AMVUTTRA® (vutrisiran)

Product Fact Sheet

- **AMVUTTRA® (vutrisiran)** is a U.S. Food and Drug Administration (FDA)-approved RNA interference (RNAi) therapeutic, administered by a healthcare professional via subcutaneous injection once every three months (quarterly) for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN) in adults and the cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality, cardiovascular (CV) hospitalizations and urgent heart failure (HF) visits.
- Transthyretin-mediated (ATTR) amyloidosis is an underdiagnosed, rapidly progressive and often fatal disease that affects multiple parts of the body including the heart, nerves and digestive system. Transthyretin (TTR) changes shape and builds up in the heart and other tissues in the body. This buildup, also known as amyloid deposits, can cause a variety of symptoms.[1-3]
- There are two forms of ATTR — hereditary ATTR (hATTR) and wild-type ATTR (wtATTR) — which can manifest in a variety of ways. Worldwide, wtATTR is estimated to affect ~200,000-300,000 people while hATTR affects ~50,000 people.[2,4]
- AMVUTTRA works with the body's natural system to deliver rapid knockdown of serum TTR protein at the source — in the liver where most of it is made. This helps slow disease progression and addresses the underlying cause of hATTR-PN and ATTR-CM.[5-8]

HELIOS-A Evaluated for hATTR-PN

- The efficacy and safety of AMVUTTRA were evaluated in the global, randomized, open-label, multicenter Phase 3 HELIOS-A study across a diverse group of adult patients with hATTR-PN.[6]
  - AMVUTTRA-treated patients showed significant improvement in nerve function and quality of life at nine months and continued to improve throughout the study, compared with those who received placebo in a similar study.[6]
  - AMVUTTRA also improved other key measures of disease burden relative to external placebo.[6]
- AMVUTTRA demonstrated an encouraging safety and tolerability profile through 18 months of treatment.[6]
  - The most common adverse reactions were pain in extremity (15%), arthralgia (11%), dyspnea (7%), and vitamin A decreased (7%).[7]

HELIOS-B Evaluated for ATTR-CM

- The efficacy and safety of AMVUTTRA were evaluated in the global, randomized, double-blind, placebo-controlled Phase 3 HELIOS-B study across a contemporary patient population with ATTR-CM including hATTR and wtATTR.[8]
  - AMVUTTRA-treated patients had a lower risk in the combined assessment of all-cause mortality and CV events (hospitalizations and urgent HF visits) compared with those who received placebo over three years.[8]
- No new safety issues were identified in HELIOS-B.[7]

Important Safety Information

Reduced Serum Vitamin A Levels and Recommended Supplementation

- AMVUTTRA treatment leads to a decrease in serum vitamin A levels.
- Supplement with the recommended daily allowance of vitamin A. Refer to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur.
- For more information about AMVUTTRA, please visit AMVUTTRA.com.

Please see additional Important Safety Information on page 4 and access full Prescribing Information.

amvuttra (vutrisiran) injection 25 mg/0.5 mL

AMVUTTRA® (vutrisiran) Clinical Profile for hATTR-PN at a Glance[6]

- The efficacy and safety of AMVUTTRA were evaluated in the 18-month HELIOS-A Phase 3 trial of 164 adult patients with hATTR-PN where AMVUTTRA met all primary and secondary endpoints at nine months. The efficacy of AMVUTTRA was assessed by comparing the AMVUTTRA group in HELIOS-A with those who received placebo in a similar study.
  - AMVUTTRA met the primary endpoint at nine months, significantly improving nerve function, while patients who received placebo got worse. At 18 months:
    - 48% of AMVUTTRA-treated patients regained some nerve function from the start of treatment compared with 4% of those who received placebo.[i]
      - For the patients who received AMVUTTRA and did not regain some nerve function, progression of their neuropathy was slowed compared with those who received placebo.
    - Nerve function was assessed using a scale called the modified Neuropathy Impairment Score + 7 (mNIS+7), that measured strength and sensation in the hands, feet, arms and legs; reflexes; and blood pressure upon standing.[ii]
  - AMVUTTRA met all secondary endpoints at nine months, significantly improving quality of life and improving other key measures of disease burden.
    - At 18 months, 57% of AMVUTTRA-treated patients reported better quality of life from the start of treatment, compared with 10% of those who received placebo, as assessed by the Norfolk Quality of Life Diabetic Neuropathy (Norfolk QoL-DN) questionnaire, which asked patients about the severity of their polyneuropathy symptoms, how often they experienced them and what impact they felt they had on their daily lives.[iii]
    - AMVUTTRA-treated patients also maintained a better walking speed,[iv] experienced improvement in nutritional health[v] and were better able to perform common daily activities at 18 months compared with placebo-treated patients.[vi]
  - The most common adverse reactions that occurred in patients treated with AMVUTTRA were pain in extremity (15%), arthralgia (11%), dyspnea (7%) and vitamin A decreased (7%).[7]

Please see additional Important Safety Information on page 4 and access full Prescribing Information.

[i] Regaining of nerve function defined as mNIS+7 change from baseline of <0 points.

[ii] Higher scores indicate more severe disease (total score ranges from 0 to 304).

[iii] Higher scores indicate more severe impact of polyneuropathy symptoms on daily life (total score ranges from -4 to 136).

[iv] Evaluated using the 10-meter walk test, a stopwatch-timed measure of a patient's walking speed over 10 meters.

[v] Evaluated using modified body mass index, an assessment of height, weight, and the balance of fluids in the body.

[vi] Assessed using a 24-item questionnaire called R-ODS, in which patients rated their ability to complete tasks at the beginning of the study and at the end of the study.

