



DOSSIER · SUBSTANCE

Elamipretide (SS-31)

Elamipretide is a **mitochondria-targeted peptide** that has been investigated in numerous studies since 2009. Research has focused on **fatigue, cardiovascular diseases and rare mitochondrial myopathies**. The most intriguing finding: controlled trials show **no consistent efficacy**, but rather **genotype- and dose-dependent effects** — a reflection of the complexity of mitochondrial therapies.

280

STUDIES IN
TOTAL

74

IN HUMANS

18

OF WHICH
CONTROLLED

64

IN ANIMALS

34

IN THE LAB

Figures from the IHR study database · Last updated 2026-10-15

How to Read This Dossier

ESTABLISHED

measured in humans, with a comparison group

PLAUSIBLE

supported by mechanism, animal studies or observation

HYPOTHESIS

a likely connection that still needs to be tested

Elamipretide (SS-31) at a glance

ORIGIN:
Elamipretide (SS-31) is a synthetic tetrapeptide (D-Arg-Dmt-Lys-Phe-NH₂) that selectively binds to the inner mitochondrial membrane and interacts with cardiolipin.

EVIDENCE BASE:
280 studies reviewed · 18 controlled human studies · 56 observational studies · 4 review articles · 64 animal studies · 32 cell culture studies

- STRONGEST EVIDENCE:**
- **Heart and circulation:** A randomised study (n=24) in patients with heart failure receiving high-dose elamipretide (0.25 mg·kg⁻¹·h⁻¹) showed a significant reduction in left ventricular volume (–18 ml end-diastolic, p=0.009) without severe adverse events. Acute effects on pump function are shown; long-term data are lacking.
 - **Safety and tolerability:** The MMPOWER study (n=36) confirmed short-term tolerability of elamipretide in primary mitochondrial myopathy (PMM). The highest dose (0.25 mg/kg/h) increased 6-minute walk distance by 64.5 m (p=0.053), a surrogate for physical performance. Adverse events were mild, mainly infusion reactions.
 - **Fatigue in genetic disorders** The TAZPOWER study (n=12) in Barth syndrome (TAZ mutation) after 36 weeks of elamipretide (40 mg daily) provided initial evidence of improvements in 6-minute walk distance (+95.9 m, p=0.024) and quality of life (BTHS-SA, p=0.031). Effects are genotype-specific.
 - **Metabolism:** In a preclinical model of Barth syndrome (n=12), elamipretide significantly reduced medium- and short-chain acylcarnitines after 12 weeks (p<0.05). Clinical correlations remain to be established.

- LIMITATIONS:**
- **Generalisability** Clinical studies are small (n=12–218) and short (4–168 weeks). Genotype-specific effects preclude generalisable conclusions on efficacy in mitochondrial disorders.
 - **Long-term data** Data on chronic use are missing: cumulative toxicity, antibody formation and clinical endpoints (e.g. mortality) have not been studied.
 - **Cardiovascular efficacy** Acute effects on pump function (study ¹) were not confirmed in 28-day therapy (PROGRESS-HF, n=71). Longer studies with clinical endpoints are lacking.

ASSESSMENT:
Elamipretide is a mitochondrial protective factor with genotype-specific effects that provides initial evidence of improved physical performance in Barth syndrome, while its efficacy in other mitochondrial disorders and heart failure remains open to question.

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1. What Elamipretide Is and How It Works

Elamipretide (SS-31) is a **synthetic tetrapeptide** (D-Arg-Dmt-Lys-Phe-NH₂) that selectively binds to the **inner mitochondrial membrane**. It interacts with **cardiolipin**, a phospholipid essential for the structure and function of the respiratory chain. Developed as a **mitochondrial protective factor**, the drug is intended to reduce oxidative damage and stabilise ATP production. Unlike classical antioxidants, elamipretide acts **locally within mitochondria**, without globally disrupting cellular redox homeostasis. It is chemically synthesised; no natural sources exist.

The key mechanism lies in **stabilising the electron transport chain**. Elamipretide has been studied to influence **cardiolipin oxidation**, which occurs in mitochondrial disorders, ischaemia or ageing. This preserves the **coupling of respiration and ATP synthesis**. Preclinical studies show that the compound has **no direct antioxidant activity** but **protects mitochondrial membrane integrity**. Bioavailability is **dose-dependent**, with a short **plasma half-life**. Administration is **subcutaneous or intravenous**; oral formulations are not established.

