prescribing Information for the FDA-approved product labeling.
- This resource may contain hyperlinks that are not functional in this format.

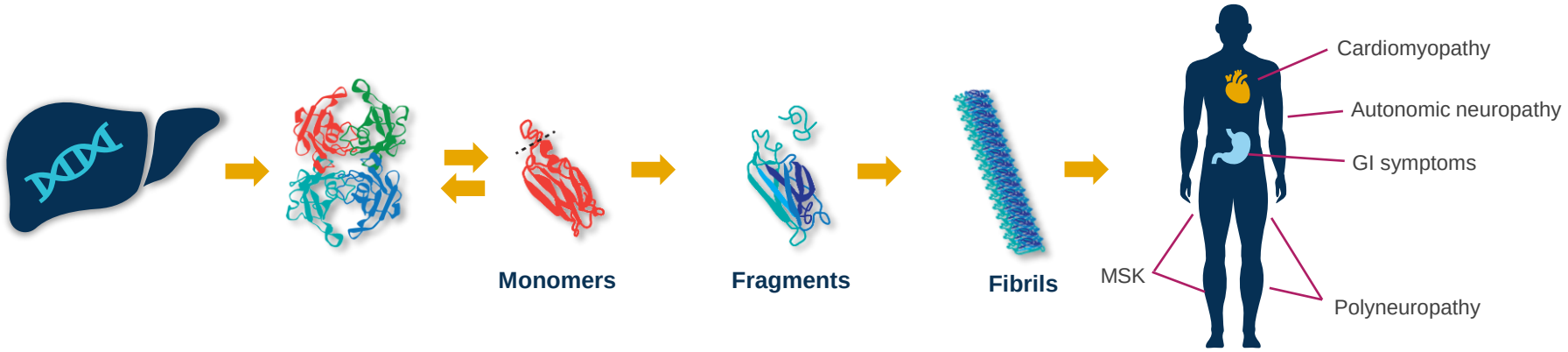
Alnylam®

ATTR Is a Progressive, Fatal Disease, Caused by Toxic TTR Amyloid Deposition, Leading to Tissue Damage and Multisystem Disease Burden[1,2]

The TTR protein is primarily **produced in the liver** and transports vitamin A and thyroxine

In ATTR, misfolded TTR proteins aggregate and form **toxic amyloid fibrils**…

…which **accumulate** in multiple organs and tissues, resulting in **progressive organ damage**[1]



Clinical Manifestations[1,3]

Cycle of toxic TTR deposition[1–3]

ATTR, transthyretin amyloidosis; GI, gastrointestinal; MSK, musculoskeletal; TTR, transthyretin;

1. Adams et al. *Nat Rev Neurol* 2019;15:387–404; 2. Ghosh et al. *Amyloid* 2023;30:379–93; 3. Adams et al. *J Neur* 2021:268:2109–122.

Alnylam®

There Are Two Types of ATTR: Hereditary or Wild-Type

ATTR Is Classified by the Sequence of the TTR Gene, Either wtATTR (No Variant) or hATTR (Variant Present)[1]

Worldwide, there are

~50,000
PATIENTS WITH
hATTR[2]

~200,000–300,000
PATIENTS WITH
wtATTR[a,3,4]

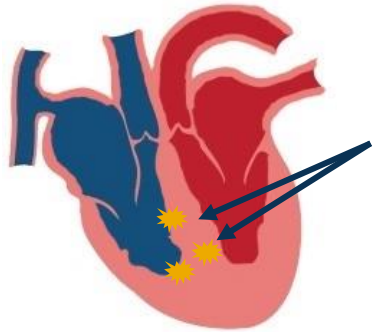
hATTR

- hATTR arises from an inherited variant in the TTR gene, resulting in misfolded amyloidogenic monomers[5,6]
- hATTR is caused by deposition of both variant and wt TTR toxic amyloid[5–7]
- Patients with hATTR commonly develop a mixed phenotype of polyneuropathy and **cardiomyopathy**[8]

wtATTR

- wtATTR is non-hereditary, but also results in misfolded wt TTR which accumulates as toxic amyloid deposits[9,10]
- Patients with wtATTR are typically aged ≥60 years and mostly have **cardiomyopathy**, although polyneuropathy may coexist[8,11]

Amyloid Deposits in the Heart Can Lead to Cardiomyopathy



Amyloid deposits form in cardiac tissue

Amyloid heart

Patients' experience[6,10,12–16]

- Progressive HF
- Cardiac arrhythmias
- Restrictive cardiomyopathy
- Intolerance of commonly used CV medications[b]

[a]Numbers may be underestimated as non-specific signs/symptoms can lead to misdiagnosis.[17] Information based on Alnylam modeling data. [b]E.g., digoxin, calcium channel blockers, ACEis, ARBs, and beta-blockers.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CV, cardiovascular; hATTR, hereditary ATTR; HF, heart failure; QOL, quality of life; TTR, transthyretin; wt, wild-type; wtATTR, wild-type ATTR.