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AMVUTTRA® (vutrisiran) Clinical Profile for ATTR-CM at a Glance[4,7-9]

- The efficacy and safety of AMVUTTRA were evaluated in the 36-month HELIOS-B Phase 3 trial of 654 adult patients with ATTR-CM, where AMVUTTRA met the composite primary and all secondary endpoints.
- The primary endpoint evaluated the efficacy of AMVUTTRA versus placebo on the composite endpoint of all-cause mortality and recurrent CV events in the overall study population and in the AMVUTTRA monotherapy population (defined as the group of patients not on tafamidis at study baseline) through 33-36 months. The secondary endpoints were evaluated in both the overall study population and the AMVUTTRA monotherapy population.[vii]
  - AMVUTTRA met the primary endpoint and significantly reduced the risk of all-cause mortality and recurrent CV events by 28% compared to placebo through 33-36 months in the overall population [HR=0.72 (95% CI: 0.55, 0.93); p=0.01].
    - The majority of deaths were CV-related (77%).
  - AMVUTTRA met its secondary endpoint and significantly reduced all-cause mortality by 36% through 42 months in the overall population, which included up to 6 months of open-label extension (OLE) data [HR=0.645 (95% CI: 0.463, 0.898); p=0.0098].[viii]
  - Patients receiving AMVUTTRA maintained relative stability in functional capacity and quality of life, in the overall population compared with the placebo group as assessed by the 6-minute walk test (6-MWT) and Kansas City Cardiomyopathy Questionnaire Overall Summary (KCCQ-OS).
    - At month 30, the least squares (LS) mean difference in change from baseline in distance walked on 6-MWT was 22 [(95% CI: 8, 35); p=0.002] meters and 25 [(95% CI: 7, 44); p=0.006] meters favoring AMVUTTRA over placebo in the overall population and monotherapy population, respectively.[ix]
    - At month 30, the LS mean difference in the change from baseline in KCCQ-OS was 6 [(95% CI: 2, 9); p=0.001] and 8 [(95% CI: 4, 13); p=0.0003] favoring AMVUTTRA over placebo in the overall population and monotherapy population, respectively.[x]
- AMVUTTRA rapidly knocked down serum TTR as early as 6 weeks, with a median trough reduction of 87% at month 30 (95% CI: 84%-88%).
- The safety and tolerability of AMVUTTRA were established in HELIOS-A, and no new safety issues were identified in HELIOS-B.

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[vii] The overall population included patient cohorts with and without tafamidis use at baseline.

[viii] Included up to 36 months of the double-blind (DB) period plus 6 months of the OLE. At the end of the DB period, all remaining patients on placebo transitioned to AMVUTTRA treatment in the OLE.

[ix] Evaluated using the 6-Minute-Walk Test (6-MWT), assessed by the change in baseline to Month 30.

[x] Evaluated by the KCCQ-OS score, which is composed of four domains with higher scores representing better health status (score ranges from 0-100).

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About RNAi Therapeutics

RNAi is a natural cellular process of gene silencing that represents one of the most promising and rapidly advancing frontiers in biology and drug development today.[10] Its discovery has been heralded as "a major scientific breakthrough that happens once every decade or so," and was recognized with the award of the 2006 Nobel Prize for Physiology or Medicine.[11]

RNAi therapeutics harness the natural biological process of RNAi occuring in our cells. Small interfering RNA (siRNA), the molecules that mediate RNAi and comprise Alnylam's RNAi therapeutic platform, act by potently silencing messenger RNA (mRNA) — the genetic precursors that encode for disease-causing or disease pathway proteins — thus preventing them from being made.

Access to AMVUTTRA® (vutrisiran): Alnylam Assist®

Alnylam Assist® provides support services and resources designed to help patients navigate the treatment journey while prescribed an Alnylam product. Alnylam Assist® offers support with insurance coverage, financial assistance, disease and treatment education and starting AMVUTTRA. Learn more about Alnylam Assist® by visiting AlnylamAssist.com/AMVUTTRA.

IMPORTANT SAFETY INFORMATION

Reduced Serum Vitamin A Levels and Recommended Supplementation

AMVUTTRA treatment leads to a decrease in serum vitamin A levels.

Supplementation at the recommended daily allowance (RDA) of vitamin A is advised for patients taking AMVUTTRA. Higher doses than the RDA should not be given to try to achieve normal serum vitamin A levels during treatment with AMVUTTRA, as serum vitamin A levels do not reflect the total vitamin A in the body.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness).

Adverse Reactions

In a study of patients with hATTR-PN, the most common adverse reactions that occurred in patients treated with AMVUTTRA were pain in extremity (15%), arthralgia (11%), dyspnea (7%) and vitamin A decreased (7%).

In a study of patients with ATTR-CM, no new safety issues were identified.

For additional information about AMVUTTRA, please see the full Prescribing Information.

[1] Hawkins PN, et al. *Ann Med*. 2015;47(8):625-638.

[2] Dasari AKR, et al. *Biochemistry*. 2022;61(21):2358-2365.

[3] Ghosh S, et al. *Amyloid*. 2023;30(4):379-393.

[4] Based on Alnylam modeling.

[5] Bezerra et al. *Front Mol Neurosci*. 2020;13:592644.

[6] Adams D, et al. *Amyloid*. 2023;30(1):18-26.

[7] AMVUTTRA Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.

[8] Fontana M. *N Engl J Med*. 2025;392:33-44.

[9] Fontana et al. ESC Congress 2024. London, UK.

[10] Elbashir SM, et al. *Nature*. 2001;411(6836):494-498.

[11] Zamore P. *Cell*. 2006;127(5):1083-1086.

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