2. What the Individual Studies Show

The key human studies and major reviews — grouped by indication, with population, duration, formulation, outcome measures and results as reported in the original papers. Numbers are included only where the study provides them.

Distribution of **controlled human studies** by indication — the numbers are not additive as a single study may be assigned to multiple indications:

INDICATION	CONTROLLED STUDIES
Fatigue and stress	10
Safety and tolerability	10
Musculoskeletal system	8
Absorption and availability	3
Heart and circulation	3

INDICATION	CONTROLLED STUDIES
Oxidative stress	1
Metabolism	1

Heart and Circulation

PROVEN In a randomised, placebo-controlled dose-finding study ⁽¹⁾, 24 patients with heart failure and reduced ejection fraction ($\leq 35\%$) received a single 4-hour infusion of elamipretide (0.005, 0.05 or 0.25 mg·kg⁻¹·h⁻¹) or placebo. At the highest dose (0.25 mg·kg⁻¹·h⁻¹, n=8), there was a significant reduction in left ventricular end-diastolic volume (-18 ml, p=0.009) and end-systolic volume (-14 ml, p=0.005) compared with placebo (n=12) at the end of infusion. Blood pressure and heart rate remained stable; no severe adverse events occurred. The study confirms safety and an acute effect on cardiac pump function, but lacks long-term data.

PLAUSIBLE An observational study ⁽¹⁶⁾ investigated elamipretide in 14 patients with atherosclerotic renal artery stenosis during percutaneous transluminal renal angioplasty (PTRA). Six patients received 0.05 mg/kg/h elamipretide intravenously before and during PTRA, eight received placebo. Three months after the procedure, blood oxygenation (BOLD-MRI) showed a 6 % reduction in renal hypoxia with elamipretide, while it increased by 47 % with placebo (p<0.05). The study suggests a protective effect against ischaemia-reperfusion injury, albeit with small sample size and no cardiac endpoints. **Hypothesis:** The acute volume changes in ¹ may reflect improved mitochondrial ATP production and thus more efficient contractility, as preclinical data suggest. Whether this slows long-term progression of heart failure remains unclear.

The PROGRESS-HF study ⁽⁴⁾ tested elamipretide in a 28-day, placebo-controlled phase 2 study with 71 patients (LVEF $\leq 40\%$). Daily subcutaneous doses of 4 mg or 40 mg elamipretide did not significantly change left ventricular end-systolic volume (LVESV) compared with placebo (4 mg: -4.4 ml; 40 mg: -1.2 ml vs. placebo: -3.8 ml). Ejection fraction also remained unchanged. The study shows that the acute effects from ¹ are not transferable to longer oral/subcutaneous therapy. What is missing: A study with longer treatment duration and clinical endpoints such as hospitalisation rate or mortality.

Safety and Tolerability

PROVEN The MMPOWER study ⁽²⁾ examined elamipretide in a randomised, placebo-controlled dose-finding trial involving 36 patients with primary mitochondrial myopathy (PMM). Participants received intravenous infusions of 0.01, 0.1 or 0.25 mg/kg/h or placebo over 2 hours. The highest dose led to an increase in 6-minute walk test (6MWT) distance of 64.5 m after 5 days (placebo: +20.4 m, p=0.053). Adverse events were mild, primarily infusion reactions. The study confirms short-term tolerability and a dose-dependent effect on physical performance.

In a phase 2 study ⁽¹¹⁾ involving 12 patients with Leber hereditary optic neuropathy (LHON), elamipretide was tested as a 1% topical eye drop solution over 52 weeks. Treatment was safe, with local irritation as the most common adverse effect. No systemic effects occurred. The study shows that elamipretide is also well tolerated locally, though without significant improvement in visual acuity. **Hypothesis:** The good tolerability may be due to selective binding to cardiolipin and lack of accumulation in healthy mitochondria, as suggested by preclinical data.

What is missing: Long-term safety data for chronic use, particularly regarding cumulative toxicity and potential antibody formation against the peptide.

Fatigue and Stress in Mitochondrial Diseases

PROVEN The MMPOWER-3 study ⁽⁵⁾ was a phase 3 trial involving 218 patients with primary mitochondrial myopathy (PMM). Participants received 40 mg elamipretide subcutaneously or placebo daily for 24 weeks. The primary endpoints – 6MWT distance and total fatigue on the *Primary Mitochondrial Myopathy Symptom Assessment* (PMMSA) – showed no significant differences between groups. The study *showed* a subjective improvement without objective performance gains.

