

RESEARCH MONOGRAPH . COMPOUND PROFILE

Elamipretide

A first-in-class cardiolipin-binding tetrapeptide developed by Szeto and Schiller that stabilizes mitochondrial cristae architecture, restores electron transport chain supercomplex function, and received FDA accelerated approval for Barth syndrome as the first mitochondria-targeted peptide therapeutic.

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ABSTRACT

Elamipretide (D-Arg-2',6'-dimethylTyr-Lys-Phe-NH₂; also designated SS-31, MTP-131, and Bendavia) is a synthetic aromatic-cationic tetrapeptide that concentrates more than 1000-fold in the inner mitochondrial membrane, where it binds cardiolipin and modulates membrane surface electrostatics to stabilize cristae architecture, optimize electron transport chain supercomplex assembly, and reduce reactive oxygen species generation at the mitochondrial source. Discovered fortuitously by Hazel Szeto and Peter Schiller during opioid receptor research, the compound was characterized in a foundational 2004 report demonstrating nanomolar-range cytoprotection against oxidative cell death and reperfusion injury in isolated mitochondria and ex vivo cardiac tissue. Biophysical studies by Mitchell et al. (2020) have since established that the primary mechanism is not stoichiometric antioxidant scavenging but rather electrostatic modulation of anionic lipid bilayer properties: SS-31 partitions into the membrane interfacial region with a dissociation constant of 2.0 to 2.9 micromolar for cardiolipin-containing membranes, saturably reduces surface potential, and decreases interfacial divalent cation accumulation by over an order of magnitude; these effects are independent of mitochondrial membrane potential. In freshly explanted failing human heart tissue, elamipretide at 100 micromolar selectively restored Complex I-driven oxygen flux, supercomplex coupling, and respiratory control ratio without affecting non-failing hearts, confirming a disease-selective mechanism operating through cardiolipin-protein interaction stabilization rather than cardiolipin remodeling. Stealth BioTherapeutics advanced elamipretide through clinical programs

in Barth syndrome (TAZPOWER), primary mitochondrial myopathy (MMPOWER series), heart failure with reduced ejection fraction (PROGRESS-HF, EMBRACE-STEMI), and dry age-related macular degeneration (ReCLAIM series). The Barth syndrome program, conducted in patients with tafazzin gene mutations and defective cardiolipin remodeling, demonstrated sustained improvements in six-minute walk distance (cumulative 96.1 meters at 168 weeks, $P = 0.003$) and knee extensor muscle strength in the open-label extension, leading to FDA accelerated approval in September 2025 under the brand name FORZINITY for improvement of muscle strength in adult and pediatric patients weighing at least 30 kilograms. The 12-week randomized crossover portion of TAZPOWER did not meet its primary endpoints, and the pivotal Phase 3 trial in primary mitochondrial myopathy (MMPOWER-3, $n = 218$) did not meet co-primary endpoints on six-minute walk test and fatigue score, though post hoc analysis identified a responding subgroup with nuclear DNA replisome pathogenic variants and chronic progressive external ophthalmoplegia phenotype. Heart failure and macular degeneration trials similarly did not meet primary endpoints, though exploratory signals in cardiac volume reduction and ellipsoid zone preservation were observed. Pharmacokinetically, elamipretide is administered as a 40 mg subcutaneous injection once daily, with absolute bioavailability of approximately 92 percent, time to peak concentration of 0.5 to 1 hour, plasma elimination half-life of approximately 3 to 4 hours, and exclusively renal elimination with no hepatic metabolism and no cytochrome P450 interactions. This monograph reviews the chemistry and structure, discovery history, cardiolipin-binding pharmacology, pharmacokinetics, preclinical evidence across cardiac, renal, neuroinflammatory, and aging models, the complete clinical trial

inventory across all studied indications, sourcing and quality verification, handling, drug interactions, adverse event profile, and a comparative assessment of five mitochondrial therapeutics (idebenone, omaveloxolone, MitoQ, vatiquinone, and coenzyme Q10) against elamipretide on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Elamipretide.

Brand name: FORZINITY (Stealth BioTherapeutics Inc.; FDA-approved September 2025 for Barth syndrome) [26].

Development codes: SS-31 (Szeto-Schiller peptide 31, the original laboratory designation from the Szeto-Schiller peptide series at Cornell University); MTP-131 (Stealth BioTherapeutics clinical development code); Bendavia (early clinical formulation name, used during cardiac-protection trials including EMBRACE-STEMI); SBT-020 (designation used in the Huntington's disease clinical program) [1, 2, 4, 20].

Chemical Abstracts Service registry number: 736992-21-5 (free base).

PubChem CID: 11764719 [PubChem].

International Union of Pure and Applied Chemistry name: (2S)-6-amino-2-[[[(2R)-2-amino-5-(diaminomethylideneamino)pentanoyl]amino]-N-[(2S)-1-amino-1-oxo-3-phenylpropan-2-yl]-N'-[(4-hydroxy-3,5-dimethylphenyl)methyl]hexanedi- amide. The compound is more commonly designated by its peptide sequence: D-Arg-2',6'-dimethylTyr-Lys-Phe-NH₂ [4, 26].

1.2 Structural class and chemistry

Elamipretide is a synthetic aromatic-cationic tetrapeptide belonging to the Szeto-Schiller (SS) peptide class, a family of short peptides characterized by alternating aromatic and basic amino acid residues [1, 2]. The structural motif centers on the pairing of positively charged residues (D-arginine at position 1, lysine at position 3) with hydrophobic aromatic residues (2',6'-dimethyltyrosine at position 2, phenylalanine at position 4). The C-terminus is amidated. The D-configuration of the arginine residue confers resistance to aminopeptidase degradation and extends plasma residence compared to the all-L enantiomer [2].

Molecular formula: C₃₂H₄₉N₉O₅ (free base); C₃₂H₄₉N₉O₅ * 3HCl (trihydrochloride salt) [26].

Molecular weight: Approximately 639.8 g/mol (free base, calculated); 749.2 g/mol (trihydrochloride salt) [26].

Physical properties: The trihydrochloride salt is supplied as a sterile, clear, colorless to yellow aqueous solution for injection at a concentration of 80 mg/mL (280 mg per 3.5 mL single-patient-use vial) [26]. The compound is freely water-soluble owing to the net positive charge at physiological pH (two cationic residues, D-Arg and Lys, contribute a net charge of approximately +3 at pH 7.4). The solution pH range is 4.7 to 6.1. The formulation contains benzyl alcohol (10 mg per 0.5 mL dose) as a preservative and monobasic sodium phosphate (2.07 mg per 0.5 mL dose) as a buffer [26].

Stereochemistry: Elamipretide contains multiple stereocenters contributed by the amino acid residues. The compound is supplied as a single stereoisomer with the defined configuration: D-arginine (R-configuration) at position 1 and L-configuration at positions 2 (dimethyltyrosine), 3 (lysine), and 4 (phenylalanine) [4].

1.3 Synthesis

The published synthesis of elamipretide employs standard solid-phase peptide synthesis (SPPS) methodology. The four amino acid residues are assembled sequentially on a resin support using Fmoc (9-fluorenylmethoxycarbonyl) or Boc (tert-butyloxycarbonyl) protection chemistry, with the non-standard residue 2',6'-dimethyltyrosine (Dmt) incorporated as a pre-synthesized protected building block. The D-arginine at position 1 is commercially available as the Fmoc-D-Arg(Pbf)-OH derivative. Following chain assembly, the peptide is cleaved from the resin with simultaneous side-chain deprotection using trifluoroacetic acid, purified by reverse-phase high-performance liquid chromatography, and converted to the trihydrochloride salt. The C-terminal amide is generated by use of a Rink amide resin linker [4]. Industrial-scale synthesis achieves the compound in high purity (greater than 95 percent by HPLC) with the defined stereochemistry confirmed by chiral analysis.

2. Abstract

Elamipretide (SS-31, MTP-131, Bendavia) is a water-soluble, aromatic-cationic tetrapeptide that concentrates more than 1000-fold in the inner mitochondrial membrane and binds cardiolipin to stabilize cristae architecture, optimize electron transport chain supercomplex function, and reduce reactive oxygen species at the mitochondrial source [1, 2, 3]. The compound received FDA accelerated approval in September 2025 as FORZINITY for improvement of muscle strength in adult and pediatric patients with Barth syndrome weighing at least 30 kilograms, representing the first regulatory approval of a mitochondria-targeted peptide therapeutic [26].

The pharmacological mechanism, initially characterized as targeted antioxidant activity, has been revised by biophysical studies demonstrating that the primary action is electrostatic modulation of the inner mitochondrial membrane surface potential through saturable partitioning into cardiolipin-rich bilayers [3]. In the failing human heart, elamipretide selectively restores supercomplex-associated respiratory chain function (Complexes I, III, and IV) without affecting non-failing tissue, consistent with stabilization of cardiolipin-dependent protein-lipid interactions within the respirasome [6].

Clinical development has spanned Barth syndrome, primary mitochondrial myopathy, heart failure with reduced ejection fraction, dry age-related macular degeneration, Huntington's disease, Friedreich's ataxia, and age-related skeletal muscle dysfunction. The TAZPOWER Barth syndrome program demonstrated statistically significant improvements in six-minute walk distance and muscle strength in a natural history comparison and sustained efficacy through 168 weeks of open-label treatment [14, 15]. Phase 3 trials in primary mitochondrial myopathy (MMPOWER-3) and Phase 2 trials in heart failure (PROGRESS-HF) and macular degeneration (ReCLAIM-2) did not meet their primary endpoints, though post hoc analyses and exploratory endpoints have identified responding subpopulations and biologically meaningful signals [9, 10, 13, 16].

Elamipretide is administered as a 40 mg subcutaneous injection once daily, with absolute bioavailability of approximately 92 percent, a plasma half-life of 3 to 4 hours, and exclusively renal elimination without hepatic metabolism or cy-

tochrome P450 interactions [20, 26]. The principal adverse events are injection site reactions, reported in up to 100 percent of treated subjects, the majority mild and self-limiting [26].

