Vutrisiran: First Approval

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Abstract

Vutrisiran (AMVUTTRA™) is a subcutaneously administered transthyretin-directed small interfering ribonucleic acid (siRNA) therapeutic (also called RNA interference, or RNAi therapeutic) being developed by Alnylam Pharmaceuticals, Inc. for the treatment of amyloid transthyretin-mediated (ATTR) amyloidosis, including hereditary ATTR (hATTR) amyloidosis and wild-type ATTR (wtATTR) amyloidosis. Vutrisiran was approved in June 2022 in the USA for the treatment of the polyneuropathy of hATTR amyloidosis in adults and received a positive opinion in the EU in July 2022 for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy. Vutrisiran is also under regulatory review for the treatment of the polyneuropathy of hATTR amyloidosis in adults in Japan and Brazil. This article summarizes the milestones in the development of vutrisiran leading to this first approval in hATTR amyloidosis.

1 Introduction

Transthyretin (TTR) is a homotetrameric protein primarily synthesized in hepatocytes; its main function is the transport of vitamin A and thyroxine [1, 2]. Transthyretin-mediated (ATTR) amyloidosis results from tissue deposition of abnormal (misfolded) TTR molecules that form amyloid fibrils, either due to inherited mutations in the TTR gene [hereditary ATTR (hATTR; also known as ATTRv, where v indicates variant) amyloidosis; amyloid deposits contain variant and wild-type ATTR (wtATTR) protein] or ageing [wtATTR amyloidosis; amyloid deposits contain non-variant wtATTR protein] [1, 2]. In hATTR amyloidosis, amyloid proteins accumulate mainly in the peripheral nerves and heart, resulting in peripheral sensory-motor neuropathy, autonomic neuropathy, and/or cardiomyopathy, as well as other disease manifestations. wtATTR amyloidosis usually presents as cardiomyopathy, although neuropathy may be seen [1, 3–5]. hATTR amyloidosis affects ≈ 50,000 people worldwide; median survival without treatment is 4.7 years following diagnosis, with a reduced survival (3.4 years) in patients presenting with cardiomyopathy. wtATTR amyloidosis has a median survival of 2.5–5.5 years if untreated [3, 5, 6].

Small interfering ribonucleic acids (siRNAs) modulate the endogenous RNA interference (RNAi) pathway, silencing messenger RNA (mRNA) encoding for disease-causing proteins and reducing production of target proteins [4]. Recent developments in the metabolic stability and
in intracellular delivery of siRNAs has led to the successful development of these agents in a range of diseases, including hATTR amyloidosis [3].

In June 2022, vutrisiran (AMVUTTRA™), a subcutaneously administered transthyretin-directed double-stranded siRNA that is being developed by Alnylam Pharmaceuticals, Inc. for the treatment of ATTR amyloidosis, was approved in the USA for the treatment of the polyneuropathy of hATTR amyloidosis in adults [7, 8]. In July 2022, vutrisiran received a positive opinion in the EU for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy [9, 10]. Vutrisiran is also under regulatory review for the treatment of the polyneuropathy of hATTR amyloidosis in adults in Japan and Brazil [8] and is being investigated in hATTR or wtATTR amyloidosis with cardiomyopathy in the ongoing global, phase 3, randomized, double-blind, placebo-controlled HELIOS-B (NCT04153149) trial [11, 12]. The recommended dosage of vutrisiran is 25 mg administered by a healthcare professional once every 3 months by subcutaneous injection from a single-dose prefilled syringe. Vutrisiran treatment leads to decreased Vitamin A levels and supplementation at the recommended daily allowance of vitamin A is advised and patients should be referred to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency (e.g. night blindness) develop [7].

### 1.1 Company Agreements

In August 2020, Alnylam Pharmaceuticals and Blackstone Life Sciences closed a research and development financing collaboration initiated in April 2020 to support the development of RNAi therapeutics, including the phase 3 HELIOS-B trial of vutrisiran in patients with ATTR amyloidosis with cardiomyopathy [13, 14].