In the TAZPOWER study ⁽³⁾ involving 12 patients with Barth syndrome, a 12-week treatment with 40 mg elamipretide daily followed by a 36-week open-label extension led to a significant improvement in 6MWT distance (+95.9 m, p=0.024) and a reduction in symptom burden on the *Barth Syndrome Symptom Assessment* (BTHS-SA, -2.1 points, p=0.031). The study shows that elamipretide can improve physical performance and reduce symptom burden in the long term for specific genetic defects (TAZ mutation). **Hypothesis:** The differing results in ⁵ and ³ may reflect the heterogeneity of mitochondrial diseases – elamipretide may act only in specific defects of cardiolipin synthesis.

What is missing: Stratified genotype-based analyses in larger studies to identify responder profiles.

Musculoskeletal System and Muscle Metabolism

However, patients reported a significant reduction in fatigue (PMMSA Total Fatigue, p=0.0006) and an improvement in fatigue (Neuro-QoL Fatigue Short Form, p=0.0115). The study *showed* that elamipretide alleviates subjective fatigue symptoms without enhancing objective performance.

A placebo-controlled study ⁽⁷⁾ in 39 healthy older adults (60–85 years) examined the effect of a single elamipretide infusion (dose not specified) on mitochondrial ATP production in muscle. Immediately after infusion, mitochondrial capacity (ATPmax) increased significantly (p=0.045), while mitochondrial coupling (P/O) remained unchanged. The study showed an acute improvement in mitochondrial energy production, though without clinical correlates such as muscle strength or endurance. **Hypothesis:** The lack of correlation between ATPmax and muscle strength may indicate a delayed translation of mitochondrial effects into muscular function.

The study showed long-term efficacy in this specific patient group. What is missing: Studies with longer treatment duration in other mitochondrial myopathies to assess generalisability of the results.

Oxidative Stress and Mitochondrial Function

PLAUSIBLE A systematic review ⁽²⁶⁾ analysed 19 studies of mitochondrial antioxidants, including three controlled studies on elamipretide. Within these elamipretide studies, significant improvement in endothelial function was observed (flow-mediated dilation, SMD: 1.19, $p=0.01$), though with high heterogeneity ($I^2=67\%$). Other endpoints such as glycaemic control or oxidative stress markers showed no consistent effects across the mitochondrial antioxidants reviewed. The evidence for elamipretide is preliminary and based on small studies with diverse populations.

In a preclinical study ⁽¹⁸⁾, elamipretide (SS-31) in cells from patients with Friedreich ataxia led to dose-dependent upregulation of frataxin, improved activity of iron-sulfur enzymes (aconitase, complexes II/III) and normalised mitochondrial membrane potential. The study provides in vitro evidence for a potential effect on mitochondrial biogenesis. **Hypothesis:** The antioxidant effect of elamipretide may extend beyond stabilising cardiolipin and directly influence the expression of mitochondrial proteins, though this remains to be clinically investigated in humans.

What is missing: Clinical studies with direct measurements of oxidative stress (e.g. 8-OHdG, F2-isoprostanes) and mitochondrial function (e.g. in vivo ATP production) under elamipretide.

Metabolism and Biomarkers

PLAUSIBLE In the TAZPOWER study ⁽¹³⁾, metabolomic biomarkers were examined in 12 patients with Barth syndrome receiving elamipretide (40 mg daily). After 12 weeks, medium- and short-chain acylcarnitines in plasma and urine were significantly reduced ($p<0.05$). Acetylcarnitine, 3-hydroxybutyrate and 3-methylglutaconate also tended to decrease but did not reach statistical significance. The study showed a normalisation of disturbed lipid metabolism, though without correlation to clinical endpoints. **Hypothesis:** The reduction in acylcarnitines may indicate improved β -oxidation and more efficient use of fatty acids as an energy source.

What is missing: Studies with larger cohorts and longer treatment duration to link elamipretide's metabolic effects with clinical outcomes.

Inflammatory Processes

PLAUSIBLE An observational study ⁽¹⁹⁾ examined the effect of elamipretide (SS-31) on leukocytes from 51 patients with type 2 diabetes. Treatment reduced mitochondrial ROS production, increased glutathione content and improved leukocyte-endothelium interaction (increased rolling velocity, reduced adhesion). SIRT1 levels rose while NF κ B-p65 and TNF α fell. The study provides evidence of anti-inflammatory and mitochondrial effects at the cellular level, though without clinical endpoints. **Hypothesis:** The reduction in NF κ B may reflect a direct antioxidant effect or improved mitochondrial function at the cellular level.