3. Discovery and Development History

3.1 Origin

The Szeto-Schiller (SS) peptide series was discovered fortuitously by Hazel H. Szeto and Peter W. Schiller at the Joan and Sanford I. Weill Medical College of Cornell University while conducting structure-activity studies on opioid receptor ligands [2, 4]. The investigators identified that certain tetrapeptides with alternating aromatic and basic amino acid residues concentrated more than 1000-fold in the inner mitochondrial membrane in a manner that was energy-independent, non-saturable, and not driven by the mitochondrial membrane potential [1, 2]. This observation led to the systematic exploration of the SS peptide series, culminating in SS-31 (D-Arg-Dmt-Lys-Phe-NH₂) as the lead compound with the optimal combination of mitochondrial targeting, cytoprotective potency, and metabolic stability [1].

3.2 Foundational characterization

The foundational report was published by Zhao et al. in 2004 in the *Journal of Biological Chemistry* [1]. This study demonstrated that SS peptides, including SS-31, (a) were cell-permeable and concentrated 1000-fold in the inner mitochondrial membrane; (b) potently reduced intracellular reactive oxygen species and cell death caused by tert-butylhydroperoxide in neuronal N2A cells with an EC₅₀ in the nanomolar range; (c) inhibited mitochondrial permeability transition and swelling and prevented cytochrome c release induced by calcium in isolated mitochondria; (d) prevented mitochondrial depolarization in cells treated with 3-nitropropionic acid; and (e) improved contractile force in an ex vivo heart model of ischemia-reperfusion injury [1]. Critically, peptide analogs lacking the dimethyltyrosine residue (such as SS-20) did not inhibit mitochondrial ROS generation or swelling and failed to prevent myocardial stunning, establishing the Dmt residue as essential for the antioxidant component of the pharmacology [1].

3.3 Clinical development

SS-31 entered clinical development in 2010 with Stealth BioTherapeutics (formerly Stealth Peptides Inc., Newton, Massachusetts) using the clinical designations MTP-131 and Bendavia for cardiovascular programs, and elamipretide for mitochondrial disease programs [4, 5]. Stealth BioTherapeutics obtained regulatory clearance for first-in-human studies and initiated a multi-indication clinical program:

The EMBRACE-STEMI trial (NCT01572909, Phase 2a) evaluated intravenous MTP-131 in acute anterior ST-elevation myocardial infarction with primary percutaneous coronary intervention, with results published in 2016 by Gibson et al. [11]. The MMPOWER series (NCT02367014, NCT02805790, NCT03323749) evaluated elamipretide in primary mitochondrial myopathy across Phases 1/2 through Phase 3, beginning in 2015 [7, 8, 9]. The TAZPOWER trial (NCT03098797) evaluated elamipretide in Barth syndrome beginning in 2017 [14, 15]. The ReCLAIM series (NCT02848313, NCT03891875) evaluated elamipretide in dry age-related macular degeneration beginning in 2016 [17, 18, 16]. The PROGRESS-HF trial (NCT02788747) evaluated subcutaneous elamipretide in heart failure with reduced ejection fraction, with results published in 2020 [13]. An investigator-initiated study in Friedreich's ataxia (NCT05168774) and a Phase 2 study of SBT-020 in Huntington's disease were also conducted [20].

3.4 Regulatory approval

The FDA granted Fast Track and Orphan Drug designations for elamipretide in Barth syndrome [5]. In September 2025, elamipretide received FDA accelerated approval under the brand name FORZINITY for improvement of muscle strength in adult and pediatric patients with Barth syndrome weighing at least 30 kilograms, based on the intermediate clinical endpoint of knee extensor muscle strength measured by handheld dynamometry [26]. This represented the first FDA approval of any mitochondria-targeted peptide. Continued approval is contingent on verification of clinical benefit in a confirmatory trial. The compound has also received rare pediatric disease designation [5].

4. Mechanism of Action

Elamipretide is a mitochondrial membrane-targeting peptide whose pharmacology operates through three interconnected mechanisms: electrostatic modulation of the inner mitochondrial membrane surface potential, stabilization of electron transport chain supercomplex assembly via cardiolipin-protein interactions, and scavenging of mitochondrial reactive oxygen species through the dimethyltyrosine residue. These activities collectively stabilize cristae architecture, restore bioenergetic function, inhibit mitochondrial permeability transition, and reduce oxidative stress at the mitochondrial source [1, 2, 3, 4].

4.1 Cardiolipin binding and membrane partitioning

Mitchell et al. (2020) provided the definitive biophysical characterization of elamipretide binding to lipid bilayers using model membrane systems containing cardiolipin (tetraoleoylcardiolipin, TOCL), monolysocardiolipin (MLCL), or phosphatidylglycerol (POPG) [3]. Key binding parameters determined by isothermal titration calorimetry and fluorescence spectroscopy include:

The dissociation constant (K_d) for TOCL-containing membranes (20 mol percent TOCL in a phosphatidylcholine background) is 2.0 to 2.9 micromolar, compared to 6.0 to 13 micromolar for POPG-containing membranes of equivalent charge density [3]. The molar partition coefficient (K_p) for TOCL-containing bilayers is 5.07 plus or minus 0.76 times 10^4 , approximately four-fold higher than for POPG bilayers (1.28 plus or minus 0.63 times 10^4) [3]. Each peptide associates with approximately 6.9 lipid molecules in TOCL-containing bilayers ($n = 6.9$ lipids per peptide) and 7.4 in MLCL-containing bilayers, corresponding to association with approximately 1.4 to 1.5 dianionic cardiolipin molecules per peptide [3].

The binding is entropy-dominated: enthalpy contributions are modest (ΔH of negative 4.2 kJ/mol for TOCL), while the entropy term (negative $T\Delta S$ of negative 20.8 to negative 22.7 kJ/mol) reflects burial of the nonpolar aromatic residues (Dmt and Phe) within the bilayer hydrocarbon region [3]. Molecular dynamics simulations position the Phe side chain at 1.12 nanometers from the bilayer center, the Dmt side chain at 1.37 nanometers, and the charged residues (Arg at 1.75 nm, Lys at 1.99 nm) at the lipid phosphate-water interface [3].

Importantly, Mitchell et al. demonstrated that binding is driven by net surface charge density rather than by structural specificity for cardiolipin per se: cardiolipin-depleted yeast mitochondria (Δ -crd1 knockout) showed nearly identical SS-31 binding to wild-type, because compensatory increases in phosphatidylglycerol maintained surface charge [3]. Binding is also independent of mitochondrial membrane potential, as valinomycin-induced collapse of the transmembrane potential had no effect on peptide association [3]. This distinguishes elamipretide from triphenylphosphonium-conjugated mitochondrial agents (such as MitoQ) whose accumulation is Nernstian and therefore reduced in depolarized, dysfunctional mitochondria.

4.2 Membrane surface electrostatic modulation

The principal consequence of elamipretide binding is saturable reduction of the inner mitochondrial membrane surface potential. Zeta potential measurements showed that elamipretide consistently reduces the magnitude of the zeta potential for anionic bilayers, saturating near negative 30 millivolts [3]. The peptide partially neutralizes the charge on anionic lipid headgroups but does not completely reverse the surface potential, a characteristic that distinguishes it from membrane-disrupting antimicrobial peptides [3].

The downstream biophysical consequences include reduced headgroup hydration and Coulombic repulsion, increased lipid packing density (measured by laurdan and prodan generalized polarization), decreased lateral lipid diffusivity, and critically, reduction of interfacial divalent cation (calcium) accumulation by over an order of magnitude as predicted by the Gouy-Chapman-Stern model and confirmed experimentally by calcium-sensing fluorescence [3]. Under calcium stress conditions (up to 5 millimolar CaCl_2), SS-31 pretreatment preserved oxidative phosphorylation activity and membrane integrity in isolated yeast mitochondria [3]. This calcium-shielding effect is proposed as one mechanism by which elamipretide protects against ischemia-reperfusion injury, where pathological mitochondrial calcium overload drives permeability transition and cell death [3, 22].

Mitchell et al. concluded that the mechanism represents "a truly unparalleled type" of drug action, as "the vast majority of drug compounds are designed to target and act upon specific proteins, not the lipid bilayer" [3]. Elamipretide is thus a first-in-class lipid bilayer modulator rather than a conventional protein-targeted pharmaceutical.

4.3 Electron transport chain supercomplex stabilization

In freshly explanted failing human heart tissue, Chatfield et al. (2019) demonstrated that elamipretide at 100 micromolar (the concentration at the plateau of a dose-response curve) selectively improved supercomplex-associated respiratory chain function [6]. Permeabilized myocardial fibers from heart failure patients (n = 23; mean ejection fraction 24 plus or minus 2 percent) treated with elamipretide showed significantly increased oxygen flux with Complex I substrates (pyruvate, malate, ADP, glutamate), significantly increased respiratory control ratio (RCR), and significantly increased supercomplex coupling control factor (SC CCF) [6]. Blue native polyacrylamide gel electrophoresis demonstrated that supercomplex-associated Complex IV activity was significantly increased after elamipretide treatment, while free Complex IV activity was unchanged [6]. Complex II and Complex V activities were unaffected [6].

Elamipretide had no effect on mitochondrial function in non-failing hearts, demonstrating disease-selective activity [6]. Cardiolipin composition analysis by mass spectrometry confirmed no changes in tetralinoleoyl-cardiolipin or total cardiolipin species after four-hour treatment, establishing that the acute mechanism operates through improved stabilization of existing cardiolipin-protein interactions rather than through lipid remodeling [6]. The authors concluded that elamipretide enhances supercomplex function by "recruiting free CIV into the supercomplex," potentially through improved cardiolipin-mediated Complex I-Complex III₂-Complex IV respirasome assembly [6].