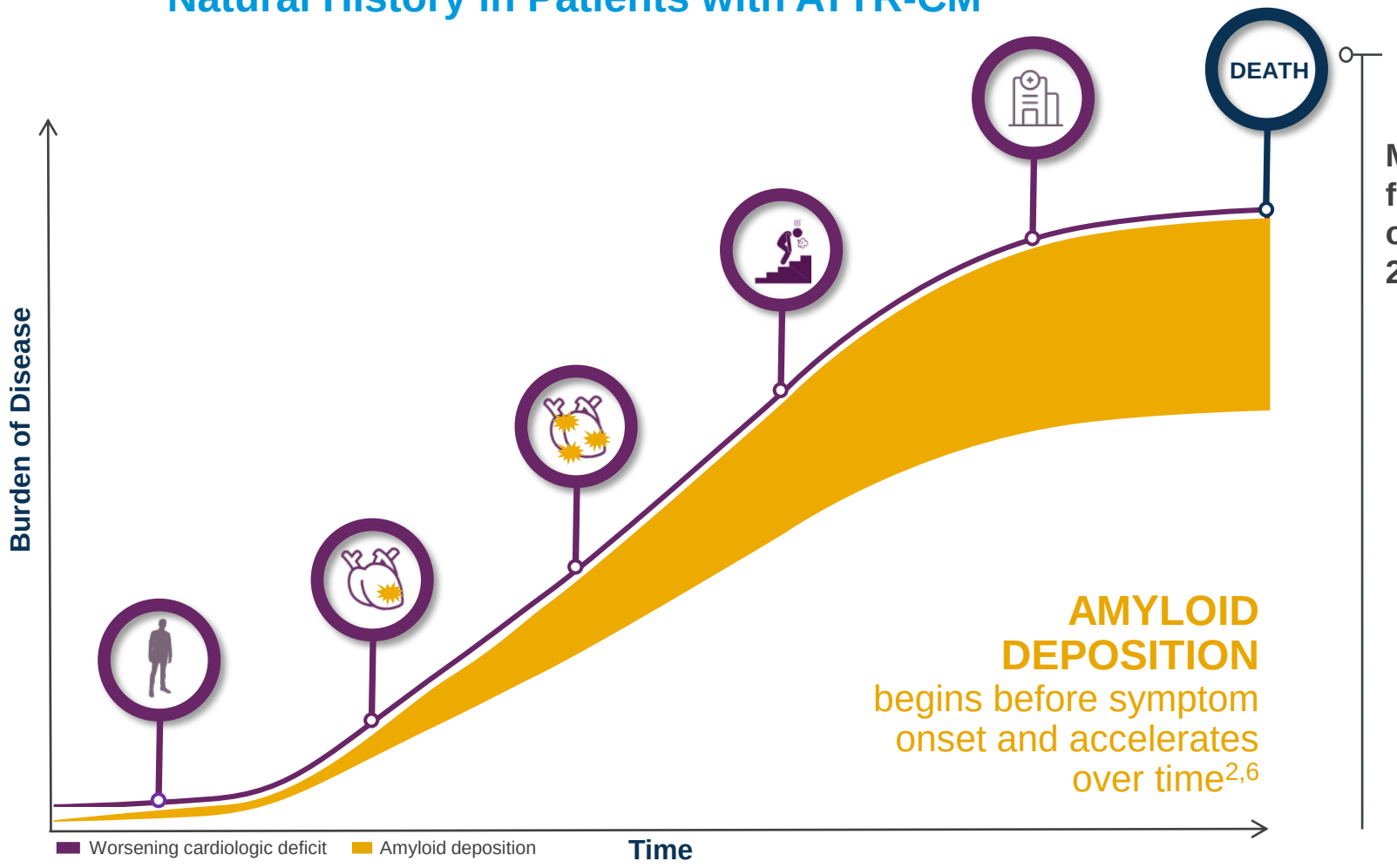
1. Ruberg et al. *J Am Coll Cardiol* 2019;73:2872–91; 2. Gertz. *Am J Manag Care* 2017;23:S107–S112; 3. Narotsky et al. *Can J Cardiol* 2016;32:1166:e1–10; 4. Manolis et al. *Eur J Intern Med* 2019;67:1–13; 5. Hawkins et al. *Ann Med* 2015;47:625–38; 6. Ruberg et al. *Circulation* 2012;126:1286–300; 7. Ghosh et al. *Amyloid* 2023;30:379–93; 8. Coelho et al. *Curr Med Res Opin* 2013;29:63–76; 9. Hanna. *Curr Heart Fail Rep* 2014;11:50–7; 10. Mohty et al. *Arch Cardiovasc Dis* 2013;106:528–40; 11. Gonzalez-Lopez et al. *Eur Heart J* 2015;36:2585–94; 12. Dungu et al. *Heart* 2012;98:1546–54; 13. Castano et al. *Heart Fail Rev* 2015;20:163–78; 14. Dharmarajan & Maurer. *J Am Geriatr Soc* 2012;60:765–74; 15. Falk. *Circulation* 2005;112:2047–60; 16. Coelho et al. A guide to transthyretin amyloidosis. Available from: https://amyloidosis.org/sites/default/files/pdf-docs/pages/resources/2023-03/2018%20ATTR.pdf (accessed May 5, 2024); 17. Nativi-Nicolau et al. *Heart Fail Rev* 2022;27:785–93.

Patients with ATTR Cardiomyopathy (ATTR-CM) Experience Substantial Disease Burden Due to Ongoing TTR Amyloid Deposition in the Heart[1,2]

Worsening cardiomyopathy manifestations can lead to:[2–5]

- loss of cardiac function
- decline in physical functioning
- decreased QOL
- increased CV-related hospitalizations
- death

Natural History in Patients with ATTR-CM



Median survival from diagnosis of ATTR-CM[a] is 2–6 years[7]

[a]Depending on disease stage.

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CV, cardiovascular; QOL, quality of life; TTR, transthyretin.

1. Ruberg et al. *J Am Coll Cardiol* 2019;73:2872–91; 2. Castano et al. *Heart Fail Rev* 2015;20:163–78; 3. Ruberg et al. *Am Heart J* 2012;64:222–8.e1; 4. Lane et al. *Circulation* 2019;140:16–26; 5. Maurer et al. *Circ Heart Fail* 2019;12:e006075; 6. Koike & Katsuno. *Biomedicines* 2019;7:11; 7. Gillmore et al. *Eur Heart J* 2018;39:2799–806.