What is missing: Clinical studies with inflammation-related endpoints (e.g. CRP, cytokines) under elamipretide, particularly in chronic inflammatory diseases.

Overall Picture

Elamipretide shows consistent effects on mitochondrial function in preclinical and clinical studies, particularly through stabilising cardiolipin and improving ATP production. Controlled trials in genetically defined mitochondrial diseases such as Barth syndrome indicate improvements in physical performance and quality of life ^(3, 8). In primary mitochondrial myopathy (PMM), results are more heterogeneous: while subjective symptoms such as fatigue are alleviated, objective performance often remains unchanged ^(5, 6). **Hypothesis:** The differing efficacy may relate to underlying genetic defects – elamipretide may act only in disorders of cardiolipin synthesis or remodelling.

In cardiovascular indications, data are preliminary. Acute effects on cardiac pump function ⁽¹⁾ and ischaemia-reperfusion injury ⁽¹⁶⁾ are promising, while longer-term therapy showed no significant changes in left ventricular volumes ⁽⁴⁾. The safety profile of elamipretide is well established across studies, with local reactions as the most common adverse effect. What is systematically missing: long-term safety and efficacy data, stratified genotype-based analyses and larger studies with clinical endpoints (e.g. hospitalisation rate, mortality).

Study methodology of the evidence base

Clinical studies on elamipretide include randomised, placebo-controlled designs with small to moderate sample sizes ($n=12-218$). Typical treatment durations range from 4 weeks ^(4, 6) to 168 weeks ⁽⁸⁾, with most studies focusing on short-term effects. Primary endpoints often include functional parameters such as the 6-minute walk test (6MWT) or patient-reported symptom scales (e.g., PMMSA, BTHS-SA). In cardiovascular studies, imaging techniques (echocardiography, MRI) are used to assess structural changes ^(1, 4). Systematic limitations include the lack of genotype stratification in many studies, short treatment duration, and a focus on surrogate parameters rather than clinical outcomes. Additionally, direct measurements of mitochondrial function (e.g., in vivo ATP production) are absent in most clinical trials.

Why elamipretide is not a straightforward solution for mitochondrial disorders

EVIDENCE:

Elamipretide does not improve symptoms in all patients with mitochondrial myopathies in controlled studies. **Genotype-dependent effects** (e.g., in the post-hoc analysis of MMPOWER-3) indicate that **only certain mutations** respond to the drug. Even in **Barth syndrome**, a monogenic disorder, **effectiveness was inconsistent** in the long-term TAZPOWER study. The **PROGRESS-HF** trial examined the prevention of left ventricular ejection fraction decline in heart failure; results were inconsistent. These findings suggest that **mitochondrial dysfunction** cannot be addressed solely through **cardiolipin stabilisation**.

PLAUSIBLE:

The **short half-life** and **subcutaneous administration** limit practical use. Preclinical data show that elamipretide has been studied primarily in **acute stress scenarios** (e.g., ischaemia), not in **chronic mitochondrial damage**. The **lack of oral bioavailability** further complicates **long-term therapy**. The question of whether elamipretide as **monotherapy is sufficient** therefore remains **unanswered**—combined approaches (e.g., with gene replacement therapies) may be

necessary.

3. How Robust the Research Is

Research clusters around **three key areas**: **fatigue syndromes** (multiple studies, mostly in primary mitochondrial myopathy), **cardiovascular diseases** (controlled trials, particularly in heart failure), and **rare genetic disorders** such as **Barth syndrome**. A notable feature is the **high number of observational studies across various compounds**, including elamipretide, that describe **associations** between mitochondrial dysfunction and clinical symptoms but do not test **causality**. The **most frequently cited controlled trials** for elamipretide (e.g., MMPOWER-3, TAZPOWER) investigate **dose-dependent effects** and **long-term safety**, not primarily efficacy.

The **methodological strengths** of the field lie in the **precise characterisation of the target structure**: elamipretide binds specifically to **cardiolipin**, which is **well-established preclinically**. The **limitations** become apparent in **translatability**: animal and cell models do not reflect the **genetic heterogeneity** critical in human mitochondrial disorders. Controlled human studies are **small** and **short**. The question of **efficacy** remains open because **genotype-specific effects** do not allow for **generalised conclusions**.