In April 2019, Alnylam and Sanofi concluded the research and option phase of the 2014 RNAi therapeutics alliance in rare genetic diseases. The material collaboration terms for several RNAi therapeutics, including vutrisiran, continued unchanged [15]. In January 2018, Alnylam entered into a strategic restructuring of its exclusive development and marketing agreement with Sanofi, for development and commercialization of certain products for treating rare genetic diseases [16]. Under the terms of the agreement, Alnylam obtained global development and commercialization rights to the investigational RNAi therapeutics programmes for the treatment of ATTR amyloidosis, including vutrisiran, and Sanofi would receive royalties based on net sales of...
these ATTR amyloidosis products. The material terms of the Alnylam-Sanofi alliance (which had been expanded in January 2014 [17]) were unchanged [18, 19]. In October 2012, Alnylam and Sanofi originally entered an exclusive development and marketing agreement to develop and commercialize RNAi therapeutics targeting TTR for the treatment of ATTR amyloidosis in Japan and other Asia-Pacific countries [20].

2 Scientific Summary

2.1 Pharmacodynamics

Vutrisiran is a chemically modified double-stranded siRNA that targets and degrades variant and wild-type TTR mRNA through RNA interference. Degradation of variant and wild-type TTR mRNA results in a reduction of serum TTR protein and TTR protein deposits in tissues [7]. Vutrisiran uses the enhanced stabilization chemistry (ESC), in which it is covalently linked to a ligand containing three GalNAc residues to enable subcutaneous delivery of the siRNA to hepatocytes (the GalNAc ligand binds to the asialoglycoprotein receptor expressed on the surface of hepatocytes). The ESC platform enhances the pharmacodynamic and pharmacokinetic properties of vutrisiran, enabling a lower dose and reduced dosing frequency compared with earlier TTR gene silencers [3, 4, 7].

Single subcutaneous doses of vutrisiran 5 mg, 25 mg, 50 mg, 100 mg, 200 mg, or 300 mg reduced serum TTR in a dose-dependent manner in a phase 1 trial (NCT02797847) in healthy volunteers; mean maximum serum TTR reductions from baseline ranged from 57% to 97% over the dose range. After a single 25 mg dose of vutrisiran (n = 12), the mean maximum TTR reduction was 80%, which was maintained for 90 days (n = 12). In this trial 12 Japanese and 24 non-Japanese subjects were administered vutrisiran 25 mg or 50 mg; mean maximum TTR reductions in the 25 mg and 50 mg cohorts were comparable in Japanese and non-Japanese subjects [3].

In the phase 3 HELIOS-A trial (NCT03759379), administration of subcutaneous vutrisiran 25 mg every 3 months in patients with hATTR amyloidosis (n = 122) resulted in a rapid (≤ 3 weeks after starting treatment) and sustained (over 18 months) reduction in serum TTR levels, similar to the reduction in serum TTR levels seen with intravenous (IV) patisiran 0.3 mg/kg every 3 weeks in the trial reference group (n = 42) [21]. After 18 months of treatment, the steady state mean peak serum TTR reduction from baseline with vutrisiran was 87.6% and the steady state mean trough reduction from baseline was 81.0%. The steady state mean peak serum TTR reduction from baseline with patisiran was 86.0% and the steady state mean trough reduction from baseline was 79.0%.

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state mean trough reduction from baseline was 74.7%. The fluctuation between steady state peak and trough TTR levels was lower with vutrisiran (median peak/trough reduction from baseline 91.6%/86.2%; difference 5.4%) than patisiran (median peak/trough reduction from baseline 88.3%/78.2%; difference 10.1%) [21]. At month 18, the TTR reduction in the vutrisiran arm was noninferior to that in the patisiran arm, based on comparisons of mean trough serum TTR levels over 18 months in the TTR per-protocol population (secondary endpoint). The extent of the reduction in TTR was not affected by TTR genotype (45.1% of participants were V30M and 54.9% had 1 of 24 other mutations [21]), or patient age, sex, body weight or race [7, 21].