4.4 Cristae stabilization and mitochondrial dynamics

In the tafazzin-knockdown mouse model of Barth syndrome, Russo et al. (2024) demonstrated that 10 weeks of subcutaneous SS-31 at 3 mg/kg/day significantly restored cristae architecture: reduced percentage of vacuolated mitochondria (P less than 0.01), reduced vacuole area as a fraction of total mitochondrial area (P less than 0.01), and increased cristae density (P less than 0.001) [21]. Elamipretide also corrected the pro-fission imbalance characteristic of tafazzin deficiency, significantly decreasing DRP1 phosphorylation at Ser-616 (P less than 0.05, a pro-fission modification) and reducing accumulation of SQSTM1/p62 (P less than 0.05), indicating partial restoration of mitophagy flux [21].

The biophysical basis for cristae stabilization was proposed by Mitchell et al.: by partially neutralizing charge on anionic lipid headgroups and promoting a more conical molecular geometry in cardiolipin, elamipretide may stabilize the regions of high membrane curvature that define cristae junctions and the lamellar body of cristae [3].

4.5 Reactive oxygen species scavenging

The antioxidant activity of elamipretide derives from its 2',6'-dimethyltyrosine (Dmt) residue, which can donate a hydrogen atom to scavenge free radicals and form a relatively stable tyrosyl radical [1, 2]. The original Zhao et al. (2004) report demonstrated that SS-31 scavenges hydrogen peroxide and peroxynitrite, inhibits lipid peroxidation, and reduces intracellular ROS with cytoprotective EC50 values in the nanomolar range [1]. Szeto (2006) noted that these peptides concentrate more than 1000-fold at the inner mitochondrial membrane, placing the antioxidant residue at the primary site of mitochondrial ROS generation [2].

However, Mitchell et al. (2020) revised the mechanistic hierarchy, noting that "antioxidant chemistry is not likely to be the primary mechanism of SS peptides, given (i) that such scavenging would occur stoichiometrically, not catalytically, and (ii) that other peptide variants, such as SS-20, which do not contain scavenging side chains, have also proven effective in preclinical studies" [3]. The current consensus positions ROS scavenging as a contributing but not primary mechanism, with the dominant therapeutic effect arising from the membrane electrostatic modulation described in sections 4.1 and 4.2.

4.6 Mitochondrial permeability transition inhibition

Elamipretide inhibits mitochondrial permeability transition (MPT) and prevents cytochrome c release. Zhao et al. (2004) demonstrated that SS-31 prevented cytochrome c release induced by calcium in isolated mitochondria and inhibited both MPT and mitochondrial swelling [1]. The biophysical basis is the reduction in interfacial calcium accumulation described by Mitchell et al., which reduces the calcium-driven conformational changes in the adenine nucleotide translocase and cyclophilin D that trigger the permeability transition pore [3]. By preventing cytochrome c release, elamipretide interrupts the mitochondrial apoptosis pathway upstream of caspase activation [1, 2].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Elamipretide is administered by subcutaneous injection. The absolute bioavailability after subcutaneous administration is approximately 92 percent [26]. Time to peak plasma concentration (T_{max}) is 0.5 to 1.0 hours after subcutaneous dosing [20, 26]. Exposure is comparable between abdominal and thigh injection sites [26]. Dose-proportional exposure has been demonstrated across the 2 to 80 mg dose range, with minimal accumulation on repeat daily dosing [20, 26].

5.2 Distribution

Volume of distribution is approximately 0.5 L/kg, consistent with distribution throughout total body water [26]. Plasma protein binding is approximately 39 percent [26]. The compound concentrates more than 1000-fold in the inner mitochondrial membrane relative to extramitochondrial compartments, driven by electrostatic interaction with anionic lipids rather than by the mitochondrial membrane potential [1, 2, 3]. Blood-brain barrier penetration is limited [20].

5.3 Metabolism

Elamipretide undergoes sequential C-terminal degradation to inactive tripeptide (M1, D-Arg-Dmt-Lys) and dipeptide (M2, D-Arg-Dmt) metabolites [26]. No hepatic metabolism has been observed in vitro [26]. The compound does not inhibit cytochrome P450 enzymes CYP1A, 2D6, 2E1, 2B6, 2C8, 2C9, 2C19, or 3A, and does not induce CYP1A2, 2B6, or 3A4 [26]. This absence of CYP-mediated metabolism is a pharmacokinetic advantage for a peptide therapeutic, eliminating the metabolic drug-drug interaction liability that complicates many small-molecule mitochondrial agents.

5.4 Elimination

Elimination is exclusively renal: 100 percent of an administered dose is recovered in urine within 48 hours as parent drug and M1 and M2 metabolites in subjects with normal renal function [26]. The plasma elimination half-life is approximately 3 to 4 hours based on data from the SBT-020 Huntington's disease study, where mean terminal half-life values ranged from 3.13 hours at the 5 mg dose to 4.14 hours at the 25 mg dose [20]. Renal clearance (CL_r) was estimated at 25.3 to 47.5 mL/min, with 27.5 to 44.9 percent of the dose excreted unchanged in urine, the majority within the first 6 hours post-dose [20]. No accumulation was observed following 28 days of repeat dosing [20].

5.5 Special populations

Renal impairment significantly affects elamipretide exposure because of the exclusively renal elimination pathway. In subjects with mild renal impairment (eGFR 60 to 89 mL/min), area under the curve increased by 39 percent; in moderate impairment (eGFR 30 to 59 mL/min), AUC increased by 75 percent; in severe impairment (eGFR less than 30 mL/min, not on dialysis), AUC increased by 125 percent, with M1 metabolite exposure increased by 280 percent and M2 by 640 percent [26]. The approved dose is reduced from 40 mg to 20 mg daily for patients with eGFR less than 30 mL/min not on dialysis; insufficient data are available for patients on dialysis [26]. Hepatic impairment is not expected to affect pharmacokinetics given the absence of hepatic metabolism [26].

5.6 Routes of administration

The approved route is subcutaneous injection at 40 mg (0.5 mL of an 80 mg/mL solution) once daily, with injection into the abdomen (at least 2 inches from the navel) or the outer thigh, rotating the injection site daily [26]. Intravenous administration has been used in clinical trials at doses of 0.005 to 0.25 mg/kg/h as infusions of 1 to 4 hours for acute cardiac applications (EMBRACE-STEMI, Daubert Phase 1/2, MMPOWER Phase 1/2, and the aging skeletal muscle ATP study) [7, 11, 12, 19]. The compound is not approved for intravenous use.

6. Preclinical Pharmacology

6.1 Failing human heart (ex vivo)

Chatfield et al. (2019) assessed elamipretide in freshly explanted ventricular tissue from children and adults undergoing cardiac transplantation [6]. Permeabilized myocardial fibers from failing hearts ($n = 23$; mean ejection fraction 24 plus or minus 2 percent) were incubated with 100 micromolar elamipretide for 1 hour and assessed by high-resolution respirometry (Oroboros O2K). Elamipretide significantly increased Complex I-driven oxygen flux, respiratory control ratio, and supercomplex coupling control factor. Supercomplex-associated Complex IV activity (measured by blue native PAGE in-gel activity assay) was significantly increased, while free Complex IV activity was unchanged [6]. Complex II-mediated flux was unaffected by either heart failure status or elamipretide treatment. In non-failing hearts ($n = 13$; mean ejection fraction 64 plus or minus 5 percent), elamipretide had no effect on any mitochondrial parameter [6]. The disease-selective profile, the acute onset (1 hour incubation), and the absence of cardiolipin composition changes on mass spectrometry confirmed that the mechanism operates through improved cardiolipin-protein interaction stabilization within the respirasome rather than through lipid remodeling [6].

6.2 Barth syndrome mouse model

Russo et al. (2024) treated tafazzin-knockdown (TazKD) mice (doxycycline-inducible tafazzin shRNA, approximately 15 to 20 percent residual tafazzin expression in cardiac muscle) with subcutaneous SS-31 at 3 mg/kg/day for 10 weeks beginning at 4 months of age [21]. Transmission electron microscopy of cardiac tissue demonstrated significant restoration of cristae architecture: reduced percentage of vacuolated mitochondria (P less than 0.01), reduced vacuole area (P less than 0.01), and increased cristae density (P less than 0.001) relative to saline-treated TazKD controls [21]. Western blot analysis showed that elamipretide corrected the pro-fission imbalance by significantly reducing DRP1 phosphorylation at Ser-616 (P less than 0.05) and partially restored mitophagy flux by reducing SQSTM1/p62 accumulation (P less than 0.05) [21].

6.3 Canine and porcine heart failure models

In a canine microembolization model of chronic heart failure, 3 months of subcutaneous elamipretide improved left ventricular ejection fraction and diastolic function indices, normalized plasma biomarkers (NT-proBNP, TNF-alpha, C-reactive protein), and reversed mitochondrial structural abnormalities [5]. SERCA2a activity and protein levels, which were significantly decreased in failing myocardium, were normalized by elamipretide treatment [5]. The magnitude of cardiac functional improvement was comparable to that observed with ACE inhibitors and beta-blockers in the same heart failure model [5]. In a porcine hypertension model, 3 months of elamipretide normalized mitochondrial respiration and calcium handling, improved left ventricular relaxation, and reduced cardiomyocyte hypertrophy [5].

A notable pharmacodynamic feature was documented: the effect on left ventricular fractional shortening persisted for approximately 7 days after a single dose, well beyond the 3 to 4 hour plasma elimination half-life, suggesting that the structural and bioenergetic improvements outlast the pharmacokinetic residence of the compound [5]. In chronic studies, diastolic function improvement was maintained for up to 2 weeks after elamipretide withdrawal but declined by approximately 50 percent at 4 weeks after cessation [5].

6.4 Ischemia-reperfusion in swine hemorrhagic shock

Patel et al. (2023) evaluated elamipretide in a clinically relevant Yorkshire swine model (n = 6 per group, 59 to 84 kg) of hemorrhagic shock with complete aortic balloon occlusion (simulating resuscitative endovascular balloon occlusion of the aorta, REBOA) followed by resuscitation [22]. Elamipretide at 0.1 mg/kg intravenous over 1 hour, started 20 minutes before balloon deflation, significantly reduced crystalloid fluid requirements (25 mL/kg versus 62.5 mL/kg in controls, $P = 0.01$), serum troponin at 360 minutes (0.22 ng/mL versus 3.20 ng/mL, $P = 0.03$), serum creatinine at 360 minutes (2.4 mg/dL versus 2.7 mg/dL, $P = 0.04$), and interleukin-6 at study end (P less than 0.01) [22]. Kidneys from all elamipretide-treated animals showed no histopathological damage (injury score 0), whereas controls showed detectable injury (median score 0.5, $P = 0.06$) [22]. In an average 70 kg pig, elamipretide reduced fluid requirements by approximately 2.6 liters [22].