4. Common Claims — and What the Data Show

CLAIM	EVIDENCE BASE
Elamipretide works for all forms of fatigue	Proven: Controlled trials show no efficacy in non-specific fatigue . Effects are documented only in primary mitochondrial myopathy , not in chronic fatigue syn
Elamipretide prevents deterioration in age-related macular degeneration	Plausible: The ReCLAIM-2 study investigated the prevention of worsening geographic atrophy growth ; no significant deceleration was observed. Ellipsoid zon
Elamipretide improves heart function in all heart failure patients	Verified: The PROGRESS-HF study examined the prevention of ejection fraction deterioration; no significant improvement was observed. Effects were only det
Elamipretide is a universal antioxidant	Proven: Elamipretide does not act as a radical scavenger but stabilises cardiolipin . It exhibits no systemic antioxidant effect .

5. Profile: Molecule and Charge

Elamipretide (SS-31) is not a single molecule but a **mixture** — there is no single molecular formula or fixed molecular mass. What can be described are functional groups, charge behaviour, and redox properties; this is the focus of the next section.

6. Charge, Electrons, Radicals

Electrochemical properties and human measurements: Elamipretide (SS-31) targets mitochondrial processes, particularly the regulation of reactive oxygen species (ROS). As a cationic peptide, it interacts with the anionic phospholipid cardiolipin in the inner mitochondrial membrane, stabilising the cardiolipin–cytochrome c supercomplex ²². This interaction reduces ROS production without acting as a classical antioxidant. In humans, the effect on ROS was measured in leukocytes: after SS-31 treatment, ROS levels decreased while mitochondrial membrane potentials and glutathione content remained stable ¹⁹. Modulation of inflammatory markers such as NFκB-p65 and TNFα was also observed ¹⁹. In leukocytes from type 2 diabetes patients, SS-31 reduced expression of ER stress markers (GRP78, CHOP) and influenced autophagy proteins (Beclin1, LC3 II/I) ²¹. ROS reduction was also seen in cardiac muscle cells in heart failure, where SS-31 specifically addressed mitochondrial calcium homeostasis and ROS formation ²⁰.

Redox modulation and clinical relevance: The electrochemical action of elamipretide disrupts pathological ROS cascades rather than acting through direct electron transfer or radical scavenging. In preclinical and human cell models (e.g., MCF-7, T47D), SS-31 lowered ROS levels and improved activity of mitochondrial respiratory chain complexes (III, V). Stabilisation of cardiolipin by SS-31 also prevents cytochrome c release, inhibiting apoptotic pathways ²². Whether these effects result from direct charge neutralisation or conformational changes in membrane proteins remains unclear. The next step would be to examine how ROS modulation impacts long-term mitochondrial biogenesis and cellular redox homeostasis.

7. Interactions with Other Substances

Which other substances on this platform have been **co-investigated or discussed** with elamipretide in human studies or reviews — combinations, comparisons, or shared pathways. The number refers to studies in which both appear.

SUBSTANCE	SHARED STUDIES	OF WHICH CONTROLLED IN HUMANS
Stress, cortisol and inflammation	11	1
Chronic inflammation	8	0
Iron	4	0
MOTS-c and mitochondrial peptides	3	0
NAD precursors (NMN, NR)	2	0

Elamipretide (SS-31) specifically binds to the phospholipid cardiolipin in the inner mitochondrial membrane and stabilises it. As cardiolipin is essential for the function of the respiratory chain and its interaction with cytochrome c, elamipretide may indirectly influence the efficiency of ATP synthesis, as shown in preclinical cell culture data ²⁴. Whether this binding alters the uptake or efficacy of other mitochondrially active substances (e.g. coenzyme Q10, iron preparations) has not been investigated in the available studies ²³.

To date, no clinical or preclinical data exist on interactions of elamipretide with drugs, nutrients or other active substances. A cell culture study suggests that elamipretide may act synergistically with vitamin B6 and VEGF, though without direct statements on interactions ²⁵. Whether binding to cardiolipin affects the pharmacokinetics of other substances remains an open question requiring targeted interaction studies.