After 9 months of treatment in HELIOS-A, N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were unchanged from baseline in both the overall population and in the predefined cardiac subpopulation [those with pre-existing evidence of cardiac amyloid involvement (baseline left ventricular wall thickness ≥ 1.3 cm and no aortic valve disease or hypertension in medical history)] of the vutrisiran arm, whereas NT-proBNP had increased in the external placebo arm [22]. At 18 months, the geometric mean NT-proBNP level decreased from baseline with vutrisiran in the overall population [from 273.01 to 227.15 ng/L (n = 122)] and in the cardiac subpopulation [from 748.07 to 614.37 ng/L (n = 40)], but increased in the external placebo populations [from 531.3 to 844.4 ng/L in the overall population (n = 77) and from 711.10 to 1116.75 ng/L in the cardiac subpopulation (n = 36)] [22]. Scintigraphy imaging at month 18 in vutrisiran recipients showed that cardiac 99mTc uptake was reduced in 68.1% (measured by normalized left ventricular total uptake; 32/47 patients) and 64.6% (measured by heart-to-contralateral lung ratio; 31/48) of all evaluable patients and in 100% (25/25) and 76.9% (20/26) of those who were Perugini grade ≥ 2 at baseline [22].

Over 9 months of treatment with vutrisiran in HELIOS-A, mean steady state serum vitamin A levels were reduced by 62% [7]; reductions in serum vitamin A levels paralleled reductions in serum TTR levels in the vutrisiran and patisiran treatment groups [21]. No clinically relevant QT interval prolongation was evident when vutrisiran was administered at a dose 12 times the recommended subcutaneous dosage of 25 mg once every 3 months [7].

### 2.2 Pharmacokinetics

Peak plasma levels of vutrisiran increased dose proportionally and $AUC_{\text{last}}$ and $AUC_{\infty}$ values were slightly greater than dose proportional after a single subcutaneous 5 mg, 25 mg, 50 mg, 100 mg, 200 mg or 300 mg dose in a phase 1 trial (NCT02797847) in healthy volunteers [3]; however, accumulation was not evident after repeated administration of vutrisiran 25 mg every 3 months in patients with hATTR amyloidosis [7]. Plasma concentrations of vutrisiran were detectable at 10 minutes after subcutaneous administration [3] and peak plasma concentrations were seen at a median 4 h after subcutaneous administration of a 25 mg single dose in healthy volunteers [7]. The apparent volume of distribution of vutrisiran is estimated to be 10.1 L [7]. Vutrisiran is 80% plasma protein bound; however, plasma protein binding is concentration dependent and decreases with increasing vutrisiran concentrations (from 78% at 0.5 µg/mL to 19% at 50 µg/mL). Vutrisiran distributes mainly to the liver after subcutaneous administration [7].

Vutrisiran is metabolized by endo- and exonucleases to short nucleotide fragments of varying sizes within the liver. After a 25 mg single dose of subcutaneous vutrisiran in healthy volunteers, the median elimination half-life was 5.2 h and the median apparent clearance was 21.4 L/h [7]. The primary pathway for excretion of vutrisiran is via the kidneys, although the fraction of renal clearance to total clearance was 15.5–27.5% after a single 5–300 mg subcutaneous dose in healthy volunteers, indicating that renal excretion is a minor route of elimination. The mean renal clearance of vutrisiran was 4.5–5.7 L/h after a single subcutaneous 5–300 mg dose in healthy volunteers and the mean fraction of unchanged vutrisiran in urine after a 25 mg dose was ≈ 19.4% and most was excreted within the first 12 h after administration [3, 7].