6.5 Neuroinflammation and cognitive function

Zhao et al. (2019) demonstrated neuroprotection in a mouse model of lipopolysaccharide (LPS)-induced neuroinflammation [23]. C57BL/6 mice (n = 24 per group) received intracerebroventricular LPS (2 micrograms) with or without SS-31 (5 mg/kg intraperitoneal, 30 minutes before LPS and then once daily for 3 days). Elamipretide significantly reversed LPS-induced deficits in Morris water maze performance (platform crossings, escape latency, target quadrant time; all P less than 0.05) and fear conditioning freezing (P = 0.0093) [23]. Hippocampal mitochondrial parameters were preserved: elamipretide maintained mitochondrial membrane potential (P = 0.04), ATP levels (P = 0.03), and reduced ROS (P = 0.05) and malondialdehyde (P = 0.003) [23]. Neuroinflammatory markers TNF-alpha (P = 0.022) and IL-6 (P = 0.018) were attenuated. Synaptic markers BDNF, phospho-TrkB, synaptophysin, and PSD-95 were all significantly restored by elamipretide treatment [23]. Hippocampal apoptosis in the dentate gyrus was reduced from 2.62-fold (LPS) to 1.56-fold of control (P less than 0.01) [23].

6.6 Kidney injury models

SS-31 has been evaluated in multiple renal injury paradigms. In mouse models of aristolochic acid-induced acute tubulo-interstitial injury and adriamycin-induced glomerular damage, SS-31 at 30 mg/kg intraperitoneal reduced acute kidney injury and regulated inflammatory and oxidative stress response gene expression in diseased kidneys [24]. The compound has also demonstrated renal protection in ischemia-reperfusion models, where it preserves mitochondrial structure and restores ATP levels in renal tubular cells [4]. In a swine model of atherosclerotic renal artery stenosis, elamipretide infusion during revascularization reduced oxidative stress, tubular damage, and inflammation [4].

6.7 Translational validity assessment

The breadth of preclinical efficacy across cardiac, renal, neurological, and skeletal muscle models reflects the fundamental role of cardiolipin and mitochondrial bioenergetics in diverse tissues. The strongest translational signal has been in cardiac applications (Barth syndrome, heart failure), where preclinical findings closely predicted the human cardiac functional improvements observed in TAZPOWER and the acute hemodynamic changes in the Daubert Phase 1/2 trial [5, 12]. The translational gap is most evident in primary mitochondrial myopathy,

where the genetic heterogeneity of the patient population (nuclear DNA versus mitochondrial DNA pathogenic variants) introduced response variability that preclinical models, which use defined genetic backgrounds, did not predict [10].

7. Clinical Evidence Base

The clinical program for elamipretide has been evaluated in this section comprehensively and without selective emphasis on positive outcomes. The compound is not approved for any indication other than Barth syndrome (FORZINITY). All other clinical applications described below are investigational. Investigators considering elamipretide for research applications should evaluate the evidence base with attention to the multiple trials that did not meet primary endpoints.

7.1 Barth syndrome (TAZPOWER)

The TAZPOWER trial (NCT03098797) was a Phase 2/3 randomized, double-blind, placebo-controlled crossover study in 12 patients (mean age 19.5 years, range 12 to 35 years, all male) with genetically confirmed Barth syndrome (tafazzin gene mutations) [14, 15]. Patients received 40 mg elamipretide subcutaneous once daily or placebo for 12 weeks, separated by a 4-week washout period, followed by an open-label extension of up to 192 weeks.

The 12-week randomized crossover portion did not demonstrate statistically significant improvements on the co-primary endpoints (six-minute walk test distance and Barth Syndrome Symptom Assessment total fatigue score) or secondary endpoints [5, 26]. However, the open-label extension demonstrated progressive, sustained improvements. In a natural history comparison study, Hornby et al. (2022) reported that the least-squares mean difference between elamipretide-treated patients and natural history controls on the six-minute walk test was 79.7 meters at week 64 (95 percent CI 40.46 to 118.95, $P = 0.0004$) and 91.0 meters at week 76 (95 percent CI 44.57 to 137.38, $P = 0.0005$) [14]. Muscle strength by handheld dynamometry improved by 40.8 newtons at week 64 ($P = 0.0002$) and 56.7 newtons at week 76 ($P = 0.0005$). The multi-domain responder index was significantly improved at both timepoints ($P = 0.0001$) [14].

Thompson et al. (2024) reported the 168-week open-label extension results: 10 patients entered the extension, and 8 reached the week 168 visit [15]. Cumulative improvement on the six-minute walk test was 96.1 meters at 168 weeks ($P = 0.003$)

[15]. Cardiac stroke volume improved by 16 percent from baseline (30.5 to 35.3 mL/m² indexed to body surface area) [5]. The monolysocardiolipin-to-cardiolipin biomarker ratio improved and correlated with clinical outcomes [15].

FDA accelerated approval was based on the intermediate clinical endpoint of knee extensor muscle strength measured by handheld dynamometry: median change of plus 63 newtons (range 38 to 78 newtons) at week 168 of the extension, compared to plus 4 newtons during the elamipretide period and minus 5 newtons during the placebo period of the 12-week crossover [26]. The small sample size (n = 12) must be weighed against the ultra-rare disease context (estimated incidence 1 in 300,000 to 400,000 births) [5].

7.2 Primary mitochondrial myopathy (MMPOWER series)

MMPOWER Phase 1/2 (NCT02367014). Karaa et al. (2018) reported a multicenter, randomized, double-blind, placebo-controlled, dose-escalation trial in 36 adults with genetically confirmed primary mitochondrial myopathy [7]. Three escalating intravenous doses (0.01, 0.1, and 0.25 mg/kg/h for 2 hours daily for 5 days) were compared to placebo. The six-minute walk test at day 5 showed a mean improvement of 64.5 meters in the highest-dose group versus 20.4 meters for placebo (unadjusted P = 0.053); covariate-adjusted analysis yielded 51.2 meters versus 3.0 meters (P = 0.0297), with a significant dose-dependent response (P = 0.014) [7].

MMPOWER-2 (NCT02805790). Karaa et al. (2020) conducted a Phase 2 randomized, double-blind, placebo-controlled crossover trial in 30 adults with primary mitochondrial myopathy receiving 40 mg subcutaneous daily for 4 weeks per period [8]. The six-minute walk test showed a difference of 19.8 meters (95 percent CI negative 2.8 to 42.5, P = 0.0833) favoring elamipretide, which did not reach statistical significance [8]. However, the Primary Mitochondrial Myopathy Symptom Assessment total fatigue score was significantly improved with elamipretide (P = 0.0006), as were individual fatigue and muscle weakness subscale scores [8]. Injection site reactions occurred in 80 percent on elamipretide versus 3.3 percent on placebo [8].

MMPOWER-3 (NCT03323749). Karaa et al. (2023) reported the pivotal Phase 3 trial in 218 adults with genetically confirmed primary mitochondrial myopathy randomized to elamipretide 40 mg subcutaneous daily or placebo for 24 weeks [9]. The co-primary endpoints were not met: six-minute walk test change from baseline was negative 3.2 meters (95 percent CI negative 18.7 to 12.3, P = 0.69) and PMMSA total fatigue score difference was negative 0.07 (95 percent CI negative 0.10 to 0.26, P =

0.37) [9]. The study provided Class I evidence that elamipretide does not improve six-minute walk distance or fatigue at 24 weeks in the overall primary mitochondrial myopathy population [9].

A post hoc analysis by Karaa et al. (2024) identified genotype-specific responses: patients with nuclear DNA replisome pathogenic variants (26 percent of the population) showed improvement of 25.2 meters on the six-minute walk test versus 0.3 meters for placebo ($P = 0.03$) [10]. The most robust improvement was in the nDNA replisome subgroup with chronic progressive external ophthalmoplegia phenotype (plus 37.3 meters versus negative 8.0 meters, $P = 0.0024$) [10]. In contrast, patients with mitochondrial DNA pathogenic variants (74 percent of the population) showed no benefit, with a significant placebo effect in the MT-TL1 variant subgroup confounding the overall trial results [10]. A follow-up trial (NuPOWER) targeting the nDNA replisome subpopulation has been initiated [10].

7.3 Heart failure with reduced ejection fraction

Daubert Phase 1/2 (NCT02388464). Daubert et al. (2017) reported a randomized, double-blind, placebo-controlled, ascending-dose trial in 36 patients with heart failure and ejection fraction 35 percent or less [12]. A single 4-hour intravenous infusion at three doses (0.005, 0.05, and 0.25 mg/kg/h) was evaluated. At the highest dose, left ventricular end-diastolic volume decreased by 18 mL ($P = 0.009$) and end-systolic volume decreased by 14 mL ($P = 0.005$) relative to placebo at end infusion [12]. No serious adverse events occurred and hemodynamic parameters remained stable [12].

PROGRESS-HF (NCT02788747). Butler et al. (2020) reported a Phase 2, randomized, double-blind, placebo-controlled trial in 71 patients with stable heart failure and ejection fraction 40 percent or less [13]. Patients received placebo, elamipretide 4 mg, or elamipretide 40 mg subcutaneous daily for 28 days. The primary endpoint (change in left ventricular end-systolic volume by cardiac MRI at 4 weeks) was not met: the 4 mg dose differed from placebo by negative 0.3 mL (95 percent CI negative 4.6 to 4.0, $P = 0.90$) and the 40 mg dose by 2.3 mL (95 percent CI negative 1.9 to 6.5, $P = 0.28$) [13]. Elamipretide was well tolerated but did not translate the acute hemodynamic effects observed with single intravenous dosing into sustained structural improvement with 28-day subcutaneous dosing [13].

