SS-31

What Human Research Suggests About Mitochondrial Energy, Muscle Function, Cardiolipin and Cellular Stress

A conversational scientific review that starts with the strongest human evidence, then connects those findings to mitochondrial bioenergetics, cardiolipin biology and the broader translational research program.

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RESEARCH-USE SCOPE

This report discusses published human, translational and mechanistic research on SS-31 (elamipretide). Findings obtained with regulated pharmaceutical elamipretide do not establish that a Vanguard Compound Research material is safe, effective or suitable for administration. This report does not provide a dose, route, treatment protocol or medical recommendation. For laboratory research only; not for human or veterinary use.

THE HUMAN QUESTION

What could SS-31 realistically mean in people?

SS-31 is unusual among mitochondrial research peptides because the human evidence is no longer limited to small exploratory studies. Elamipretide has been tested across randomized trials in primary mitochondrial disease, heart failure, age-related macular degeneration, renal ischemia and older adults with low mitochondrial function. In 2025, the FDA granted accelerated approval to a specific elamipretide drug product for Barth syndrome based on knee-extensor muscle strength as an intermediate endpoint. At the same time, several large or well-controlled trials have been neutral on their primary endpoints. [1][2][5][8][10]

Cardiolipin	Membrane structure	Bioenergetics	Human outcomes
inner-membrane target	cristae / protein assembly	electron transport / ATP	strength / function / symptoms

That sequence is the central scientific idea, but it should not be read as a guarantee that a mitochondrial signal will translate into a clinical benefit. Human trials show both positive and negative examples, which makes SS-31 scientifically interesting precisely because the evidence can be separated into mechanism, measurable mitochondrial physiology and disease-specific outcomes. [5][7][11][12]

Four questions worth separating

Barth syndrome Why did FDA grant accelerated approval even though the randomized phase did not meet its primary endpoints?	**Primary mitochondrial myopathy** What did the 218-person phase 3 trial show, and what can a post-hoc genotype signal actually tell us?
Mitochondrial energy Can elamipretide measurably change ATP-production capacity in living human muscle?	**Broader translation** What happened in heart, kidney and retinal studies, and where did biological signals fail to become primary-endpoint wins?

1 | BARTH SYNDROME

The clearest human signal - and an unusually nuanced approval

Short answer

The U.S. FDA granted accelerated approval to Forzinity (elamipretide) in September 2025 to improve muscle strength in adults and children with Barth syndrome weighing at least 30 kg. The randomized crossover portion of the pivotal study did not show superiority on its two primary endpoints, and the knee-strength difference was also not apparent during the randomized phase. The approval relied on sustained increases in knee extensor strength seen during the small open-label extension, with a confirmatory randomized trial required. [1][2][15]

SPIBA-201 enrolled only 12 participants with genetically confirmed Barth syndrome. During the initial controlled phase, elamipretide was not superior to placebo on 6-minute walk distance or the Barth Syndrome Symptom Assessment fatigue endpoint. Median knee-extensor strength changed by -5 N on placebo and +4 N on elamipretide at week 12. [1]