Age, sex, bodyweight, race, and mild or moderate kidney impairment or mild hepatic impairment do not have clinically significant effects on vutrisiran pharmacokinetics [3, 7]. Vutrisiran has not been studied in patients with severe kidney impairment, end-stage kidney disease, moderate or severe hepatic impairment, or in patients with prior liver transplant [7].

In vitro, vutrisiran was neither a substrate nor inhibitor of cytochrome P450 enzymes and is not expected to cause drug-drug interaction by inducing CYP enzymes. Vutrisiran is not expected to modulate drug transporter activities [7].
Features and properties of vutrisiran

Alternative names

Class: Amides; Amino sugars; Drug conjugates; Pyrrolidines; Small interfering RNA

Mechanism of action: Prealbumin expression inhibitors; RNA interference

Route of administration: Subcutaneous

Pharmacodynamics: Chemically modified double-stranded siRNA that targets and degrades mutant and wild-type TTR mRNA through RNA interference, resulting in reductions of serum TTR protein and TTR protein deposits in tissues. In a dose-ranging trial, reduced serum TTR in a dose-dependent manner and reduced vitamin A levels

Pharmacokinetics: C_{max} dose proportional, AUC slightly more than dose proportional but no accumulation at the approved 25 mg dose. Protein binding is concentration dependent and decreases with increasing vutrisiran concentrations. Distributed mainly to the liver. Median T_{max} 4 h, Vd/F 10.1 L, median t_{1/2} 5.2 h, median CL/F 21.4 L/h, mean CLR 4.5–5.7 L/h

Adverse events

Most frequent: Pain in extremities, arthralgia, injection-site reactions

ATC codes

WHO ATC code: N07X-X18 (Vutrisiran)

EphMRA ATC code: A16A (Other Alimentary Tract and Metabolism Products)

2.3 Therapeutic Trials

Subcutaneous vutrisiran administered every 3 months significantly improved neuropathy impairment versus the external placebo control in patients with polyneuropathy caused by hATTR amyloidosis in the phase 3 randomized, open-label HELIOS-A trial (NCT03759379) [7, 21]. In this study, 164 patients were randomized to receive subcutaneous vutrisiran 25 mg once every 3 months (n = 122) or IV patisiran 0.3 mg/kg every 3 weeks as a reference group (n = 42) for 18 months. The primary efficacy endpoint was the change from baseline to month 9 in modified Neuropathy Impairment Score +7 (mNIS+7) [7, 21]; efficacy assessments were based on a comparison of the vutrisiran arm with an external placebo group (n = 77) from the phase 3 APOLLO trial of patisiran (NCT01960348) [23] in patients with hATTR amyloidosis with polyneuropathy [7, 21].

Treatment with vutrisiran in HELIOS-A resulted in significant improvements in mNIS+7 at month 9 compared with external placebo [least squares mean (LSM) change from baseline −2.24 vs +14.76; LSM treatment difference −17.0 (95% CI −21.78 to −12.22); p < 0.001] [7, 21]. 50.4% of vutrisiran recipients showed improvement from baseline in mNIS+7 compared with 18.2% in the external placebo group [OR 4.8 (95% CI 2.4–9.5); nominal p < 0.001] [21]. The clinical meaningfulness of the effects of vutrisiran on mNIS+7 was shown in the significant improvements with vutrisiran at month 9 compared with external placebo in the patient-reported Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score [LSM change from baseline −3.3 vs +12.9; LSM treatment difference −16.2 (95% CI −21.7 to −10.8); p < 0.001]. 53.4% of vutrisiran recipients showed improvement from baseline in the Norfolk QoL-DN total score at month 9 compared with 23.4% in the external placebo group [OR 4.0 (95% CI 2.1–7.8); nominal p < 0.001] [21]. Gait speed, assessed by changes from baseline in the 10-meter walk test, was also significantly improved at month 9 with vutrisiran compared with the external placebo group [LSM change from baseline −0.001 vs −0.133 m/s; LSM treatment difference 0.131 m/s (95% CI 0.070–0.193); p < 0.001] [7, 21]. Improvements in mNIS+7 and the Norfolk QoL-DN total score at month 9 favoured vutrisiran relative to external placebo, regardless of patient age, sex, race, geographic region, NIS score, V30M genotype status, previous tetramer stabilizer use, disease stage and cardiac subpopulation status [7, 21].

