FDA Approval of Vutrisiran Brings New Treatment for ATTR-CM

When Sean Riley started getting numbness in his hands, he saw a local surgeon who performed carpal tunnel surgery on both his wrists. At the time, he didn't think much of his symptoms, knowing carpal tunnel was common, he attributed his symptoms to the typing he occasionally did. Then, the numbness appeared in his left foot and ankle.

Riley continued with his daily living, but about two years later, he started to feel dizzy and had an uneasiness in his chest. An ambulance took him to the hospital, where they performed the typical tests for someone presenting with a cardiac event, but they all came back negative. The doctor tried to rule out cancer and other malignancies via a CT scan, but once again, could not detect anything was wrong.

It took seven years from the onset of his symptoms for Riley to finally be diagnosed with Hereditary Amyloidosis — a rare and progressive disease that is even more deadly if diagnosed late. While there is currently no cure for the disease, Alnylam Pharmaceuticals has recently secured approval from the U.S. Food and Drug Administration (FDA) for its drug Amvuttra (vutrisiran) for the treatment of cardiomyopathy of wild-type and hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce the chance of cardiovascular death, hospitalizations, and urgent heart failure visits.

Transthyretin amyloidosis: undiagnosed and untreated

Transthyretin amyloidosis, also called ATTR, is a rapidly progressive and ultimately fatal disease caused by misfolded transthyretin proteins. As these proteins accumulate as amyloid fibrils in

multiple organs, they can cause irreversible damage over time and lead to premature death (1). When amyloid deposits build up in the heart, the walls can become stiff, preventing the left ventricle from properly relaxing to fill with blood, a condition known as cardiomyopathy. As the disease progresses, the heart is eventually unable to adequately squeeze and pump out blood, leading to heart failure.

There are two types of ATTR amyloidosis with cardiomyopathy (ATTR-CM): hereditary ATTR-CM (hATTR), estimated to affect around 50,000 people worldwide, and wild-type ATTR-CM (wtATTR), affecting approximately 200,000 - 300,000 people worldwide. In hereditary ATTR-CM, which can be passed down in families, a variant in the transthyretin gene causes amyloid deposits in the heart, nerves, and potentially other organs. Typically, symptoms present later in life but may start as early as 30. Wild-type ATTR-CM occurs without a transthyretin gene variant and doesn't run in families and typically presents much later in life.

Symptoms can include shortness of breath even when at rest or with minimal exertion, lower extremity swelling, increased heart rate, abnormal heart rhythms, and confusion or trouble thinking. Other symptoms may include carpal tunnel syndrome and pain and numbness in the hands and feet, known as peripheral neuropathy.

"Despite recent advances, there remains a significant need for patients living with ATTR-CM and I've witnessed, firsthand, the impact that ATTR amyloidosis can have on families, including diminished quality of life and the loss of loved ones," said Muriel Finkel, President of the Amyloidosis Support Groups.

Patients with ATTR-CM have a median survival rate of two to six years after diagnosis (1), and most patients remain undiagnosed and untreated. In the condition's early stages, its symptoms may mimic other conditions like heart failure caused by high blood pressure, hypertension, or hypertrophic cardiomyopathy.

Sean Riley saw an inventory of specialists prior to diagnosis — internists, endocrinologists, oncologists, neurologists, and even a psychologist because they believed he could be a hypochondriac. Riley continued to advocate for himself until he was diagnosed despite beginning to feel like a nuisance to some of the doctors.

The challenge of undiagnosed and untreated patients remains relevant today. However, advances in noninvasive imaging techniques in the past decade have led to more patients receiving earlier diagnoses (1).

Inotersen and eplontersen are ASOs that have been approved to treat ATTR-PN. Eplontersen's safety and efficacy are also currently being evaluated in the CARDIO-TTRansform Phase 3 trial in a cohort of over 1,400 ATTR-CM patients, and the trial outcome is expected to readout in 2026.

However, until recently, the only approved treatment option for ATTR-CM in the US was tafamidis. While it is approved in many other countries to treat ATTR-PN in early stages, it has not received FDA-approval for this indication. Tafamidis is an oral medication that helps stabilize the transthyretin molecule by binding to the transthyretin protein, preventing it from misfolding and forming harmful amyloid deposits, and it has been shown to reduce disease progression and mortality.

Attruby (acoramidis) is an oral medication that was approved in November 2024 to treat adults with ATTR-CM, to reduce death and hospitalization related to heart problems. Like tafamidis, acoramidis is a TTR stabilizer.

While patients undergoing treatment with the limited available therapies show a reduction in all-cause mortality and cardiovascular hospitalizations compared to placebo, overall mortality remains high, and quality of life and functional capacity continue to deteriorate (1). However, the March 2025 approval of vutrisiran to treat ATTR-CM marks the first and only therapy approved by the FDA for the treatment of both polyneuropathy (hATTR-PN) in adults — which it received earlier approval for in June 2022 – and ATTR-CM.

The FDA's green light for the therapy was based largely on the HELIOS-B Phase 3 clinical trial data first published in The New England Journal of Medicine in August 2024 (1).