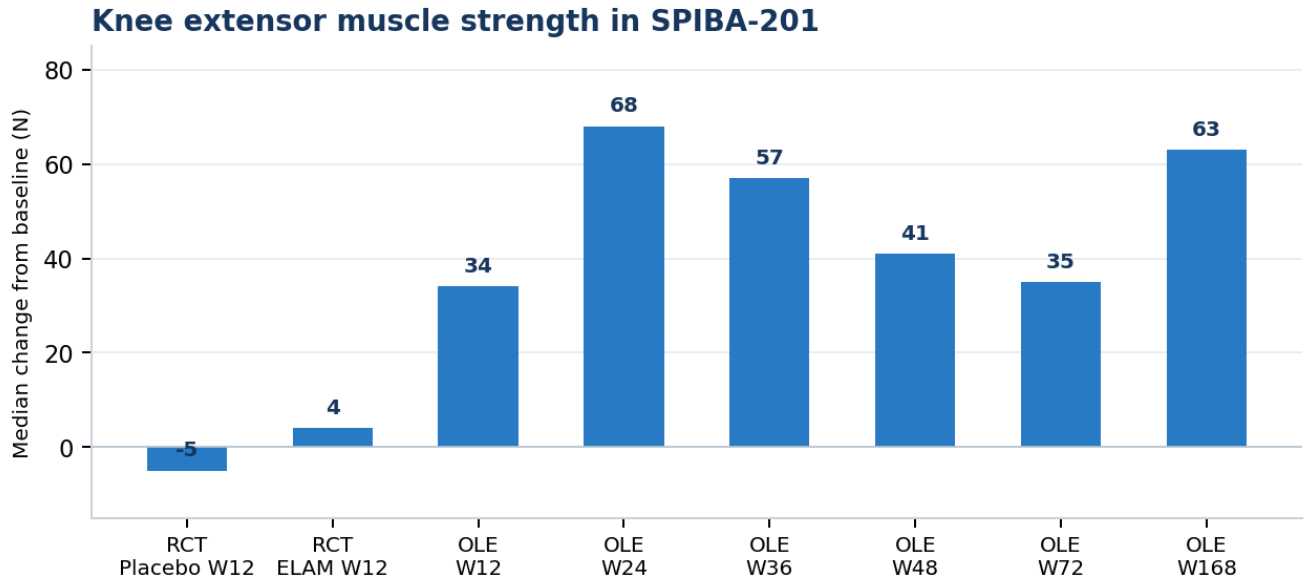


Figure 1. FDA label values for median change in knee-extensor strength. The open-label extension (OLE) showed larger increases over time, reaching a median +63 N at week 168 among eight continuing participants. Open-label data are vulnerable to expectancy, training, attrition and other biases, so the long-term signal is not equivalent to a randomized treatment effect. [1][4][15]

The useful interpretation

Barth syndrome provides real human evidence that long-term elamipretide exposure can coincide with sustained strength and functional changes in a disease directly tied to abnormal cardiolipin biology. It also illustrates the central limitation of the evidence: the strongest long-term gains were observed without a concurrent control group. FDA therefore used accelerated approval and required confirmation of clinical benefit rather than treating the evidence as fully settled. [1][2][15][16]

2 | PRIMARY MITOCHONDRIAL MYOPATHY

Did a larger phase 3 trial confirm broad functional benefit?

Short answer

No. MMPOWER-3 randomized 218 people with genetically confirmed primary mitochondrial myopathy and did not meet either co-primary endpoint at 24 weeks. The 6-minute walk distance improved in both groups, with no advantage for elamipretide, and fatigue scores were also not significantly different. [5]

The phase 3 population was genetically heterogeneous: roughly three quarters had mitochondrial-DNA abnormalities and the remainder had nuclear-DNA defects. Elamipretide-treated participants improved by 14.1 m on the 6-minute walk test, while placebo participants improved by 17.3 m. The between-group difference was -3.2 m (95% CI -18.7 to 12.3; p=0.69). [5]