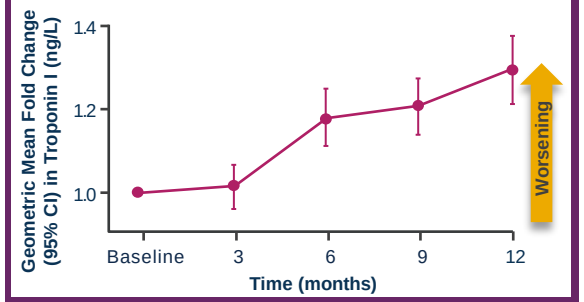
Alnylam®

ATTR-CM Has an Aggressive Disease Course[1]

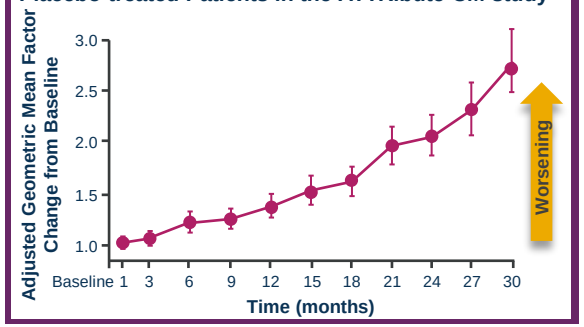
Rapid Disease Progression Is Associated with Continuous Cardiac Dysfunction[1–6]

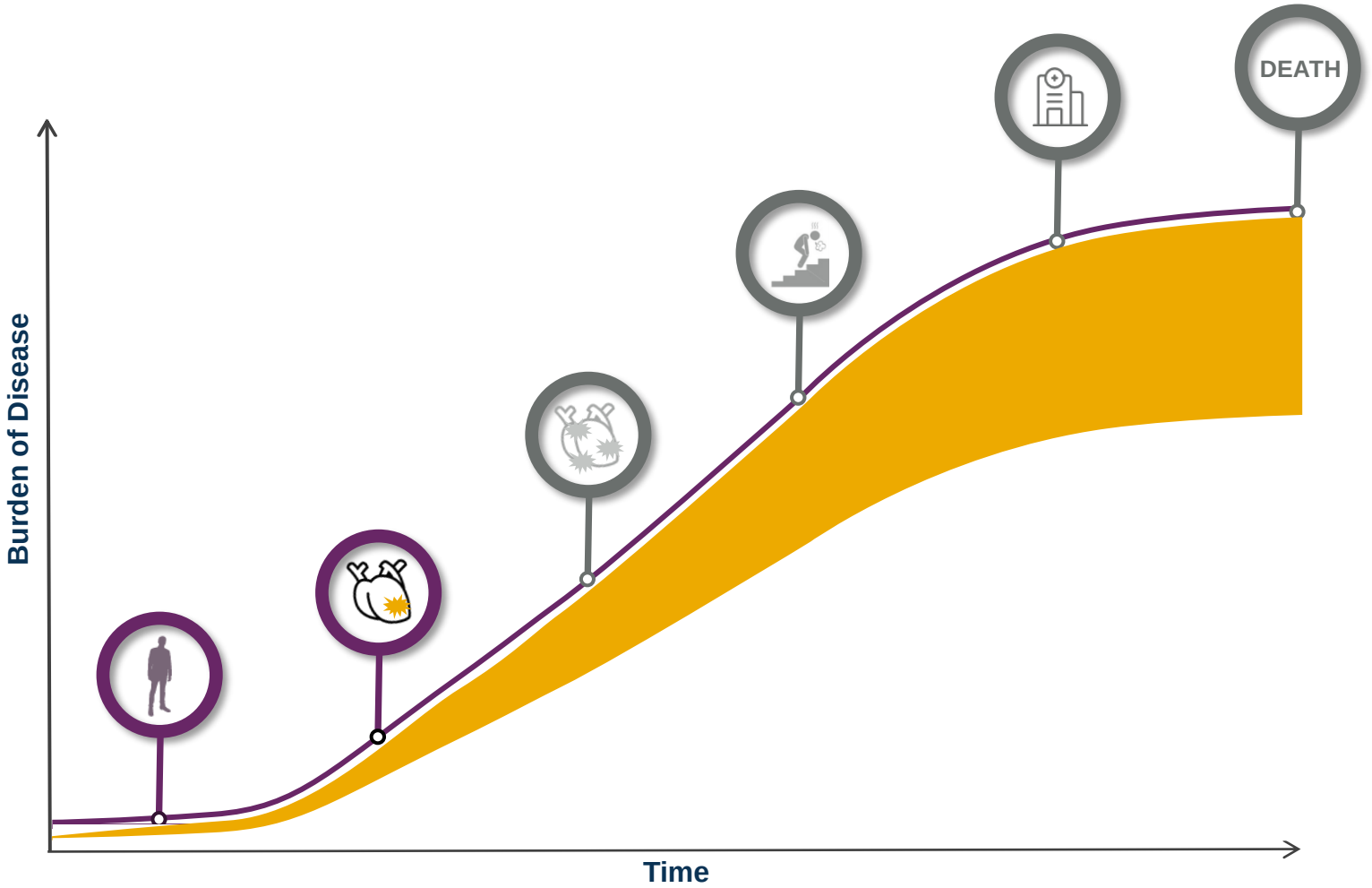
Continuous increases in **biomarkers over time** have been reported among placebo-treated patients with ATTR-CM in the APOLLO-B[a,b] and ATTRibute-CM[c] studies[5,6]

Change from Baseline in Troponin I levels in Placebo-treated Patients in the APOLLO-B study[a,b,5]



Change from Baseline in NT-proBNP levels in Placebo-treated Patients in the ATTRibute-CM study[c,6]





[a]The APOLLO-B study is a placebo-controlled Phase 3 trial of patisiran in patients with ATTR-CM, funded by Alnylam.[5] [b]25% of placebo-treated patients were receiving tafamidis at baseline in APOLLO-B study.[5] [c]The ATTRibute-CM study is a placebo-controlled Phase 3 trial of acoramidis in patients with ATTR-CM, funded by BridgeBio Pharma.[6]

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CI, confidence interval; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide.