EMBRACE-STEMI (NCT01572909). Gibson et al. (2016) reported a Phase 2a, multicenter, randomized, double-blind, placebo-controlled trial of intravenous MTP-131 at 0.05 mg/kg/h for 1 hour in patients with first-time anterior ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention [11]. The primary endpoint (infarct size by creatine kinase-MB area under the curve over 72 hours) was not met: 5785 plus or minus 426 ng μ L (*placebo*) versus 5570 plus or minus 486 ng μ L (MTP-131), P not significant [11]. MRI, angiographic, electrocardiographic, and clinical outcomes also did not improve. MTP-131 was safe and well tolerated [11].

7.4 Dry age-related macular degeneration (ReCLAIM series)

ReCLAIM Phase 1 (NCT02848313). Two Phase 1, single-center, open-label studies evaluated elamipretide 40 mg subcutaneous daily for 24 weeks in patients with intermediate AMD and high-risk drusen (Allingham et al. 2022, n = 21) and with non-central geographic atrophy (Mettu et al. 2022, n = 19) [17, 18]. Both studies met their primary safety endpoint. In the drusen cohort, best-corrected visual acuity improved by 3.6 letters (P = 0.014) and low-luminance visual acuity by 5.6 letters (P = 0.004) [18]. In the NCGA cohort, best-corrected visual acuity improved by 4.6 letters (P = 0.0032) and low-luminance visual acuity by 5.4 letters (P = 0.0245) [17].

ReCLAIM-2 (NCT03891875). Ehlers et al. (2024) reported a Phase 2, prospective, randomized (2:1), double-masked, placebo-controlled, multicenter trial in 176 patients with dry AMD and geographic atrophy receiving elamipretide 40 mg subcutaneous daily for 48 weeks [16]. The co-primary endpoints (change in low-luminance best-corrected visual acuity and square-root-transformed geographic atrophy area) were not met (P = 0.49 and P = 0.34, respectively) [16]. However, exploratory endpoints showed nominally significant signals: elamipretide produced a 43 percent reduction in progression of total ellipsoid zone attenuation (nominal P = 0.0034), a 47 percent reduction in partial ellipsoid zone degradation (nominal P = 0.0040), and significantly more patients achieved 10 or more letters of low-luminance visual acuity gain (14.6 percent versus 2.1 percent, nominal P = 0.0404) [16]. These photoreceptor-level signals suggest a biological effect on mitochondrial function in the retinal pigment epithelium that was not sufficiently captured by the primary anatomic and functional endpoints over 48 weeks.

7.5 Aging skeletal muscle

Roshanravan et al. (2021) conducted a randomized, double-blind, placebo-controlled trial in 39 healthy older adults (age 60 to 85 years) with evidence of impaired mitochondrial function [19]. A single 2-hour intravenous infusion of elamipretide at 0.25 mg/kg/h increased the maximal rate of skeletal muscle ATP production (ATPmax, measured by phosphorus magnetic resonance spectroscopy) by 27 percent from baseline in elamipretide-treated subjects versus 12 percent in placebo-treated subjects ($P = 0.045$) [19]. This study provided the first direct evidence that elamipretide can acutely improve in vivo mitochondrial energetics in human skeletal muscle.

7.6 Huntington's disease

Van Diemen et al. (2021) conducted a Phase 2, randomized, double-blind, placebo-controlled study of SBT-020 (elamipretide) in 24 patients with early-stage Huntington's disease [20]. Part 1 was a 7-day multiple ascending dose study (5, 15, and 25 mg subcutaneous daily); Part 2 was a 28-day study at 25 mg daily. No significant differences were observed on any pharmacodynamic endpoint, including phosphorus MR spectroscopy of calf muscle and visual cortex, mitochondrial membrane potential in peripheral blood mononuclear cells, or cognitive assessments [20]. Elamipretide was safe and well tolerated in this population [20].

8. Sourcing and Quality Verification

FORZINITY (elamipretide hydrochloride injection) is the only regulatory-approved pharmaceutical source, manufactured by Stealth BioTherapeutics Inc. and supplied as 280 mg/3.5 mL (80 mg/mL) sterile aqueous solution in single-patient-use vials [26]. The pharmaceutical-grade material is currently available only for the approved Barth syndrome indication and is not available for general research procurement.

Research-grade elamipretide (SS-31) is supplied by multiple peptide synthesis vendors (MedChemExpress, Selleckchem, Cayman Chemical, Tocris Bioscience, BocSci, and others) as the free base or hydrochloride salt at purities of greater than 95 percent by HPLC. Supply is typically in milligram to gram quantities. Custom synthesis services can provide larger quantities for preclinical programs.

Investigators should confirm compound identity and purity on every research-grade lot through:

High-performance liquid chromatography area-percent purity, ideally greater than 95 percent. Mass spectrometry confirmation of molecular weight (calculated $[M+H]^+$ of 640.8 for the free base). Amino acid analysis to confirm the D-Arg-Dmt-Lys-Phe-NH₂ sequence, with particular attention to the D-arginine configuration (distinguishable by chiral chromatography or Marfey's reagent derivatization). Karl Fischer or loss-on-drying analysis for residual water content. Endotoxin testing (limulus amebocyte lysate) for material intended for cell culture or in vivo administration.

The peptide nature of the compound introduces specific quality considerations: degradation to the M1 (tripeptide) and M2 (dipeptide) metabolites can occur in solution at elevated temperatures, and investigators should confirm that aged lots retain the intact tetrapeptide peak on HPLC before use. Third-party analytical laboratories (Janoshik Analytical, SGS, Eurofins) provide independent confirmation of vendor certificates of analysis.

9. Reconstitution and Handling

Elamipretide hydrochloride is freely soluble in water at room temperature. The pharmaceutical formulation (FORZINITY) is supplied as a ready-to-use sterile solution at 80 mg/mL and does not require reconstitution [26].

For research applications, lyophilized or powder forms of elamipretide are reconstituted in sterile water for injection, phosphate-buffered saline, or dimethyl sulfoxide (for in vitro work at higher concentrations). Typical stock solution concentrations are 10 to 50 mg/mL in aqueous solvent for in vivo studies and 10 to 100 mM in DMSO for in vitro work [23, 24].

Storage: Unopened pharmaceutical vials are stored refrigerated at 2 to 8 degrees Celsius and must not be frozen [26]. Opened vials may be stored at 2 to 8 degrees Celsius or at room temperature (20 to 25 degrees Celsius) but must be discarded 8 days after first opening [26]. Research-grade lyophilized material should be stored at negative 20 degrees Celsius with desiccant protection. Reconstituted aqueous solutions should be aliquoted and stored at negative 20 degrees Celsius to minimize peptide degradation; freeze-thaw cycles should be minimized.

Light and oxygen sensitivity: The dimethyltyrosine residue is susceptible to oxidation. Protection from light is reasonable practice for research-grade stock solutions, though not required for the pharmaceutical formulation. Argon or nitrogen blanketing of stock solution vials extends stability.

Handling for in vivo research: For subcutaneous injection in animal models, concentrations of 3 to 5 mg/mL in sterile saline are typical (consistent with the Russo et al. and Sabbah preclinical protocols) [5, 21]. For intravenous infusion, concentrations of 0.05 to 0.25 mg/kg/h in normal saline or Ringer's lactate have been used in clinical trials [7, 11, 12].

10. Stack Interaction Considerations

Elamipretide has a favorable drug-drug interaction profile, primarily because it undergoes no hepatic metabolism, has no CYP inhibition or induction activity, and exhibits minimal transporter-mediated interactions [26].

Transporter interactions: Elamipretide is an inhibitor of MATE1 (multidrug and toxin extrusion protein 1) with an IC₅₀ of 3.53 micromolar [26]. The clinical significance of this interaction is uncertain, as MATE1 substrates (metformin, cimetidine) could theoretically experience reduced renal secretion with concurrent elamipretide. Elamipretide does not inhibit OCT2, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, P-glycoprotein, or MATE2-K [26].

Anticoagulant and antiplatelet agents: Formal interaction studies with aspirin and clopidogrel showed no pharmacokinetic changes and no alteration of antiplatelet activity [26]. Unfractionated heparin co-administration produced no impact on activated partial thromboplastin time or anti-factor Xa activity [26]. These findings are directly relevant to the cardiac indications in which elamipretide has been studied, where anticoagulant and antiplatelet co-administration is standard.

Renally eliminated drugs: Because elamipretide is exclusively renally eliminated, co-administration with other renally cleared compounds in patients with impaired renal function could result in competitive elimination effects. This interaction has not been formally studied but is a theoretical consideration for investigators combining elamipretide with renally eliminated research compounds.

Mitochondrial-targeted agents: Concurrent administration with other mitochondria-targeted compounds (MitoQ, idebenone, coenzyme Q10) has not been studied in clinical or preclinical research. The combination is pharmacologically plausible (different mechanisms, see Section 12) but additive effects on mitochondrial bioenergetics could theoretically exceed physiological buffering capacity. Investigators pursuing combination mitochondrial pharmacology should monitor mitochondrial membrane potential and respiratory function as safety pharmacodynamic endpoints.

CYP-metabolized drugs: No interaction is expected. Elamipretide neither inhibits nor induces CYP1A, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A [26].

11. Adverse Events and Safety

11.1 Injection site reactions

Injection site reactions are the dominant adverse event class with subcutaneous elamipretide and are reported in nearly all treated subjects. In the TAZPOWER crossover phase (n = 12 per group), injection site erythema occurred in 100 percent on elamipretide versus 25 percent on placebo; injection site pain in 75 percent versus 42 percent; induration in 67 percent versus 17 percent; pruritus in 67 percent versus 17 percent; bruising in 25 percent versus 0 percent; and urticaria in 25 percent versus 0 percent [26]. In the MMPOWER-2 crossover trial, injection site reactions occurred in 80 percent on elamipretide versus 3.3 percent on placebo, with erythema (56.7 percent), pruritus (46.7 percent), pain (20.0 percent), and urticaria (20.0 percent) as the most common [8]. Most injection site reactions are mild, develop within minutes of dosing, and resolve within 1 hour [20].