8. Overdose, Tolerability, Limits

PROVEN In controlled human studies, elamipretide has been investigated at doses up to 40 mg/day administered subcutaneously over 24 weeks. Tolerability was good, with predominantly mild to moderate adverse effects. The most common adverse effect was local reactions at the injection site (80 % of participants), which were mostly mild ^{6 5}. No serious adverse events or deaths occurred ^{6 4}. In a phase 3 study with 176 participants, no significant differences in the frequency of drug-related adverse effects were observed between elamipretide and placebo ^{9 4}. Laboratory, echocardiographic and clinical safety parameters were monitored in several studies without evidence of toxicity ¹.

PROVEN Data on overdose or upper limits are not available from the studies reviewed. The highest tested dose was 40 mg/day administered subcutaneously over 24 weeks ⁵. In short-term studies (e.g. single infusions), no dose-dependent safety risks were observed, although the highest dose showed a significant reduction in left ventricular end-diastolic (~18 ml) and end-systolic (~14 ml) volumes ¹. Long-term safety data are still pending ¹. It remains to be clarified whether higher doses or longer durations of use entail additional risks or whether the good tolerability is confirmed.

9. The Most Robust Studies

Ranked by evidence quality, not by prominence. The full evaluation includes significantly more studies; only the most robust are listed here.

Controlled Human Studies

- ¹ Novel Mitochondria-Targeting Peptide in Heart Failure Treatment: A Randomized, Placebo-Controlled Trial of Elamipretide (2017)
- ² Randomized dose-escalation trial of elamipretide in adults with primary mitochondrial myopathy (2018)
- ³ A phase 2/3 randomized clinical trial followed by an open-label extension to evaluate the effectiveness of elamipretide in Barth syndrome, a genetic ... (2021)
- ⁴ Effects of Elamipretide on Left Ventricular Function in Patients With Heart Failure With Reduced Ejection Fraction: The PROGRESS-HF Phase 2 Trial (2020)
- ⁵ Efficacy and Safety of Elamipretide in Individuals With Primary Mitochondrial Myopathy: The MMPOWER-3 Randomized Clinical Trial (2023)
- ⁶ A randomized crossover trial of elamipretide in adults with primary mitochondrial myopathy (2020)
- ⁷ In vivo mitochondrial ATP production is improved in older adult skeletal muscle after a single dose of elamipretide in a randomized trial (2021)
- ⁸ Long-term efficacy and safety of elamipretide in patients with Barth syndrome: 168-week open-label extension results of TAZPOWER (2024)

- ⁹ ReCLAIM-2: A Randomized Phase II Clinical Trial Evaluating Elamipretide in Age-related Macular Degeneration, Geographic Atrophy Growth, Visual ... (2025)
- Effect of mitochondrial-targeted antioxidants on glycaemic control, cardiovascular health, and oxidative stress in humans: A systematic review and ... (2022)
- ¹⁰ Genotype-specific effects of elamipretide in patients with primary mitochondrial myopathy: a post hoc analysis of the MMPOWER-3 trial (2024)
- ¹¹ Elamipretide Topical Ophthalmic Solution for the Treatment of Subjects with Leber Hereditary Optic Neuropathy: A Randomized Trial (2024)
- Psychometric performance of the Primary Mitochondrial Myopathy Symptom Assessment (PMMSA) in a randomized, double-blind, placebo-controlled crossover ... (2022)
- ¹² Identifying responders to elamipretide in Barth syndrome: Hierarchical clustering for time series data (2023)
- Initial Psychometric Evaluation of the Barth Syndrome Symptom Assessment (BTHS-SA) for Adolescents and Adults in a Phase 2 Clinical Study (2025)
- RePOWER: An International, Prospective, Non-Interventional Registry of Patients With Primary Mitochondrial Myopathy (2026)
- ¹³ Metabolomic biomarkers from patients with Barth syndrome treated with elamipretide: insights from the TAZPOWER study (2020)
- ¹⁴ In Vivo Mitochondrial ATP Production Is Improved in Older Adult Skeletal Muscle After a Single Dose of Elamipretide in a Randomized Trial (2020)

Observational Human Studies

- ¹⁵ The mitochondrial-targeted compound SS-31 re-energizes ischemic mitochondria by interacting with cardiolipin (2013)
- ¹⁶ Phase 2a Clinical Trial of Mitochondrial Protection (Elamipretide) During Stent Revascularization in Patients With Atherosclerotic Renal Artery ... (2017)
- Targeting Mitochondrial Calcium Handling and Reactive Oxygen Species in Heart Failure (2017)
- ¹⁷ Elamipretide: A Review of Its Structure, Mechanism of Action, and Therapeutic Potential (2025)
- ¹⁸ Peptide SS-31 upregulates frataxin expression and improves the quality of mitochondria: implications in the treatment of Friedreich ataxia (2017)
- ¹⁹ The mitochondrial antioxidant SS-31 increases SIRT1 levels and ameliorates inflammation, oxidative stress and leukocyte-endothelium interactions in ... (2018)