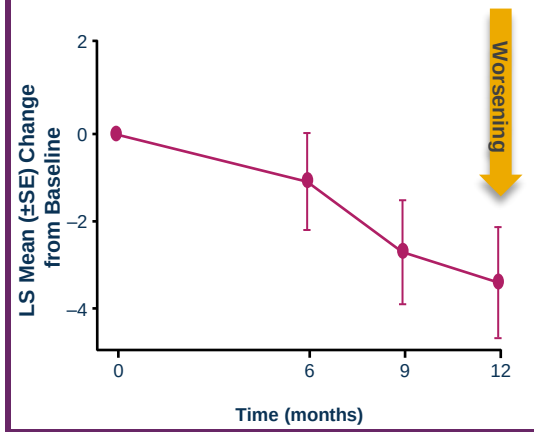
1. Lane et al. *Circulation* 2019;140:16–26; 2. Maurer et al. *N Engl J Med* 2018;379:1007–16; 3. Ruberg et al. *Circulation* 2012;126:1286–300; 4. Bhuiyan et al. *Circ Heart Fail* 2011;4:121–8; 5. Maurer et al. *N Engl J Med* 2023;389:1553–65; 6. Gillmore et al. *N Engl J Med* 2024;390:132–42.

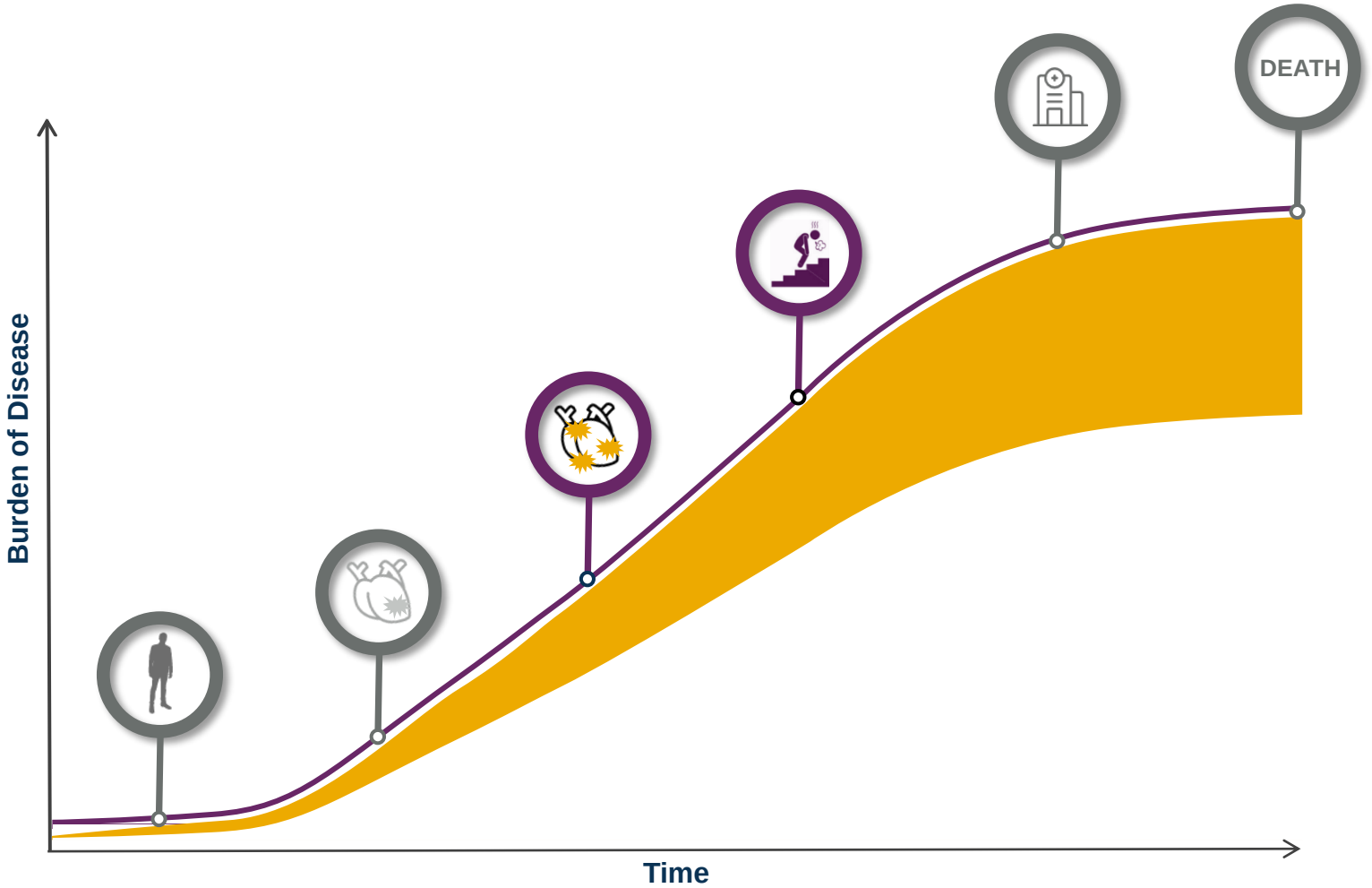
ATTR-CM Has an Aggressive Disease Course

Rapid Disease Progression in Deterioration of Functional Capacity and QOL[1–6]

Progressive worsening of **6-MWT** and **KCCQ-OS** has been observed in placebo-treated patients with ATTR-CM in the ATTR-ACT[a], APOLLO-B[b,c] and ATTRibute-CM[d] studies[2,5,6]

Change from Baseline in KCCQ-OS in Placebo-treated Patients in the APOLLO-B study[b,c,5]





The ATTR-ACT study is a placebo-controlled Phase 3 trial of tafamidis in patients with ATTR-CM, funded by Pfizer.[2] [b]The APOLLO-B study is a placebo-controlled Phase 3 trial of patisiran in patients with ATTR-CM, funded by Alnylam.[5] [c]25% of placebo-treated patients were receiving tafamidis at baseline in the APOLLO-B study.[5] [d]The ATTRibute-CM study is a placebo-controlled Phase 3 trial of acoramidis in patients with ATTR-CM, funded by BridgeBio Pharma.[6]

6-MWT, 6-minute walk test; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; LS, least squares; QOL, quality of life; SE, standard error