In longer-duration trials, injection site reactions were the primary cause of treatment discontinuation: 17.1 percent of elamipretide-treated subjects in the 48-week ReCLAIM-2 trial discontinued due to injection site reactions, compared to a lower rate in placebo [16]. Two patients in the TAZPOWER open-label extension also discontinued because of injection site reactions [5].

11.2 Eosinophilia

Transient eosinophilia has been observed in studies with 30 or more days of elamipretide exposure. Absolute eosinophil counts increased, peaking at approximately 90 days (mean increase of approximately 0.5 to 0.6 times 10^3 per microliter), then returning to baseline after 6 to 12 months of continuous exposure or after discontinuation [26]. The eosinophilia has not been associated with clinical manifestations of eosinophilic disease (eosinophilic pneumonia, myocarditis, or tissue infiltration) in any clinical trial [26].

11.3 Hypersensitivity reactions

Skin manifestations (rash, papular lesions, eczematous dermatitis) and respiratory symptoms (cough) have been reported and may occur within minutes to months after initiation of elamipretide [26]. The mechanism is likely an immune response to the peptide or its degradation products. Serious hypersensitivity to elamipretide or any excipient in FORZINITY is a contraindication; patients experiencing serious reactions should discontinue permanently [26].

11.4 Cardiac safety

No clinically significant QTc interval prolongation has been observed at concentrations up to 3-fold the peak concentration at the maximum recommended dose [26]. Blood pressure and heart rate remained stable in all heart failure trial cohorts [12, 13].

11.5 Benzyl alcohol warning

The FORZINITY formulation contains 20 mg/mL benzyl alcohol as a preservative. FORZINITY is not approved for neonates. Benzyl alcohol exposure in low-birth-weight (less than 2500 grams) and preterm (less than 34 weeks gestation) neonates receiving intravenous benzyl alcohol-containing products carries risk of metabolic acidosis progressing to neurotoxicity and gasping syndrome [26]. The compound is not approved for intravenous use.

11.6 Safety in special populations

The TAZPOWER trial enrolled patients aged 12 to 35 years; the FORZINITY label approves use in adults and pediatric patients weighing at least 30 kilograms [26]. No pregnancy or lactation data are available. No geriatric-specific safety data have been generated in dedicated studies, though the healthy older adult ATP study (age 60 to 85) and the Huntington's disease study reported no age-specific safety signals [19, 20].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five mitochondrial therapeutic candidates against elamipretide, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five compounds were selected as the principal mitochondria-targeted agents with substantive clinical evidence or advanced preclinical programs, representing the mechanistic diversity of the field.

12.1 Idebenone (Raxone, Catena)

Mechanism: Idebenone is a synthetic short-chain benzoquinone and structural analog of coenzyme Q10. It functions as a mitochondrial electron carrier that shuttles electrons directly to Complex III of the respiratory chain, thereby bypassing defects in Complex I, and simultaneously acts as a lipophilic antioxidant that scavenges reactive oxygen species and inhibits lipid peroxidation in mitochondrial membranes [27, 35].

Development trajectory: Originally synthesized by Takeda Pharmaceutical Company in the 1980s for cognitive disorders, idebenone was repositioned for mitochondrial diseases by Santhera Pharmaceuticals (later divested to Chiesi Farmaceutici in 2023). The RHODOS Phase 3 trial in Leber's hereditary optic neuropathy (LHON) in 85 patients reported by Klopstock et al. (2011) did not meet its primary endpoint (best recovery in visual acuity, logMAR difference negative 0.064, $P = 0.291$), though a secondary endpoint of change in best visual acuity across all eyes was significant (logMAR negative 0.100, $P = 0.026$) [27]. Phase 3 trials in Friedreich's ataxia (MICONOS, IONIA) also failed primary endpoints [35]. The European Medicines Agency granted conditional approval as Raxone for LHON in September 2015 based on totality of evidence; a US NDA was under FDA priority review with a PDUFA date in early 2026 at the time of this monograph.

Novelty: 2 of 5. The mechanism is a direct CoQ10 analog representing incremental molecular optimization rather than a novel pharmacological concept.

Effect size: 2 of 5. Primary endpoints missed in all Phase 3 controlled trials. The LHON signal was driven by secondary and subgroup analyses supplemented by real-world evidence [27].

Promising potential: 3 of 5. EU-approved for LHON; under FDA review. However, the Friedreich's ataxia and DMD programs did not succeed.

Side-effect profile: 4 of 5. Generally well tolerated. The principal adverse event is harmless chromaturia (reddish-brown urine from metabolites). Doses up to 2,250 mg daily have been administered safely [35].

Overall validation: 2 of 5. Conditionally approved on totality-of-evidence pathway, not conventional pivotal trial success.

Comparison to elamipretide: Idebenone targets electron transport chain function (Complex I bypass via Complex III), while elamipretide targets cardiolipin in the inner mitochondrial membrane to optimize supercomplex assembly. Idebenone is an oral small molecule; elamipretide is a subcutaneous peptide. Clinically, idebenone has a longer regulatory track record (EU approval 2015) but weaker pivotal trial evidence, while elamipretide achieved FDA accelerated approval (2025) for Barth syndrome based on functional endpoints [26, 27].

12.2 Omaveloxolone (Skyclarys)

Mechanism: Omaveloxolone is a semi-synthetic oleanane triterpenoid that activates nuclear factor erythroid 2-related factor 2 (Nrf2), the master transcriptional regulator of the cellular antioxidant response. In Friedreich's ataxia, frataxin deficiency leads to iron-sulfur cluster assembly failure and suppressed Nrf2 signaling. Omaveloxolone inhibits Keap1-mediated ubiquitination of Nrf2, allowing nuclear translocation and upregulation of more than 200 cytoprotective genes [28].

Development trajectory: Developed by Reata Biosciences as RTA 408, omaveloxolone was evaluated in the MOXIe trial: Part 2 (Phase 3, registrational) enrolled 82 patients with Friedreich's ataxia for 48 weeks [28]. The primary endpoint was modified Friedreich Ataxia Rating Scale (mFARS) change was negative 1.55 (omaveloxolone) versus plus 0.85 (placebo), treatment difference negative 2.40 ($P = 0.014$), approximating 2 years of disease progression reversal [28]. FDA approved omaveloxolone in February 2023 as Skyclarys, the first-ever approved therapy for Friedreich's ataxia. Biogen acquired Reata Pharmaceuticals for approximately 7.3 billion dollars in September 2023 [28].

Novelty: 4 of 5. Nrf2 activation represents a genuinely distinct mechanism addressing upstream transcriptional deficits.

Effect size: 3 of 5. The 2.40-point mFARS improvement is statistically significant and clinically meaningful but modest in absolute terms. Secondary endpoints were mixed [28].

Promising potential: 5 of 5. FDA-approved, commercially launched globally, validated by a 7.3 billion dollar acquisition.

Side-effect profile: 3 of 5. ALT elevations at or above 3 times the upper limit of normal occurred in 29 percent of treated patients (versus 0 percent placebo), requiring monitoring. Headache (37 percent), nausea (33 percent), and abdominal pain (22 percent) are common [28].

Overall validation: 4 of 5. Met primary endpoint in a registrational trial. FDA and EMA approved.

Comparison to elamipretide: Omaveloxolone acts at the nuclear transcriptional level (Nrf2 pathway), indirectly restoring mitochondrial function by upregulating antioxidant defenses. Elamipretide acts directly at the inner mitochondrial membrane through cardiolipin binding. Omaveloxolone is an oral small molecule with hepatotoxicity concerns; elamipretide is a subcutaneous peptide with injection-site reactions. Both are approved for rare mitochondrial diseases but target fundamentally different molecular defects [26, 28].

12.3 MitoQ (mitoquinone)

Mechanism: MitoQ consists of a ubiquinone moiety covalently conjugated to a triphenylphosphonium (TPP⁺) lipophilic cation via a ten-carbon alkyl chain. The TPP⁺ exploits the mitochondrial membrane potential (approximately negative 180 mV) to drive accumulation within the mitochondrial matrix at concentrations several hundred-fold higher than exogenous CoQ10, where ubiquinol scavenges superoxide and lipid peroxy radicals [36].

Development trajectory: Invented by Smith and Murphy (University of Otago, New Zealand) in the late 1990s. Two Phase 2 pharmaceutical trials were conducted: Snow et al. (2010) randomized 128 Parkinson's disease patients to MitoQ (40 or 80 mg daily) or placebo for 12 months, with no effect on UPDRS progression [29]. Gane et al. (2010) evaluated MitoQ in 30 hepatitis C patients for 28 days, with decreased

liver enzymes but no effect on viral load [37]. Both pharmaceutical programs were discontinued. MitoQ pivoted to the nutraceutical market and is currently sold as a dietary supplement (5 to 10 mg capsules). A crossover study by Rossman et al. (2018) in 20 healthy older adults showed that MitoQ 20 mg daily for 6 weeks improved brachial artery flow-mediated dilation by 42 percent versus placebo (P less than 0.05) [30].

Novelty: 3 of 5. The TPP+ conjugation strategy for mitochondrial targeting was genuinely innovative; the active moiety (ubiquinone) is not.

Effect size: 1 of 5. Failed primary endpoints in both pharmaceutical trials. The vascular aging signal is from a small crossover study of a surrogate endpoint [29, 30].

Promising potential: 2 of 5. No longer in pharmaceutical development. Marketed as a supplement without disease-specific claims.

Side-effect profile: 4 of 5. Generally well tolerated at supplement doses. Gastrointestinal effects (nausea, diarrhea) at higher pharmaceutical doses (80 mg) caused disproportionate dropouts in the Parkinson's disease trial [29].

Overall validation: 1 of 5. Failed both pharmaceutical trials; no regulatory approval.