At month 18 in HELIOS-A, significant improvements in mNIS+7 continued to be observed in vutrisiran recipients compared with the external placebo group [LSM change from baseline −0.46 vs +28.1; LSM treatment difference −28.6 (95% CI −34.0 to −23.1); p < 0.001] [21]. 48.3% of vutrisiran recipients showed an improvement from baseline in mNIS+7 compared with 3.9% of external placebo recipients [OR 22.9 (95% CI 6.8–76.9); nominal p < 0.001] [21]. Likewise, significant improvements in the Norfolk QoL-DN total score were seen at month 18 with vutrisiran compared with external placebo [LSM change from baseline −1.2 vs +19.8; LSM treatment difference −21.0 (95% CI −27.1 to −14.9); p < 0.001]; 56.8% of vutrisiran recipients had an improvement from baseline in the Norfolk QoL-DN total score compared with 3.9% of external placebo recipients [OR 22.9 (95% CI 6.8–76.9); nominal p < 0.001] [21]. Likewise, significant improvements in the Norfolk QoL-DN total score were seen at month 18 with vutrisiran compared with external placebo [LSM change from baseline −1.2 vs +19.8; LSM treatment difference −21.0 (95% CI −27.1 to −14.9); p < 0.001]; 56.8% of vutrisiran recipients had an improvement from baseline in the Norfolk QoL-DN total score compared with 3.9% of external placebo recipients [OR 22.9 (95% CI 6.8–76.9); nominal p < 0.001]. Improvements in mNIS+7 and the Norfolk QoL-DN total score at month 18 favoured vutrisiran relative to external placebo, regardless of patient age, sex, race, geographic region, NIS score, V30M genotype status, previous tetramer stabilizer use, disease stage and cardiac subpopulation status [21].
Significant improvements with vutrisiran compared with external placebo were seen at 18 months in the 10-metre walk test [LSM change from baseline − 0.024 vs − 0.264 m/s; LSM treatment difference 0.239 m/s (95% CI 0.154–0.325); \( p < 0.001 \)], modified body mass index (mBMI) [LSM change from baseline +25.0 vs −115.7; LSM treatment difference 140.7 (95% CI 108.4–172.9); \( p < 0.001 \)] and Rasch-built Overall Disability Scale [LSM change from baseline −1.5 vs −9.9; LSM treatment difference 8.4 (95% CI 6.5–10.4); \( p < 0.001 \)] [21].

At baseline in the vutrisiran arm, the mean mNIS+7 score was 60.6, the mean Norfolk QoL-DN was 47.1, the mean 10-metre walk test was 1.01 m/s and the mean mBMI was 1057.5; respective mean values at baseline for these endpoints in the external placebo group were 74.6, 55.5, 0.79 m/s and 989.9 [7, 21]. 70% of patients were in Stage 1 of hATTR amyloidosis with polyneuropathy and 30% were in Stage 2 [7]. Vutrisiran and patisiran recipients who completed the randomized phase of HELIOS-A were eligible to enter a randomized treatment extension period in which all patients receive either subcutaneous vutrisiran 25 mg once every 3 months or subcutaneous vutrisiran 50 mg once every 6 months [21].