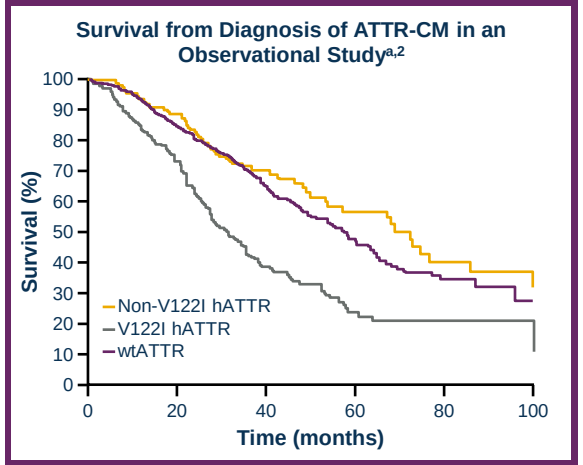
1. Lane et al. *Circulation* 2019;140:16–26; 2. Maurer et al. *N Engl J Med* 2018;379:1007–16; 3. Maurer et al. *HFSA* 2018; 4. Ruberg et al. *Circulation* 2012;126:1286–300; 5. Maurer et al. *N Engl J Med* 2023;389:1553–65; 6. Gillmore et al. *N Engl J Med* 2024;390:132–42.

Alnylam®

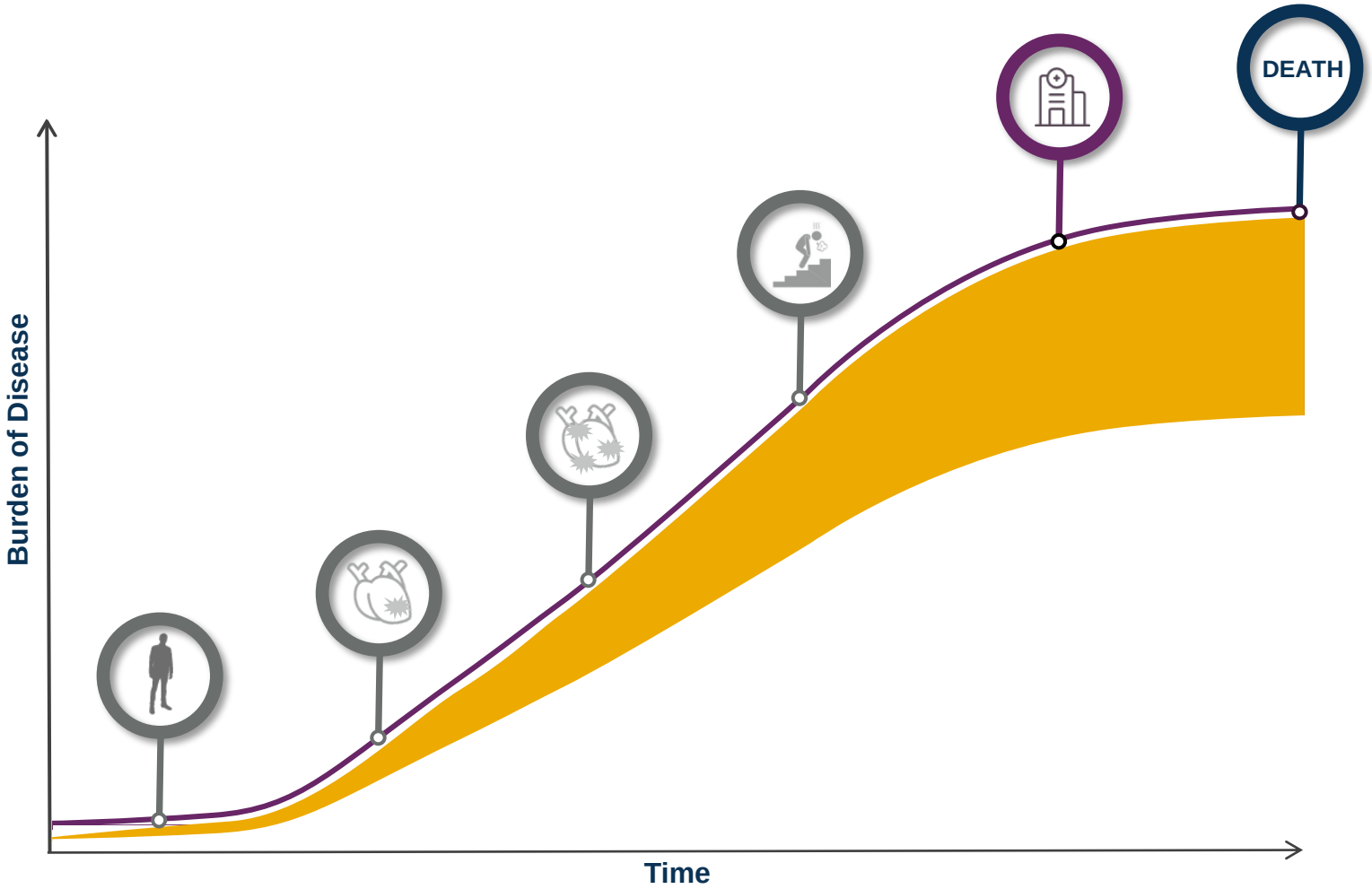
ATTR-CM Has an Aggressive Disease Course

Rapid Disease Progression Is Associated with Frequent Hospitalization and Is Eventually Fatal[1–3]

ATTR-CM is an aggressive disease with a **median survival** from diagnosis of 2–6 years depending on disease stage and genotype[1]



A higher rate of **CV hospitalization**, 0.7 per year, was observed among placebo-treated patients during the 30-month ATTR-ACT study[b,3]



[a]Observational study of patients referred to the UK National Amyloidosis Center. Core support of the center is provided by the National Health Service England, and the UK National Institute for Health Research Biomedical Research Center and Unit Funding Scheme. IQVIA's participation in the hospital episode statistical analysis component of the study was funded by GlaxoSmithKline.[2] [b]The ATTR-ACT study is a placebo-controlled Phase 3 trial of tafamidis in patients with ATTR-CM, funded by Pfizer.[3]

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; CV, cardiovascular; hATTR, hereditary ATTR; wtATTR, wild-type ATTR.