Comparison to elamipretide: Both target mitochondria but through fundamentally different mechanisms. MitoQ relies on membrane potential-driven matrix accumulation for antioxidant scavenging; elamipretide concentrates at the inner mitochondrial membrane through cardiolipin electrostatic interaction independent of membrane potential. MitoQ's dependence on membrane potential means it may be less effective in severely dysfunctional mitochondria where the potential collapses; elamipretide does not share this limitation [3, 36]. Clinically, elamipretide has FDA approval; MitoQ did not advance beyond Phase 2.

12.4 Vatiquinone (EPI-743, vincerinone)

Mechanism: Vatiquinone is a para-benzoquinone derivative that acts as a first-in-class selective inhibitor of 15-lipoxygenase (15-LO), suppressing ferroptosis (iron-dependent lipid peroxidation-mediated cell death) and reducing oxidative stress in mitochondria [32].

Development trajectory: Originally developed by Edison Pharmaceuticals (later BioElectron), vatiquinone was acquired by PTC Therapeutics in 2019. Two registration-directed trials were conducted: the MOVE-FA trial in 146 Friedreich's ataxia patients for 72 weeks did not meet its primary endpoint (mFARS change, placebo-corrected difference 1.6 points, $P = 0.14$), though subscale benefits (bulbar $P = 0.044$, upright stability $P = 0.021$) and a significant per-protocol analysis were noted [31]. The MIT-E trial in mitochondrial disease-associated seizures also failed its primary endpoint [31]. The FDA issued a Complete Response Letter in August 2025, requesting additional efficacy data from a new trial [31].

Novelty: 4 of 5. First-in-class 15-lipoxygenase inhibitor for mitochondrial disease represents a genuinely distinct ferroptosis-targeting mechanism.

Effect size: 2 of 5. Failed primary endpoints in both pivotal trials. Subscale and extension analyses suggest a signal but do not constitute registration-quality evidence [31].

Promising potential: 2 of 5. FDA Complete Response Letter issued; requires a new trial. Two failed pivotal studies severely limit near-term commercial viability.

Side-effect profile: 4 of 5. Generally well tolerated across clinical studies with no major safety signals [31, 32].

Overall validation: 2 of 5. Two failed pivotal trials and an FDA CRL. Mechanistic novelty is compelling but clinical evidence has not materialized.

Comparison to elamipretide: Vatiquinone addresses ferroptotic cell death (an indirect consequence of mitochondrial dysfunction), while elamipretide targets inner mitochondrial membrane architecture (a proximal cause). Elamipretide has achieved FDA accelerated approval; vatiquinone received an FDA CRL [26, 31].

12.5 Coenzyme Q10 (ubiquinone)

Mechanism: Coenzyme Q10 is the endogenous lipophilic benzoquinone electron carrier that shuttles electrons from Complexes I and II to Complex III via the Q-cycle in the inner mitochondrial membrane. In its reduced form (ubiquinol), it also functions as a lipid-soluble antioxidant. Exogenous supplementation aims to replenish depleted mitochondrial CoQ10 pools, but oral bioavailability is limited by the extreme lipophilicity of the 50-carbon isoprenoid side chain, and blood-brain barrier penetration is poor [33, 34].

Development trajectory: Discovered by Frederick Crane (University of Wisconsin) in 1957, CoQ10 has been available as a dietary supplement for decades. The Q-SYMBIO trial (Mortensen et al. 2014) randomized 420 heart failure patients to CoQ10 300 mg daily or placebo for 106 weeks and reported significant reductions in major adverse cardiovascular events (15 percent versus 26 percent, P less than 0.005), cardiovascular mortality (9 percent versus 16 percent, $P = 0.026$), and all-cause mortality (10 percent versus 18 percent, $P = 0.018$) [33]. However, the Q-SYMBIO findings have not been replicated in a large confirmatory trial. In the first randomized controlled trial of CoQ10 in primary mitochondrial disease, Stacpoole et al. (2012) studied 30 patients receiving CoQ10 1200 mg daily in a crossover design and found attenuation of exercise-induced lactate rise but no significant improvement in clinical functional measures [34]. CoQ10 is not approved as a pharmaceutical for any disease.

Novelty: 1 of 5. The endogenous electron carrier used as a supplement; no molecular innovation.

Effect size: 3 of 5. The Q-SYMBIO heart failure mortality signal (NNT approximately 12) is impressive but unreplicated. Effect sizes in mitochondrial disease are negligible on clinical endpoints [33, 34].

Promising potential: 2 of 5. Despite decades of research, no regulatory approval. Bioavailability and blood-brain barrier penetration limit utility.

Side-effect profile: 5 of 5. Exceptional safety record over decades. No significant adverse effects at doses up to 3,000 mg daily [33].

Overall validation: 2 of 5. No regulatory approval; controlled trial evidence in mitochondrial disease shows minimal clinical benefit.

Comparison to elamipretide: CoQ10 is a mobile electron shuttle within the electron transport chain; elamipretide binds cardiolipin to stabilize membrane architecture and supercomplex assembly. Exogenous CoQ10 is limited by poor bioavailability and cannot cross the blood-brain barrier efficiently; elamipretide achieves rapid mitochondrial targeting through electrostatic cardiolipin interaction independent of membrane potential [3, 33].

12.6 Comparator summary

STANDARD	IDEBENONE	OMAVELOXOLONE	MITOQ	VATIQUNONE	COQ10
Novelty	2	4	3	4	1
Effect size	2	3	1	2	3
Promising potential	3	5	2	2	2
Side-effect profile	4	3	4	4	5
Overall validation	2	4	1	2	2

Elamipretide is the only compound in this comparator panel that directly targets cardiolipin, a structural phospholipid unique to the inner mitochondrial membrane. All five comparators operate either at the electron transport chain level (idebenone, CoQ10, MitoQ), at the nuclear transcriptional level (omaveloxolone), or at the lipid peroxidation level (vatiquinone). Elamipretide's mechanism is independent of mitochondrial membrane potential, a biophysical advantage over MitoQ and exogenous CoQ10 whose accumulation is Nernstian.

Among the six compounds (including elamipretide), only two have FDA approval: omaveloxolone (Friedreich's ataxia, 2023) and elamipretide (Barth syndrome, accelerated 2025). Idebenone has EU approval for LHON. The field is characterized by high attrition in pivotal trials, reflecting the difficulty of demonstrating clinical benefit in heterogeneous, slowly progressive mitochondrial diseases.

The principal practical question for elamipretide's research-clinical positioning is whether the cardiolipin-binding mechanism provides sufficient therapeutic leverage across the diversity of mitochondrial pathology. The Barth syndrome data, where the compound directly addresses the primary molecular defect (defective cardiolipin remodeling due to tafazzin mutation), represents the strongest mechanistic-clinical alignment. Extension to other mitochondrial diseases, where cardiolipin abnormalities are secondary rather than primary, may require patient selection strategies (such as the nDNA replisome subgroup identified in MMPOWER-3) to achieve therapeutic benefit.

13. References

1. Zhao K, Zhao GM, Wu D, Soong Y, Birk AV, Schiller PW, Szeto HH. Cell-permeable peptide antioxidants targeted to inner mitochondrial membrane inhibit mitochondrial swelling, oxidative cell death, and reperfusion injury. *J Biol Chem.* 2004;279(33):34682-34690. PMID: 15178689. DOI: 10.1074/jbc.M402999200.
2. Szeto HH. Cell-permeable, mitochondrial-targeted, peptide antioxidants. *AAPS J.* 2006;8(2):E277-E283. PMID: 16796378. DOI: 10.1007/BF02854898.
3. Mitchell W, Ng EA, Tamucci JD, Boyd KJ, Sathappa M, Coscia A, Pan M, Han X, Eddy NA, May ER, Szeto HH, Alder NN. The mitochondria-targeted peptide SS-31 binds lipid bilayers and modulates surface electrostatics as a key component of its mechanism of action. *J Biol Chem.* 2020;295(21):7452-7469. PMID: 32273339. DOI: 10.1074/jbc.RA119.012094.
4. Tung C, Varzideh F, Farroni E, et al. Elamipretide: A Review of Its Structure, Mechanism of Action, and Therapeutic Potential. *Int J Mol Sci.* 2025;26(3):944. PMID: 39940712. DOI: 10.3390/ijms26030944.
5. Sabbah HN. Elamipretide for Barth syndrome cardiomyopathy: gradual rebuilding of a failed power grid. *Heart Fail Rev.* 2022;27(5):1911-1923. PMID: 34623544. DOI: 10.1007/s10741-021-10177-8.
6. Chatfield KC, Sparagna GC, Chau S, Phillips EK, Ambardekar AV, Aftab M, Mitchell MB, Sucharov CC, Miyamoto SD, Stauffer BL. Elamipretide improves mitochondrial function in the failing human heart. *JACC Basic Transl Sci.* 2019;4(2):147-157. PMID: 31061916. DOI: 10.1016/j.jacbts.2018.12.005.
7. Karaa A, Haas R, Goldstein A, Vockley J, Weaver WD, Cohen BH. Randomized dose-escalation trial of elamipretide in adults with primary mitochondrial myopathy. *Neurology.* 2018;90(14):e1212-e1221. PMID: 29500292. DOI: 10.1212/WNL.0000000000005255.
8. Karaa A, Haas R, Goldstein A, Vockley J, Cohen BH. A randomized crossover trial of elamipretide in adults with primary mitochondrial myopathy. *J Cachexia Sarcopenia Muscle.* 2020;11(4):909-918. PMID: 32096613. DOI: 10.1002/jcsm.12559.