### 2.4 Adverse Events

Subcutaneous vutrisiran was generally well tolerated during 18 months’ treatment in the HELIOS-A trial (NCT03759379) [21]. Almost all vutrisiran (97.5%; \( n = 122 \)) and patisiran (97.6%; \( n = 42 \)) recipients reported an adverse event, an outcome comparable with the adverse events rate reported in the external placebo arm (97.4%; \( n = 77 \)) [21]. Most adverse events reported in vutrisiran recipients were mild or moderate in severity; severe adverse events were reported in 15.6% of vutrisiran recipients compared with 38.1% of patisiran recipients and 36.4% of those in the external placebo group [21]. Serious adverse events were reported in 26.2% of vutrisiran recipients, 42.9% of patisiran recipients and 40.3% of those in the external placebo arm [21]. Two patients (1.6%) experienced serious adverse events considered related to vutrisiran (dyslipidemia and urinary tract infection). No cardiac adverse events related to vutrisiran were reported in HELIOS-A and there were no drug-related treatment discontinuations or deaths with vutrisiran [21]. The most common adverse events (≥ 10%) in vutrisiran recipients were falls (18% in the vutrisiran arm, vs 14.3% in the patisiran arm and 28.6% in the external placebo arm), pain in extremity (14.8% vs 7.1% and 10.4%), diarrhea (13.9% vs 16.7% and 37.7%), peripheral edema (13.1% vs 9.5% and 22.1%), urinary tract infection (13.1% vs 19.0% and 18.2%), arthralgia (10.7% vs 9.5% and 0%) and dizziness (10.7% vs 0% and 14.3%). Only pain in the extremities and arthralgia occurred more frequently in vutrisiran than external placebo recipients [21].

Injection site reactions, all of which were transient and mild in severity, were reported in five (4.1%) vutrisiran recipients [7, 21]. There were no safety signals related to vutrisiran in relation to liver function tests, renal function tests or hematology in HELIOS-A [21].

Four vutrisiran recipients (3.3%) developed antidrug antibodies (ADAs) in HELIOS-A [21]. ADA titers were transient and low [21] and did not appear to affect vutrisiran pharmacokinetics, pharmacodynamics, clinical efficacy and safety [7, 21].

### 2.5 Ongoing Clinical Trials

Both HELIOS trials of quarterly subcutaneous vutrisiran 25 mg [HELIOS-A in hATTR amyloidosis with polyneuropathy (NCT03759379) and HELIOS-B [12] in ATTR amyloidosis with cardiomyopathy (NCT04153149)] are ongoing. The HELIOS-A randomized treatment extension period is also investigating the efficacy of a subcutaneous 50 mg biannual dosing regimen as well as the 25 mg quarterly regimen [10, 11].

### 3 Current Status

Vutrisiran received its first approval on 13 June 2022 for the treatment of the polyneuropathy of hATTR in adults in the USA [7, 8]. On 21 July 2022, vutrisiran received a positive
opinion in the EU for the treatment of hATTR amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy [9, 10].

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Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