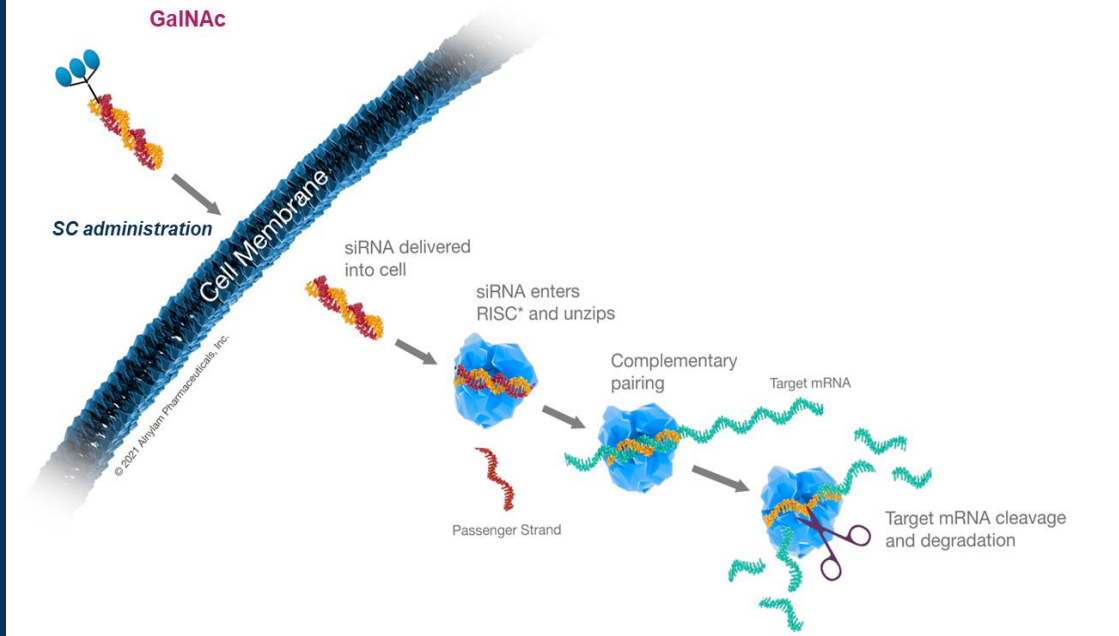
1. Gillmore et al. *Eur Heart J* 2018;39:2799–806; 2. Lane et al. *Circulation* 2019;140:16–26; 3. Maurer et al. *N Engl J Med* 2018;379:1007–16

Alnylam®

Vutrisiran Is an Investigational RNAi Therapeutic in Development for ATTR-CM

- **Mechanism of action:** Vutrisiran is a SC ESC-GalNAc-conjugate RNAi therapeutic targeting TTR mRNA in the liver, which has been observed to rapidly knock down both wild-type and variant TTR[a,1–3]
- **Dosing**: Using ESC to increase potency and enhance metabolic stability of the siRNA, vutrisiran's delivery platform supported studying infrequent (q3M) dosing[1] in the ATTR-CM pivotal study
- **Current indication**: Vutrisiran is approved for adults with hATTR-PN in the US[3–4]

RNAi Enables Selective and Reversible mRNA Targeting to Decrease the Expression of TTR[1–3]



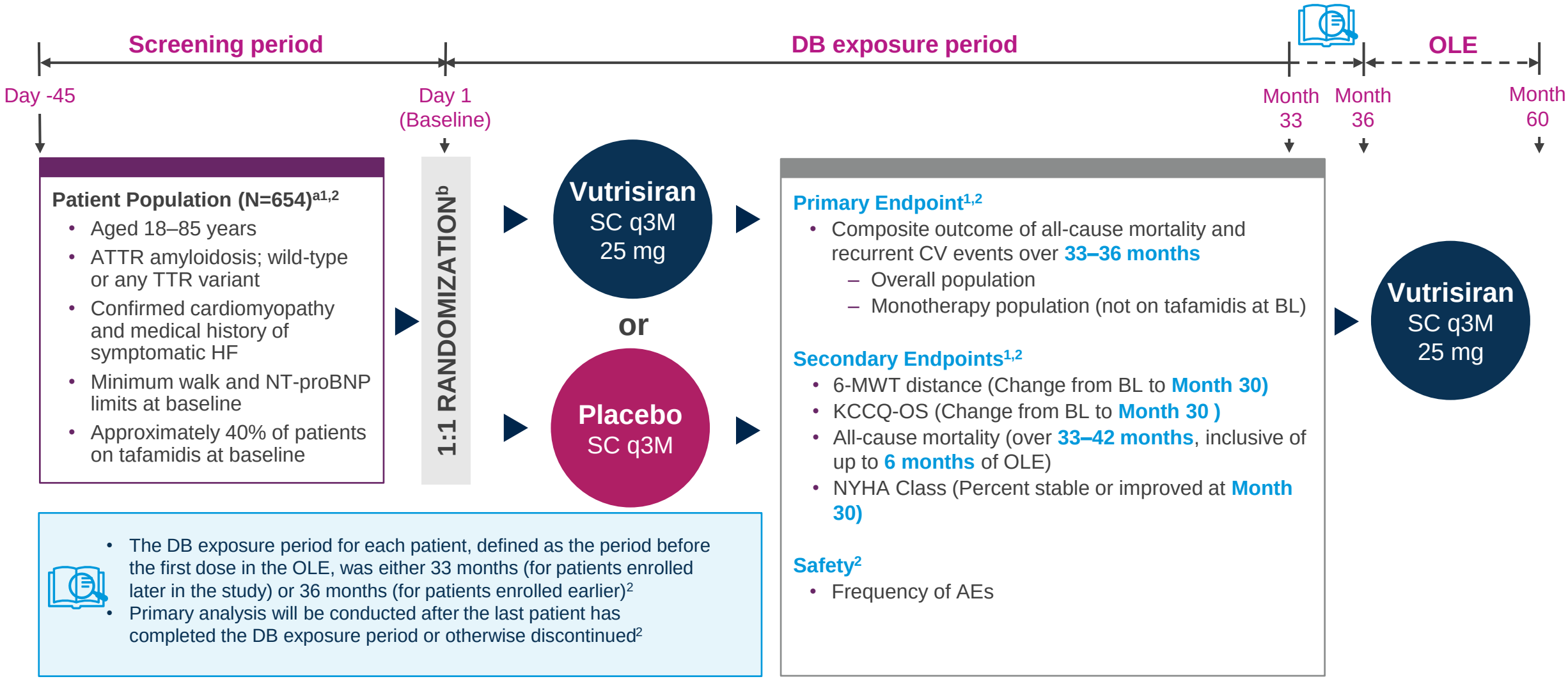
[a]First measured at 3 weeks in the HELIOS-A study

