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DOI: 10.5582/ddt.2025.01111

Elamipretide: The first cardiolipin-directed mitochondrial therapeutic for Barth syndrome approved under accelerated approval

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SUMMARY: Barth syndrome (BTHS) is a rare X-linked mitochondrial disorder caused by *tafazzin* mutations that impair cardiolipin remodeling, leading to mitochondrial dysfunction and symptoms such as cardiomyopathy, myopathy, and neutropenia. On September 19, 2025, the U.S. Food and Drug Administration (FDA) granted accelerated approval to elamipretide, the first therapy directly targeting the mitochondrial etiology of BTHS. Elamipretide binds to cardiolipin on the inner mitochondrial membrane, stabilizing respiratory chain supercomplexes, enhancing electron transport efficiency, and reducing reactive oxygen species production. In a randomized, double-blind, placebo-controlled, crossover trial, elamipretide resulted in no significant improvement in the 6-minute walk test or fatigue scores; however, sustained benefits were observed during a 168-week open-label extension. The most common adverse events were mild injection-site reactions. As a condition of accelerated approval, a confirmatory trial is required. Elamipretide represents a promising therapy addressing an unmet medical need in BTHS and provides a foundation for future mitochondria-targeted treatments.

Keywords: Barth syndrome, elamipretide, X-linked mitochondrial disorder, mitochondria-targeted therapeutic drugs

Barth syndrome (BTHS) is an X-linked recessive genetic mitochondrial disorder caused by mutations in the *tafazzin* gene located at region q28 of the X chromosome (*1*). The estimated incidence of BTHS is approximately 1 in 300,000 to 400,000 individuals, making it as a rare disease (*2,3*). Dysfunction of tafazzin impairs the synthesis of cardiolipin, a principle phospholipid component of the inner mitochondrial membrane, resulting in reduced stability of the mitochondrial structure and the electron transport chain, abnormal mitochondrial energy metabolism, and the onset of symptoms such as cardiomyopathy, skeletal myopathy, growth delay, neutropenia and increased urinary excretion of 3-methylglutaconic acid (3-MGCA) (*4*). The management of BTHS requires a multidisciplinary approach aimed at providing symptomatic support and preventing complications, including pharmacological management of dilated cardiomyopathy, cardiac transplantation, antibiotic prophylaxis, and granulocyte colony-stimulating factor (G-CSF) therapy. Currently, no targeted therapies address the underlying etiology of the disease.

On September 19, 2025, the U.S. Food and Drug Administration (FDA) granted accelerated approval to elamipretide for the treatment of BTHS, marking the first approval of a therapeutic agent directly targeting the mitochondrial etiology of disease (*5*). Elamipretide has a pharmacological effect by specifically binding to cardiolipin on the inner mitochondrial membrane, which promotes and stabilizes the assembly of respiratory chain supercomplexes, thereby enhancing electron transport efficiency and overall mitochondrial function (6). This mechanism significantly reduces electron leakage and excessive generation of reactive oxygen species (ROS), while simultaneously improving adenosine triphosphate (ATP) synthesis (*6*). In addition, elamipretide suppresses cardiolipin peroxidation and prevents cytochrome c release, effectively blocking the mitochondria-mediated apoptotic pathway and restoring normal mitochondrial cristae morphology (*6*). Collectively, these pleiotropic actions correct the fundamental biochemical abnormalities characteristic of BTHS, including a disrupted mitochondrial structure and impaired energy metabolism.

The efficacy and safety of elamipretide were assessed in a randomized, double-blind, placebo-controlled,

crossover trial followed by an open-label, single-arm extension study (*7*). The randomized phase enrolled 12 patients genetically confirmed to have BTHS. Participants were randomly assigned to receive either elamipretide 40 mg or a placebo administered once daily by subcutaneous injection for 12 weeks, followed by a 4-week washout period before crossing over to the alternate treatment. The primary endpoints were changes in the 6-minute walk test (6MWT) distance and the Barth Syndrome Symptom Assessment (BTHS-SA) total fatigue score. Compared to a placebo, elamipretide did not result in statistically significant improvements in the 6MWT distance or BTHS-SA fatigue scores during the randomized phase (*7*). However, during the open-label extension (OLE) period, in which ten of the twelve participants were enrolled and eight completed the 168-week treatment, sustained improvements from the OLE baseline were observed at all time points in both the 6MWT distance and mean BTHS-SA total fatigue scores (*8*). Moreover, although increases in knee extensor muscle strength — a secondary endpoint — were not detected during the randomized phase, they became apparent during the extension period (*9*). The most frequently reported adverse events were injection-site reactions, including erythema, pain, induration, pruritus, bruising, and urticaria (*8,9*).

As a condition of the accelerated approval, the FDA requires a randomized, double-blind, placebo-controlled trial to confirm the efficacy and safety of elamipretide. Nevertheless, elamipretide represents a promising therapeutic option that may address the current unmet medical need in BTHS and offers hope for improving patients' quality of life. Moreover, its innovative mechanism — specifically targeting mitochondrial cardiolipin — provides valuable insights and inspiration for the development of novel targeted therapies for other mitochondrial disorders.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received October 7, 2025; Revised November 9, 2025; Accepted November 17, 2025.

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Released online in J-STAGE as advance publication November 20, 2025.