References

1. Aimo A, Castiglione V, Rapezzi C, et al. RNA-targeting and gene editing therapies for transthyretin amyloidosis. Nat Rev Cardiol. 2022. https://doi.org/10.1038/s41569-022-00683-z.
2. Ando Y, Adams D, Benson MD, et al. Guidelines and new directions in the therapy and monitoring of ATTRv amyloidosis. Amyloid. 2022. https://doi.org/10.1080/13506129.2022.2052838.
3. Habtemariam BA, Karsten V, Attarwala H, et al. Single-dose pharmacokinetics and pharmacodynamics of transthyretin targeting N-acetylgalactosamine-small interfering ribonucleic acid conjugate, vutrisiran, in healthy subjects. Clin Pharmacol Ther. 2021;109(2):372–82.
4. Tschöpe C, Elseenhoury A. Treatment of transthyretin amyloid cardiomyopathy: the current options, the future, and the challenges. J Clin Med. 2022;11(8):2148.
5. Luigetti M, Romano A, Di Paolantonio A, et al. Diagnosis and treatment of hereditary transthyretin amyloidosis (hATTR) polyneuropathy: current perspectives on improving patient care. Ther Clin Risk Manag. 2020;16:109–23.
6. Alnylam Pharmaceuticals Inc. Hereditary ATTR amyloidosis; 2022. https://www.alnylam.com/. Accessed 4 Jul 2022.
7. Alnylam Pharmaceuticals Inc. AMVUTTRA (vutrisiran): US prescribing information; 2022. https://www.amvuttra.com/. Accessed 27 June 2022.
8. Alnylam Pharmaceuticals Inc. Alnylam announces FDA approval of AMVUTTRA™ (vutrisiran), an RNAi therapeutic for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults [media release]. 13 June 2022. https://investors.alnylam.com/.
9. European Medicines Agency. Amvuttra (vutrisiran): Committee for Medicinal Products for Human Use (CHMP) summary of opinion; 2022. https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-amvuttra_en.pdf. Accessed 28 Jul 2022.
10. Alnylam Pharmaceuticals Inc. Alnylam receives positive CHMP opinion for vutrisiran for the treatment of hereditary transthyretin-mediated (hATTR) amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy [media release]. 22 Jul 2022. https://investors.alnylam.com/.
11. Alnylam Pharmaceuticals Inc. Alnylam announces new advances in ATTR amyloidosis program [media release]. 11 May 2021. http://www.alnylam.com.
12. Shilling R, Karsten V, Silliman N, et al. Study design and rationale of HELIOS-B: a phase 3 study to evaluate the clinical efficacy and safety of vutrisiran in patients with ATTR amyloidosis with cardiomyopathy [abstract no. 1323–359]. J Am Coll Cardiol. 2020;75(11 Suppl. 1):3579.
13. Blackstone Life Sciences. Blackstone and Alnylam close $150 million R&D financing to advance RNAi therapeutics for cardiovascular disease [media release]. 17 Aug 2020. http://www.blackstone.com.
14. Blackstone Life Sciences, Alnylam Pharmaceuticals Inc. Blackstone and Alnylam enter into $2 billion strategic financing collaboration to accelerate the advancement of RNAi therapeutics [media release]. 8 May 2020. http://www.blackstone.com.
15. Sanofi, Alnylam Pharmaceuticals Inc. Sanofi and Alnylam conclude research and option phase of 2014 rare disease alliance [media release]. 8 Feb 2021. https://www.alnylam.com.
16. Alnylam Pharmaceuticals Inc. Alnylam and Sanofi enter into strategic restructuring of RNAi therapeutics rare disease alliance [media release]. 7 Jan 2018. https://investors.alnylam.com/.
17. Genzyme, Alnylam Pharmaceuticals Inc. Genzyme and Alnylam expand collaboration on rare genetic diseases [media release]. 13 Jan 2014. http://www.genzyme.com.
18. Alnylam Pharmaceuticals Inc. Genzyme exercises its right to purchase additional shares of Alnylam common stock [media release]. 26 Mar 2014. http://www.alnylam.com.
19. Alnylam Pharmaceuticals Inc. Alnylam announces closing of previously announced alliance with Genzyme for discovery, development, and commercialization of RNAi therapeutics as genetic medicines [media release]. 27 Feb 2014. http://www.alnylam.com.
20. Alnylam Pharmaceuticals Inc., Genzyme. Alnylam and Genzyme form alliance to develop and commercialize RNAi therapeutics in Asia [media release]. 22 Oct 2012. http://www.alnylam.com.
21. Adams D, Tournev IL, Taylor MS, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. Amyloid. 2022. https://doi.org/10.1080/13506129.2022.2091985.
22. Garcia-Pavia P., Gillmore J, Kale P, et al. HELIOS-A: 18-month exploratory cardiac results from the phase 3 study of vutrisiran in patients with hereditary transthyretin-mediated amyloidosis. In: Heart Failure 2022 and World Congress on Heart Failure; 2022.
23. Adams D, Gonzalez-Duarte A, O’Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med. 2018;379(1):11–21.

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