Vutrisiran: targeting the disease at its source

Vutrisiran is an RNA interference (RNAi) therapy that works by targeting and silencing specific messenger RNA (mRNA), providing knockdown of the transthyretin (TTR) gene before the wild-type and variant transthyretin protein can be made. By quickly lowering TTR production, the drug reduces the deposition of TTR fibrils, which form the amyloid that causes permanent cardiovascular damage and eventually death in patients with ATTR-CM. Vutrisiran uses Alnylam's Enhanced Stabilization Chemistry (ESC) GalNAc-conjugate delivery platform, designed for increased potency and stability that allows for fewer subcutaneous injections at only four doses per year.

Clinical trial results: a significant drop in the risk of cardiac events

The HELIOS-B trial, funded by Alnylam, was a double-blind, randomized trial that assigned 655 patients to receive either 25 mg of vutrisiran or a placebo every 12 weeks for up to 36 months for treatment of ATTR-CM (1).

The primary endpoint was a composite of death from any cause and recurrent cardiovascular events. Secondary endpoints included death from any cause and changes from baseline in the distance covered on the 6-minute walk test and Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score (1).

The trial, which met all 10 of its primary and secondary endpoints, showed that vutrisiran treatment in the overall patient population led to a lower risk of all-cause mortality (ACM) and

cardiovascular (CV) events by 28% compared to placebo during the treatment period of up to 36 months (1). That same study population experienced a significant 36% mortality drop through 42 months including an open-label extension period of the study (1). Additionally, vutrisiran treatment in the overall population resulted in less of a decline in the distance covered on the 6-minute walk test than the placebo and less of a drop in the KCCQ-QS score (1). All endpoints were assessed separately in the overall population and the monotherapy population (the patients who were not receiving tafamidis at baseline) (1), with similar benefits found in the monotherapy population.

The rate of adverse events (AEs) was similar in both the vutrisiran and placebo groups, with serious AEs occurring in approximately 62% and 67% of patients, respectively. No new safety concerns were found in the study beyond those already identified in the previous HELIOS-A trial assessing patients with hATTR-PN; the most common AEs in those treated with vutrisiran were pain in extremities (15%), arthralgia (11%), dyspnea (7%), and decreases in vitamin A (7%) (1).

The study authors note that several limitations should be considered when interpreting the trial results, including the fact that tafamidis was a permitted background therapy at baseline, to which patients were not randomly assigned.

"Therefore, this trial does not allow for a randomized comparison of vutrisiran alone with tafamidis alone," the authors state. "In addition, although 40% of the patients were taking tafamidis at baseline, the trial was not powered to show statistical significance within this subgroup" (1).

The authors also note that most of the patients were White men, mostly with wild-type forms of the condition. However, this demographic is consistent with ATTR-CM patient populations (1).

"I would like to extend my deepest gratitude to the patients who participated in our clinical trials, their families and caregivers, the clinical researchers, regulators, and my colleagues at Alnylam who made this approval possible. Today represents a significant milestone in our nearly twenty years of partnership with the ATTR amyloidosis community, but we are not stopping here. We will continue to innovate for patients with ATTR amyloidosis so they can live longer, better, healthier lives," said Yvonne Greenstreet, MBChB, Chief Executive Officer of Alnylam in a press release.

Amyloidosis Support Groups, a nonprofit organization focused on helping patients with cardiac amyloidosis, shared that the approval of vutrisiran is a significant moment for patients living with the disease and represents a beacon of hope for the community.

Now that there are three approved ATTR-CM treatments — Pfizer's tafamidis, BridgeBio's acoramidis, and Alnylam's vutrisiran — patients have more options than ever.

The future of transthyretin amyloidosis treatment: amazing strides

Before Sean Riley was diagnosed, he had never heard of amyloidosis, nor was he aware that the tingling sensation in his hands and feet were telltale early symptoms of the disease. While Riley says the diagnosis can be daunting, he says that medicine has advanced and improved the disease outlook.

"We're at a point now where it doesn't have to be a fatal disease, it can be a manageable disease… there's just amazing strides being made towards finding more advanced treatments and eventually a cure for this disease," he says.

The recent FDA approval of vutrisiran is one such stride, offering a new treatment option that has demonstrated significant benefits in reducing mortality and improving quality of life. With favorable outcomes from the HELIOS-B trial, vutrisiran represents a significant advancement in managing this rare disease.

References:

1. Fontana M, Berk JL, Gillmore JD, Witteles RM, Grogan M, Drachman B, Damy T, Garcia-Pavia P, Taubel J, Solomon SD, Sheikh FH, Tahara N, González-Costello J, Tsujita K, Morbach C, Pozsonyi Z, Petrie MC, Delgado D, Van der Meer P, Jabbour A, Bondue A, Kim D, Azevedo O, Hvitfeldt Poulsen S, Yilmaz A, Jankowska EA, Algalarrondo V, Slugg A, Garg PP, Boyle KL, Yureneva E, Silliman N, Yang L, Chen J, Eraly SA, Vest J, Maurer MS; HELIOS-B Trial Investigators. Vutrisiran in Patients with Transthyretin Amyloidosis with Cardiomyopathy. N Engl J Med. 2025 Jan 2;392(1):33-44. doi: 10.1056/NEJMoa2409134. Epub 2024 Aug 30. PMID: 39213194.