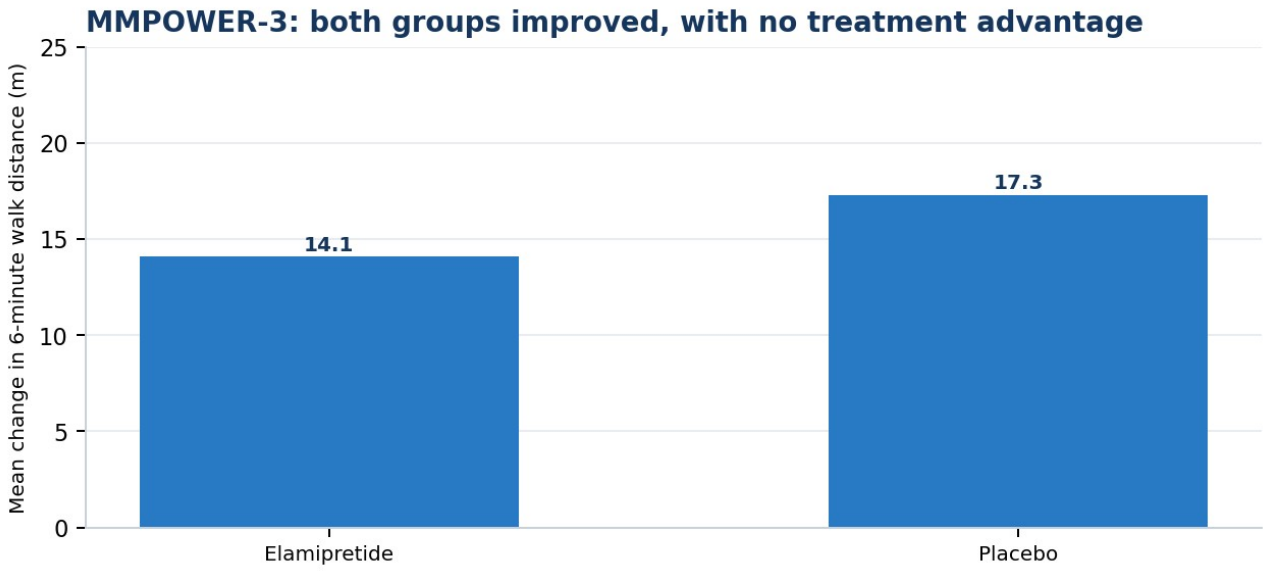


Figure 2. MMPOWER-3 change in 6-minute walk distance at week 24. A positive change occurred in both groups, but placebo improved numerically more; the between-group difference was not statistically significant. [5]

What about the nuclear-DNA subgroup?

A post-hoc analysis found a 25.2 m between-group difference favoring elamipretide among participants with nuclear-DNA defects, while the mitochondrial-DNA subgroup did not show benefit. That signal helped motivate a genetically enriched follow-up phase 3 program. It is scientifically important, but because it arose from subgroup and post-hoc analyses after an overall negative trial, it should be treated as hypothesis-generating rather than a confirmed indication. [5][6][17]

Why this matters scientifically

SS-31 may not behave as a single "mitochondrial enhancer" across every genetic disorder that impairs oxidative phosphorylation. Disease mechanism, genotype, baseline mitochondrial reserve and the endpoint being measured may strongly influence whether a biological effect becomes clinically visible.

3 | DIRECT HUMAN MITOCHONDRIAL ENERGETICS

Can SS-31 change ATP-production capacity in living human muscle?

Short answer

A small randomized trial suggests it can - at least transiently. In 39 older adults selected for low mitochondrial function, a single elamipretide infusion increased the relative change in skeletal-muscle ATP-production capacity more than placebo immediately after treatment. The effect was not different from placebo by day 7, and improved ATP capacity did not produce a measurable improvement in the study's muscle-fatigue test. [7]

This study is valuable because it measured mitochondrial physiology in vivo rather than relying only on symptoms. Phosphorus magnetic resonance spectroscopy was used to estimate maximal ATP-production capacity (ATPmax) in hand muscle. The mean immediate increase was 27% with elamipretide versus 12% with placebo; the between-group comparison for percent change reached p=0.045. [7]