Image credit: Alnylam Pharmaceuticals. Figure adapted from data published in Coelho et al. *N Engl J Med* 2013;369:819–29.

ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; ESC, enhanced stabilization chemistry; GalNAc, *N*-acetylgalactosamine; hATTR-PN; hereditary ATTR with polyneuropathy; mRNA, messenger RNA; q3M, every 3 months; RISC, RNA-induced silencing complex; RNA, ribonucleic acid; RNAi, RNA interference; SC, subcutaneous; siRNA, small interfering RNA; TTR, transthyretin; vs, versus.

1. Habtemariam et al. *Clin Pharmacol Ther* 2021;109:372–82; 2. Nair et al. *J Am Chem Soc* 2014;136:16958–61; 3. Adams et al. *Amyloid* 2023;30:18–26; 4. Alnylam Pharmaceuticals. US Prescribing Information: AMVUTTRA® (vutrisiran) injection, for subcutaneous use. Available from: https://www.alnylam.com/sites/default/files/pdfs/amvuttra-us-prescribing-information.pdf (accessed June 10, 2024)

HELIOS-B Phase 3 Study Design



[a]655 patients were randomized but 1 patient withdrew between randomization and dosing; [b]Stratified by baseline tafamidis use (yes vs no), ATTR genotype (hATTR vs wtATTR), NYHA Class I or II and age <75 years.

6-MWT, 6-minute walk test; AE, adverse event; ATTR, transthyretin amyloidosis; ATTR-CM, ATTR with cardiomyopathy; BL, baseline; CV, cardiovascular; DB, double-blind; eGFR, estimated glomerular filtration rate; EuroQoL-5D-5L, EuroQoL-5 Dimensions-5 Levels; hATTR, hereditary ATTR; HF, heart failure; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; LV, left ventricle; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OLE, open-label extension; q3M, every 3 months; SC, subcutaneous; TTR, transthyretin; vs, versus.

1. https://www.clinicaltrials.gov/study/NCT04153149 (accessed May 31, 2024); 2. Study protocol, data on file.

Select Inclusion and Exclusion Criteria

Inclusion Criteria[1,2]

- Aged 18–85 years
- wtATTR or hATTR (any TTR variant)
- Confirmed cardiomyopathy and medical history of symptomatic HF
- 6-MWT distance ≥150 m at screening
- NT-proBNP >300 ng/L and <8500 ng/L at baseline; in patients with permanent or persistent atrial fibrillation, screening levels >600 ng/L and <8500 ng/L
- KPS ≥60%
- Tafamidis-naive patients (includes patients who have received tafamidis previously but have not received any for ≥30 days prior to screening)
- Those receiving tafamidis for an approved cardiomyopathy indication at screening

Exclusion Criteria[1,2]

- Known primary amyloidosis or leptomeningeal amyloidosis
- NYHA Class IV HF
- NYHA Class III HF and at high risk based on pre-specified criteria
- A PND score IIIa, IIIb, or IV[a] at screening visit
- eGFR <30 mL/min/1.73 m^2
- Tafamidis-naive patients who are expected to commence tafamidis treatment during screening or the first 12 months of the study
- Received prior TTR-lowering treatment
- Other non-TTR cardiomyopathy, hypertensive cardiomyopathy, cardiomyopathy due to valvular heart disease, or cardiomyopathy due to ischemic heart disease

As tafamidis is prescribed in some, but not all, regions as SOC in this patient population, patients on concurrent tafamidis at baseline were included in the study, comprising approximately 40% of the population.[2]

[a]Requires cane or stick to walk due to polyneuropathy, or is wheelchair bound.

6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; eGFR, estimated glomerular filtration rate; hATTR, hereditary ATTR; HF, heart failure; KPS, Karnofsky performance status; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide;; NYHA, New York Heart Association; PND, polyneuropathy disability; SOC, standard of care; TTR, transthyretin; wtATTR, wild-type ATTR.

1. https://www.clinicaltrials.gov/study/NCT04153149 (accessed May 31, 2024); 2. Study protocol, data on file.

Alnylam®

II Statistical Methods and Study Endpoint Rationale

Alnylam®

Rationale for Study Endpoints

- The primary endpoint, a composite of all-cause mortality and recurrent CV events, was designed to provide a robust assessment of clinically meaningful impact; similar endpoints have been used in HF trials and in the ATTR-ACT trial[1–3]
- The secondary endpoints 6-MWT and KCCQ-OS evaluating functional capacity, and health status and HRQOL, respectively, are clinically important endpoints with potential to assess disease stabilization and reflect the patient's perspective of their disease[1]
- All-cause mortality as a standalone secondary endpoint was also included, since it is designed to provide a comprehensive evaluation of the impact of vutrisiran on patient survival, and overall benefit[1]
- The severity of clinical HF symptoms was assessed by the secondary endpoint NYHA class, which is a common HF staging system routinely used by clinicians[1]

6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; CV, cardiovascular; HF, heart failure; HRQOL, health-related quality of life; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire–Overall Summary; NYHA, New York Heart Association.

1. Study protocol, data on file; 2. Lane et al. *Circulation* 2019;140:16–26; 3. Maurer et al. *N Engl J Med* 2018;379:1007–16.