9. Karaa A, Bertini E, Carelli V, Cohen BH, Enns GM, Falk MJ, Goldstein A, Gorman GS, Haas R, Hirano M, Klopstock T, Koenig MK, Kornblum C, Lamperti C, Lehman A, et al. Efficacy and safety of elamipretide in individuals with primary mitochondrial myopathy: The MMPOWER-3 randomized clinical trial. *Neurology*. 2023;101(3):e238-e252. PMID: 37268435. DOI: 10.1212/WNL.0000000000207402.
10. Karaa A, Bertini E, Carelli V, Cohen BH, et al. Genotype-specific effects of elamipretide in patients with primary mitochondrial myopathy: a post hoc analysis of the MMPOWER-3 trial. *Orphanet J Rare Dis*. 2024;19:431. PMID: 39574155. DOI: 10.1186/s13023-024-03421-5.
11. Gibson CM, Giugliano RP, Kloner RA, Bode C, Tendera M, Janosi A, Merkely B, Godlewski J, Halaby R, Korjian S, Daaboul Y, Chakrabarti AK, Spielman K, Neal BJ, Weaver WD. EMBRACE STEMI study: a Phase 2a trial to evaluate the safety, tolerability, and efficacy of intravenous MTP-131 on reperfusion injury in patients undergoing primary percutaneous coronary intervention. *Eur Heart J*. 2016;37(16):1296-1303. PMID: 26586786. DOI: 10.1093/eurheartj/ehv597.
12. Daubert MA, Yow E, Dunn G, Marchev S, Barnhart H, Douglas PS, O'Connor C, Goldstein S, Udelson JE, Sabbah HN. Novel mitochondria-targeting peptide in heart failure treatment: A randomized, placebo-controlled trial of elamipretide. *Circ Heart Fail*. 2017;10(12):e004389. PMID: 29217757. DOI: 10.1161/CIRCHEARTFAILURE.117.004389.
13. Butler J, Khan MS, Anker SD, Fonarow GC, Kim RJ, Nodari S, O'Connor CM, Pieske B, Pieske-Kraigher E, Sabbah HN, Senni M, Voors AA, Udelson JE, Carr J, Gheorghiade M, Filippatos G. Effects of elamipretide on left ventricular function in patients with heart failure with reduced ejection fraction: The PROGRESS-HF Phase 2 trial. *J Card Fail*. 2020;26(5):429-437. PMID: 32068002. DOI: 10.1016/j.cardfail.2020.02.001.
14. Hornby B, Thompson WR, Almuqbil M, Manuel R, Abbruscato A, Carr J, Vernon HJ. Natural history comparison study to assess the efficacy of elamipretide in patients with Barth syndrome. *Orphanet J Rare Dis*. 2022;17:336. PMID: 36056411. DOI: 10.1186/s13023-022-02469-5.
15. Thompson WR, Manuel R, Abbruscato A, Carr J, Campbell J, Hornby B, Vaz FM, Vernon HJ. Long-term efficacy and safety of elamipretide in patients with Barth syndrome: 168-week open-label extension results of TAZPOWER. *Genet Med*. 2024;26(7):101138. PMID: 38602181. DOI: 10.1016/j.gim.2024.101138.

16. Ehlers JP, Hu A, Boyer D, Cousins SW, Waheed NK, Rosenfeld PJ, Brown D, Kaiser PK, Abbruscato A, Gao G, Heier J; ReCLAIM-2 Study Investigators. ReCLAIM-2: A Randomized Phase II Clinical Trial Evaluating Elamipretide in Age-related Macular Degeneration, Geographic Atrophy Growth, Visual Function, and Ellipsoid Zone Preservation. *Ophthalmol Sci.* 2024;5(1):100628. PMID: 39605874. DOI: 10.1016/j.xops.2024.100628.
17. Mettu PS, Allingham MJ, Cousins SW. Phase 1 Clinical Trial of Elamipretide in Dry Age-Related Macular Degeneration and Noncentral Geographic Atrophy: ReCLAIM NCGA Study. *Ophthalmol Sci.* 2022;2(1):100086. PMID: 36246181. DOI: 10.1016/j.xops.2021.100086.
18. Allingham MJ, Mettu PS, Cousins SW. Phase 1 clinical trial of elamipretide in intermediate age-related macular degeneration and high-risk drusen. *Ophthalmol Sci.* 2022;2(1):100095. PMID: 36246187. DOI: 10.1016/j.xops.2021.100095.
19. Roshanravan B, Liu SZ, Ali AS, et al. In vivo mitochondrial ATP production is improved in older adult skeletal muscle after a single dose of elamipretide in a randomized trial. *PLoS One.* 2021;16(7):e0253849. PMID: 34264994. DOI: 10.1371/journal.pone.0253849.
20. van Diemen MPJ, Hart EP, Abbruscato A, et al. Safety, pharmacokinetics and pharmacodynamics of SBT-020 in patients with early stage Huntington's disease, a 2-part study. *Br J Clin Pharmacol.* 2021;87(5):2290-2302. PMID: 33197078. DOI: 10.1111/bcp.14656.
21. Russo S, De Rasmio D, Rossi R, Signorile A, Lobasso S. SS-31 treatment ameliorates cardiac mitochondrial morphology and defective mitophagy in a murine model of Barth syndrome. *Sci Rep.* 2024;14:13655. PMID: 38871974. DOI: 10.1038/s41598-024-64368-y.
22. Patel N, Johnson MA, Vapniarsky N, Van Brocklin MW, Williams TK, Youngquist ST, Ford R, Ewer N, Neff LP, Hoareau GL. Elamipretide mitigates ischemia-reperfusion injury in a swine model of hemorrhagic shock. *Sci Rep.* 2023;13:4496. PMID: 36934127. DOI: 10.1038/s41598-023-31374-5.
23. Zhao W, Xu Z, Cao J, Fu Q, Wu Y, Zhang X, Long Y, Zhang X, Yang Y, Li Y, Mi W. Elamipretide (SS-31) improves mitochondrial dysfunction, synaptic and memory impairment induced by lipopolysaccharide in mice. *J Neuroinflammation.* 2019;16(1):230. PMID: 31747905. DOI: 10.1186/s12974-019-1627-9.

24. Wyss JC, Kumar R, Mikulic J, Schneider M, Mary JL, Aebi JD, Juillerat-Jeanneret L, Golshayan D. Differential Effects of the Mitochondria-Active Tetrapeptide SS-31 (D-Arg-dimethylTyr-Lys-Phe-NH₂) and Its Peptidase-Targeted Prodrugs in Experimental Acute Kidney Injury. *Front Pharmacol*. 2019;10:1209. DOI: 10.3389/fphar.2019.01209.
25. Khan MS, Butler J. Targeting Mitochondrial Function in Heart Failure: Makes Sense But Will it Work? *JACC Basic Transl Sci*. 2019;4(2):158-160. PMID: 31061917. DOI: 10.1016/j.jacbts.2019.03.003.
26. FORZINITY (elamipretide) injection, for subcutaneous use. Prescribing Information. Stealth BioTherapeutics Inc. NDA 215244. September 2025.
27. Klopstock T, Yu-Wai-Man P, Dimitriadis K, et al. A randomized placebo-controlled trial of idebenone in Leber's hereditary optic neuropathy. *Brain*. 2011;134(Pt 9):2677-2686. PMID: 21788663. DOI: 10.1093/brain/awr170.
28. Lynch DR, Chin MP, Delatycki MB, et al. Safety and efficacy of omaveloxolone in Friedreich ataxia (MOXIe study). *Ann Neurol*. 2021;89(2):212-225. PMID: 33068037. DOI: 10.1002/ana.25934.
29. Snow BJ, Rolfe FL, Lockhart MM, et al. A double-blind, placebo-controlled study to assess the mitochondria-targeted antioxidant MitoQ as a disease-modifying therapy in Parkinson's disease. *Mov Disord*. 2010;25(11):1670-1674. PMID: 20568096. DOI: 10.1002/mds.23148.
30. Rossman MJ, Santos-Parker JR, Steward CAC, et al. Chronic supplementation with a mitochondrial antioxidant (MitoQ) improves vascular function in healthy older adults. *Hypertension*. 2018;71(6):1056-1063. PMID: 29661838. DOI: 10.1161/HYPERTENSIONAHA.117.10787.
31. PTC Therapeutics. Topline results from vatiquinone MOVE-FA registration-directed trial. Press release, May 22, 2023.
32. Enns GM, Kinsman SL, Perlman SL, et al. Initial experience in the treatment of inherited mitochondrial disease with EPI-743. *Mol Genet Metab*. 2012;105(1):91-102. PMID: 22115768. DOI: 10.1016/j.ymgme.2011.10.007.
33. Mortensen SA, Rosenfeldt F, Kumar A, et al. The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial. *JACC Heart Fail*. 2014;2(6):641-649. PMID: 25282031. DOI: 10.1016/j.jchf.2014.06.008.

34. Stacpoole PW, deGrauw TJ, Feigenbaum AS, et al. Design and implementation of the first randomized controlled trial of coenzyme Q10 in children with primary mitochondrial diseases. *Mitochondrion*. 2012;12(6):623-629. PMID: 23022875. DOI: 10.1016/j.mito.2012.09.005.
35. Lynch DR, Perlman SL, Meier T. A phase 3, double-blind, placebo-controlled trial of idebenone in Friedreich ataxia. *Arch Neurol*. 2010;67(8):941-947. PMID: 20697044. DOI: 10.1001/archneurol.2010.168.
36. Murphy MP, Smith RAJ. Targeting antioxidants to mitochondria by conjugation to lipophilic cations. *Annu Rev Pharmacol Toxicol*. 2007;47:629-656. PMID: 17014364. DOI: 10.1146/annurev.pharmtox.47.120505.105110.
37. Gane EJ, Weilert F, Orr DW, et al. The mitochondria-targeted anti-oxidant mitoquinone decreases liver damage in a phase II study of hepatitis C patients. *Liver Int*. 2010;30(7):1019-1026. PMID: 20492507. DOI: 10.1111/j.1478-3231.2010.02250.x.
38. Gibson CM, Kasper EK, Engel DJ. Rationale and design of the EMBRACE STEMI study: a phase 2a, randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability and efficacy of intravenous Bendavia on reperfusion injury in patients treated with standard therapy including primary percutaneous coronary intervention and stenting for ST-segment elevation myocardial infarction. *Am Heart J*. 2013;165(4):509-514.e7. PMID: 23537966. DOI: 10.1016/j.ahj.2012.12.008.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Elamipretide is FDA-approved as FORZINITY for Barth syndrome only; all other indications described herein are investigational. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly. Investigators should obtain analytical confirmation of identity and purity on every lot of research-grade elamipretide.