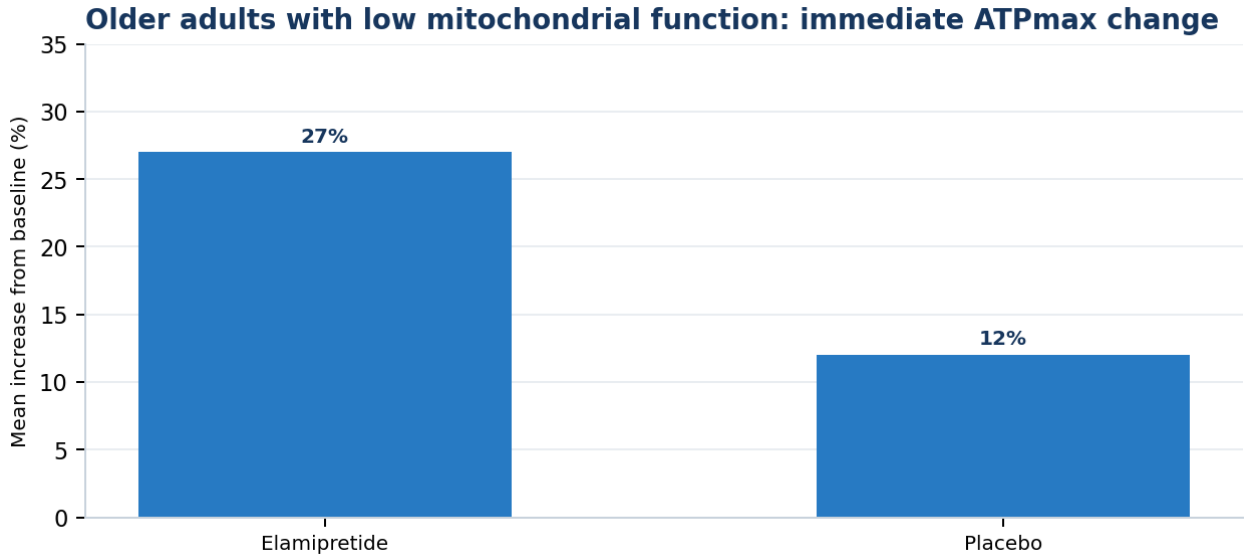


Figure 3. Immediate percentage increase in ATPmax after a single treatment in older adults with low baseline mitochondrial function. The study was small, the absolute-change analysis narrowly missed conventional significance (p=0.055), and there was no treatment difference at day 7. [7]

The translational lesson

The trial separates two questions that are often blurred together: can the molecule alter a measurable mitochondrial process, and does that alteration improve how a person functions or feels? Here, the mitochondrial signal was detectable while the functional fatigue endpoint was not. That makes the result mechanistically supportive but not evidence of a broad performance or anti-aging effect.

4 | CARDIOLIPIN AND INNER-MEMBRANE BIOLOGY

SS-31 is better described as a membrane-modulating peptide than a simple antioxidant

Short answer

Early descriptions emphasized reactive-oxygen-species reduction, but the mechanism literature now points more strongly to reversible interactions with cardiolipin and the inner mitochondrial membrane. Experimental work suggests SS-31 can alter membrane electrostatics, support cristae organization and influence cardiolipin-dependent protein assemblies involved in oxidative phosphorylation. [11][12]

Cardiolipin is an unusually anionic phospholipid concentrated in the inner mitochondrial membrane. Its distribution and physical state help organize respiratory-chain proteins, ATP synthase and other membrane complexes. SS-31 is cationic and aromatic, allowing it to associate with cardiolipin-rich membranes through electrostatic and hydrophobic interactions. [11][12]

1. Membrane association SS-31 accumulates at the inner mitochondrial membrane and interacts with cardiolipin-rich lipid environments.	**2. Electrostatic / structural effects** Studies show changes in membrane surface electrostatics and support for cardiolipin-dependent protein organization.
3. Bioenergetic consequences Improved electron-transport organization and oxidative-phosphorylation capacity are plausible downstream consequences in dysfunctional mitochondria.	**4. Physiologic readouts** Human studies then ask whether those molecular changes produce measurable ATP, strength, walking, vision, cardiac or renal effects.

What the mechanism does not prove

- Cardiolipin binding does not guarantee a clinical benefit in every condition associated with mitochondrial dysfunction.
- A reduction in oxidative stress in a cell or animal model cannot be translated automatically into anti-aging, neuroprotective or performance claims in people.
- The relationship between membrane-level effects and disease-specific clinical outcomes remains context dependent, as demonstrated by both positive and neutral human trials.

Mechanistic takeaway

The most defensible scientific description is that SS-31 engages a mitochondrial membrane target with measurable effects on mitochondrial organization and bioenergetics. Human relevance must then be established separately for each population and endpoint.