10. Summary

Evidence: Preclinically, elamipretide stabilises mitochondrial membrane integrity by binding to cardiolipin and improves ATP production in animal and cell models. In genetically defined conditions such as Barth syndrome (TAZ mutation), the TAZPOWER study showed long-term improvements in physical performance (+95.9 m in the 6MWT) and quality of life. In cardiology, a single high-dose infusion (0.25 mg·kg⁻¹·h⁻¹) showed significant effects on left ventricular function (~18 ml end-diastolic volume), whereas longer subcutaneous therapy (PROGRESS-HF) produced no structural changes. Subjective symptoms such as fatigue were alleviated in primary mitochondrial myopathy (PMM) without objective performance gains (MMPOWER-3).

Plausible and potential implications: **Plausible:** Preclinically, a systematic review of mitochondrial antioxidants ²⁶, which covers many such agents and not only elamipretide, reports reduced mitochondrial ROS production and improved endothelial function, though with high heterogeneity. In type 2 diabetes (n=51), it lowered NFκB-p65 and TNFα, suggesting anti-inflammatory effects. **Hypothesis:** Differences in outcomes between PMM and Barth syndrome may relate to specific defects in cardiolipin synthesis – elamipretide may only act where cardiolipin remodelling is impaired. Acute cardiac volume changes could reflect more efficient ATP utilisation, yet whether this slows heart failure progression remains unclear. The lack of correlation between ATPmax and muscle strength (study ⁷) suggests mitochondrial effects may translate into functional improvements with a delay, though this has not been demonstrated in humans.

What a study should clarify: Stratified analyses by genotype in larger cohorts are needed to identify responder profiles – particularly in mitochondrial myopathies. Long-term studies with clinical endpoints (hospitalisation rate, mortality) and direct measurement of mitochondrial function (e.g., in vivo ATP production) are essential to assess the translational relevance of preclinical findings. In cardiovascular indications, studies with longer treatment durations (>28 days) and inflammatory biomarkers (CRP, cytokines) are lacking. Cumulative toxicity with chronic use should also be examined, including potential antibody formation against the peptide.

11. Open Questions

- **Genotype-specific therapy:** Which mitochondrial mutations respond to elamipretide – and why?
- **Combination therapies:** Does elamipretide enhance the efficacy of gene replacement therapies or metabolites (e.g., coenzyme Q10)?
- **Long-term effects:** Are there **cumulative benefits** or **resistance development** after prolonged therapy?

12. Further Paths

Pathways, mechanisms and networks in which this compound is involved – for those looking beyond the compound itself.

- Interaction network

Topics, mechanisms and chains in which this substance appears — for those who want to look beyond the substance.

Frequently Asked Questions

Why does elamipretide not work in some patients with mitochondrial myopathy?

Evidence: The **genetic heterogeneity** of mitochondrial diseases explains the **variable effects**. In MMPOWER-3, **only specific mutations** (e.g., in the *TAZ* gene) responded to elamipretide. Other patients showed **no measurable improvement** in muscle strength or endurance. **Stabilisation of cardiolipin** appears **insufficient** to compensate for all forms of mitochondrial dysfunction. The **next study** should investigate **genotype-stratified cohorts**.

Can elamipretide be used in heart failure?

Plausible: The evidence is **inconsistent**. PROGRESS-HF examined the prevention of a decline in ejection fraction; no significant improvement was observed. However, preclinical studies showed **positive effects**. The **discrepancy** may be due to **patient selection**: in **Barth syndrome**, the **effect was more consistent**. A **controlled trial** with **genotypic stratification** would be needed to define the **target population**.

Are there oral formulations of elamipretide?

Evidence: Not yet. Elamipretide is administered **subcutaneously or intravenously** due to **low oral bioavailability**. Its **short half-life** also necessitates **multiple daily doses**, which complicates **long-term compliance**. An **oral formulation** would be a **major advance**, but this remains **unavailable** to date.

Sources

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Roshanravan B, Liu SZ, Ali AS, Shankland EG, Goss C, Amory JK et al. · 2021

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