Alnylam®

Overview of Efficacy Assessments

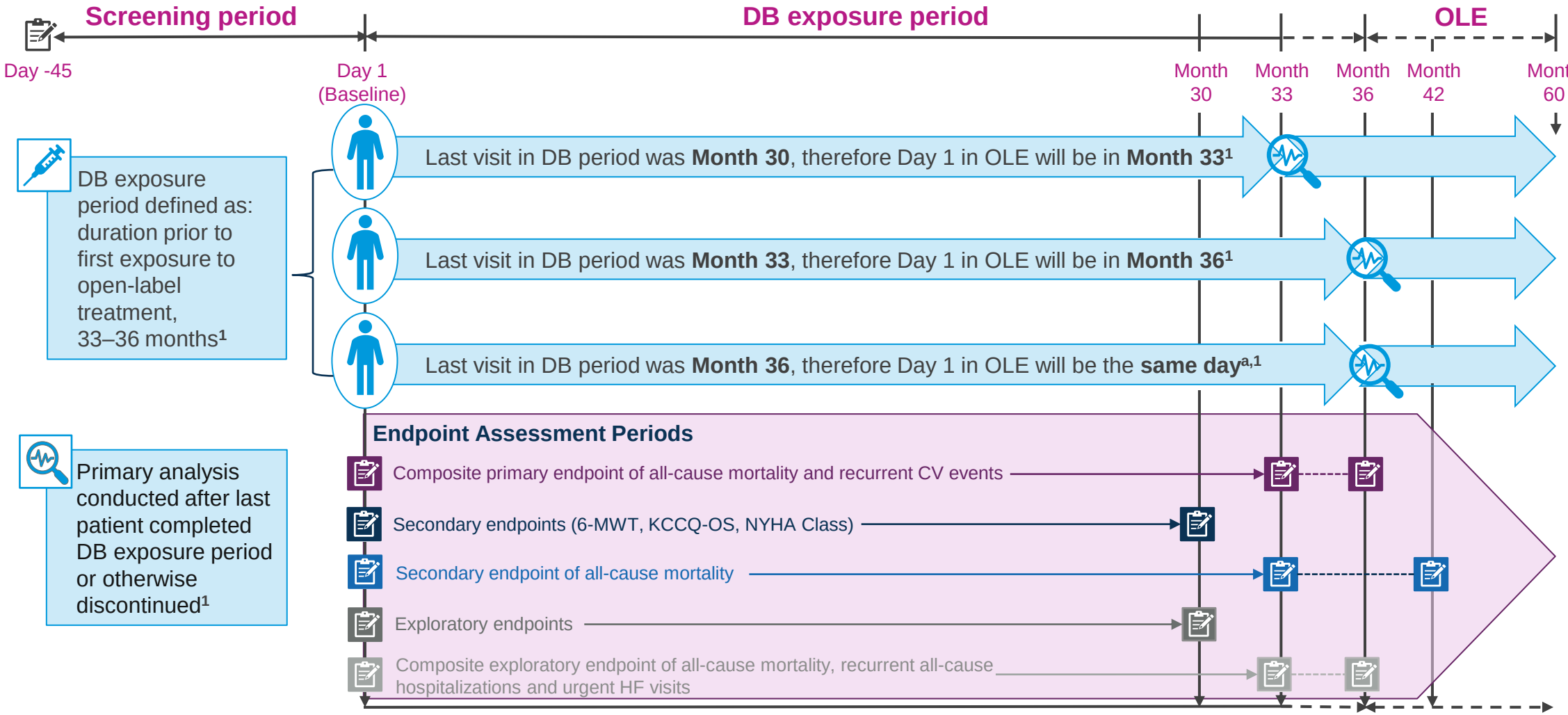
Outcome Measure	Assessments[1,2]	Evaluation
Primary Efficacy Outcome		
Composite endpoint	Composite of all-cause mortality and recurrent CV events over 33–36 months	Number of events
Secondary Efficacy Outcomes		
6-MWT	Change from baseline at 30 months in 6-MWT	Change from baseline
KCCQ-OS	Change from baseline at 30 months in QOL	Change from baseline
All-cause mortality	Assessed all-cause mortality over 33–42 months, inclusive of up to 6 months of OLE	Number of events
NYHA Class	Stable or improved at 30 months in NYHA Class	Percent of patients
Exploratory Efficacy Outcomes		
Composite endpoint	Composite outcome of all-cause mortality and recurrent all-cause hospitalizations and urgent HF visits over 33–36 months	Number of events
Cardiac biomarkers	Change from baseline at 30 months in NT-proBNP and troponin I	Change from baseline
Other	Change from baseline at 30 months in mean LV wall thickness, global longitudinal strain, eGFR, ATTR disease stage, EuroQoL-5D-5L, and Norfolk QoL-DN	Change from baseline
Time to event	Time to first and second CV events or all-cause mortality	Time to event

6-MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EuroQoL-5D-5L, EuroQoL-5 Dimensions-5 Levels; HF, heart failure; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; LV, left ventricle; Norfolk QoL-DN, Norfolk Quality of Life-Diabetic Neuropathy; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OLE, open-label extension.

1. https://www.clinicaltrials.gov/study/NCT04153149 (accessed May 31, 2024); 2. Study protocol, data on file

Timeline of DB Exposure Period and Endpoint Assessments

DB Exposure Period Based on the Timing of a Patient's Last Visit in the DB Period, Primary Analysis Timing, and the Study Endpoint Assessment Periods



[a]Study drug is not administered as part of the Month 36 visit.

6-MWT, 6-minute walk test; CV, cardiovascular; DB, double-blind; HF, heart failure; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary; NYHA, New York Heart Association; OLE, open-label extension.

1. Study protocol, data on file.

Alnylam®

RNAi Science

RNAiScience.com

- Learn about Alnylam & RNAi
- View Congress & Publication Material
- Explore Our Therapeutic Area Resources
- Discover Our RNAi-based Therapies
- Connect with Alnylam Medical

To learn more scan QR code or visit RNAiScience.com