5 | OTHER HUMAN PROGRAMS

The broader clinical record is mixed - and that is informative

Elamipretide has been tested in several organ systems where mitochondrial dysfunction is thought to contribute to disease. These programs show why mechanistic plausibility should not be confused with a guaranteed clinical effect.

Program	Population	Main controlled result	Interpretation
ReCLAIM-2	176 adults with dry AMD / geographic atrophy	Primary endpoints were not significant. Secondary analyses reported less ellipsoid-zone degradation and more >=10-letter low-luminance gains.	Suggestive retinal structural/functional signals, but not a positive primary-endpoint trial. [10]
PROGRESS-HF	71 adults with HFrEF	No significant improvement in LV end-systolic volume or ejection fraction after 4 weeks.	A plausible mitochondrial mechanism did not translate into short-term cardiac remodeling. [8]
Renal artery stenosis pilot	14 patients undergoing renal-artery stenting	Small phase 2a study reported less post-procedure hypoxia and later renal-flow/function signals.	Interesting human ischemia-reperfusion signal, but too small for broad conclusions. [9]
Older adult muscle	39 older adults with low mitochondrial function	Immediate ATPmax improved versus placebo, without a fatigue-resistance benefit.	Direct mitochondrial physiology can move even when function does not. [7]

The pattern across programs is not simply "works" or "does not work." Instead, SS-31 repeatedly shows biological plausibility and occasional objective human signals, while several rigorous trials have failed to meet prespecified primary endpoints. That combination is exactly why endpoint selection, disease biology and patient enrichment matter.

Evidence discipline

Secondary endpoints and post-hoc findings can guide the next study, but they should not be presented as if they carry the same evidentiary weight as a successful prespecified primary endpoint.

6 | HUMAN TOLERABILITY AND NEXT QUESTIONS

What does the current regulated safety record show?

Short answer

In the FDA-approved Barth syndrome program, injection-site reactions were the dominant adverse reactions. The U.S. label also warns about hypersensitivity reactions, including serious allergic reactions requiring emergency treatment. These regulated-product data describe Forzinity and should not be assumed to characterize independently manufactured research material. [1]

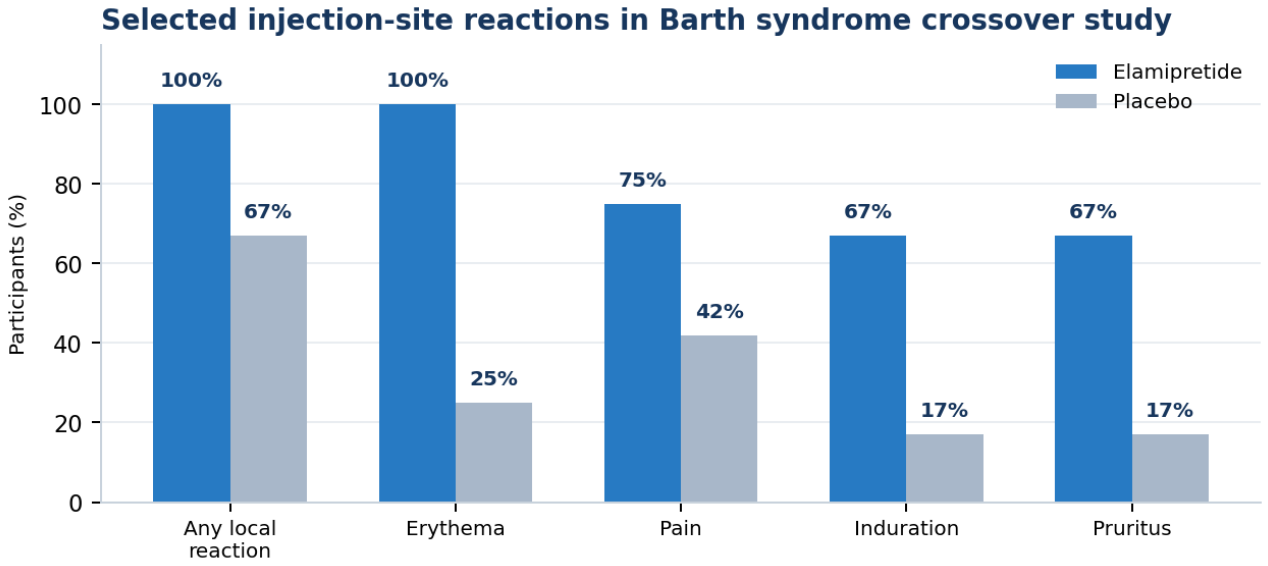


Figure 4. Selected local reactions in the 12-person placebo-controlled crossover safety population reported in the U.S. prescribing information. Small sample size means the percentages are imprecise, but local reactions were clearly common. [1]

What would move the science forward?

Confirm Barth clinical benefit A randomized post-approval trial should determine whether the muscle-strength signal translates into durable patient benefit and functional improvement.	**Resolve genotype response** Genetically enriched mitochondrial-disease studies can test whether the nuclear-DNA subgroup signal is reproducible rather than a post-hoc finding.
Connect mechanism to function Studies should pair direct mitochondrial measurements with prespecified functional endpoints to show whether bioenergetic changes matter to patients.	**Separate formulations and materials** Pharmaceutical formulation, chemical form, purity, sterility and exposure must be defined so results are not transferred across non-equivalent materials.

As of September 2026, a phase 3b/4 randomized confirmatory Barth syndrome study (4TAZPower) is listed in the Canadian clinical-trial portal, while the NuPOWER study in nuclear-DNA primary mitochondrial disease has completed enrollment/study conduct with results not yet posted in the ClinicalTrials.gov record cited here. [16][17]

7 | PRODUCT AND REGULATORY BOUNDARIES

A scientific result is inseparable from the material that produced it

SS-31 is the research name commonly used for elamipretide, a modified tetrapeptide. PubChem lists the free elamipretide molecular formula as C32H49N9O5, molecular weight 639.8 g/mol and CAS 736992-21-5. Research materials may contain different counterions or salt forms, so identity and quantitative expectations should be tied to the chemical form documented for the specific batch. [13]

Question	Method that addresses it	What remains separate
Is the expected peptide present?	LC-MS or high-resolution mass spectrometry with suitable reference criteria.	Purity, exact quantity, sterility and biological activity.
How pure is the chromatographic profile?	Qualified HPLC/UPLC method.	Exact active quantity, molecular identity and sterility.
How much active material is present?	Validated quantitative assay against an appropriate standard.	Identity, endotoxin, particulates and clinical suitability.
Is it suitable for administration?	That question cannot be answered by HPLC purity alone.	Sterility, endotoxin, particulates, stability, formulation, authorization and intended-use requirements.

Regulatory context

The U.S. FDA accelerated approval applies to the regulated Forzinity drug product and its labeled Barth syndrome indication - not to independently manufactured SS-31 research material. The FDA explicitly requires a postmarketing randomized trial to confirm clinical benefit. [1][2][15]

In Canada, Health Canada lists SS-31 among injectable peptide drugs that may be sold illegally online and states that unauthorized injectable peptides have not been assessed for safety, efficacy or quality. A July 2026 enforcement statement reiterated that unauthorized injectable peptides are prescription drugs requiring authorization before sale in Canada. [14]

Regulatory boundary

Human research relevance does not authorize human use. A research-use-only statement does not convert a material into an approved drug, sterile preparation or clinically interchangeable version of Forzinity. This report summarizes literature; it is not a Certificate of Analysis and does not provide instructions for administration.

Closing perspective

SS-31 has one of the more substantial translational evidence bases among mitochondria-targeted research peptides. The evidence supports a real cardiolipin/inner-membrane mechanism, a measurable human mitochondrial-energy signal, and a narrow FDA-approved pharmaceutical use in Barth syndrome. It also includes important negative trials. The strongest scientific presentation therefore keeps the validated signals, exploratory findings and unresolved questions clearly separated.

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