Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Elamipretide (also known as SS-31, Bendavia, and MTP-131)

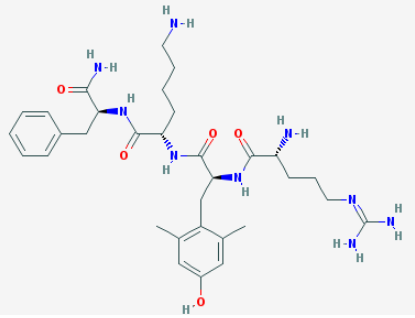
Evidence Summary

Elamipretide is approved for Barth syndrome. Some benefits have been seen in clinical trials of primary mitochondrial myopathy and age-related macular degeneration. Injection site reaction is common.

Neuroprotective Benefit: In rodent models, SS-31 improves cognitive functions by promoting mitochondrial and synaptic health. Neuroprotective benefits have not been confirmed in humans except in a single patient with a rare neurodegenerative condition.

Aging and related health concerns: Elamipretide is approved for Barth syndrome. Benefits in some outcomes have been observed in select subgroups of primary mitochondrial myopathy and age-related macular degeneration. Confirmatory trials are ongoing.

Safety: The most common adverse event with elamipretide is injection site reaction, occurring in most patients. Other adverse events include dizziness, nausea, and increased eosinophil counts (without clinical manifestations).

Availability: Rx for Barth syndrome	**Dose**: The adult and pediatric dose for Barth syndrome in patients weighing at least 30 kg is 40 mg per day, subcutaneously.	**Chemical formula:** $C_{32}H_{49}N_9O_5$ **MW**: 639.80 
Half life: plasma half-life is 4-6 hours after subcutaneous or intravenous administration	**BBB**: Permeable	
Clinical trials: The largest trial was the phase 3 study in primary mitochondrial myopathy that enrolled 218 patients, but this trial was terminated because it did not meet the primary end points.	**Observational studies**: None	

What is it?

Elamipretide (also known as SS-31, Bendavia, and MTP-131) is a small peptide (D-Arg-dimethyl-Tyr-Lys-Phe-NH2) that accumulates in mitochondria and scavenges reactive oxygen species. SS-31 binds to cardiolipin, a lipid exclusively expressed on the inner mitochondrial membrane that plays an important structural role in organizing the components of the electron transport chain into "supercomplexes" for more efficient oxidative phosphorylation with minimal generation of reactive oxygen species (Birk et al., 2013; Szeto, 2014). By binding to cardiolipin, SS-31 modulates the hydrophobic interaction between cytochrome c and cardiolipin and promotes the electron carrying function of cytochrome c (Szeto, 2014). SS-31 also inhibits the opening of the mitochondrial permeability transition pore that forms under mitochondrial stress (e.g., traumatic brain injury, stroke, neurodegenerative diseases) (Wu et al., 2016). Opening of the mitochondrial permeability transition pore can lead to mitochondrial swelling and apoptosis. SS-31 was discovered by Dr. Hazel Szeto at Weill Cornell Medical College.

In September 2025, the US FDA granted accelerated approval of elamipretide (marketed as Forzinity) to improve muscle strength in adult and pediatric patients with Barth syndrome weighing at least 30 kg

(~66 lbs)(Shirley, 2026). Barth syndrome is a rare mitochondrial cardioskeletal disease that affects ~150 people in the US. Elamipretide is the first treatment option for Barth syndrome. Because of the accelerated approval status, continued approval may be contingent upon confirmation of clinical benefit. Stealth is providing compassionate use access of elamipretide for patients weighing less than 30 kg.

Elamipretide is also being investigated in clinical trials for treating dry age-related macular degeneration and primary mitochondrial myopathy due to nDNA mutations (Stealth pipeline). In this report, elamipretide and SS-31 are used interchangeably; generally, the more recently published studies refer to the drug as elamipretide.

Neuroprotective Benefit: In rodent models, SS-31 improves cognitive functions by promoting mitochondrial and synaptic health. Neuroprotective benefits have not been confirmed in humans except in a single patient with a rare neurodegenerative condition.

Types of evidence:

- 0 clinical trials
- 1 case report of a patient with membrane protein-associated neurodegeneration
- Numerous laboratory studies
- 1 review

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

No clinical or observational studies in humans have evaluated the potential effect of elamipretide for preventing dementia or age-related cognitive decline.

A case report presented a 17-year-old patient with membrane protein-associated neurodegeneration who showed symptomatic improvements with elamipretide treatment (Patino et al., 2024). Membrane protein-associated neurodegeneration (MPAN) is a type of neurodegeneration with brain iron accumulation (NBIA) that is caused by pathogenic variants in the C19orf12 gene. The disorder is characterized by progressive spastic paresis (muscle weakness), gait changes, neuropsychiatric abnormalities, progressive dystonia (involuntary repetitive muscle contractions), and cognitive decline. Other symptoms include optic atrophy, dysphasia (difficulty swallowing), dysarthria (motor speech

disorder), bladder incontinence, axonal neuropathy, and parkinsonism. The female patient first presented to a neurology department at 17 years of age due to a progressive 4-year history of difficulty rising from the floor and multiple falls. She had a past medical history of optic nerve atrophy, but had met her early developmental milestones, including walking by 13 months of age. At 12 years of age, she developed gait imbalance resulting in multiple falls. At 13 years of age, the patient complained of blurry vision, but MRI showed normal optic nerves and brain architecture. Her neurologic exam was positive for pale optic disks on fundoscopy, mild dysarthria, slowed cognition, dystonic posturing of her ankles, and strength of 4 out of 5 in all extremities proximally and distally, hyperreflexia, and unsteady gait with a positive Trendelenburg sign (weak hip abductor muscles on the stance leg). Laboratory measures showed mildly elevated creatine kinase (299 U/L, reference range 12–191 U/L), while lactic acid (1.5 mmol/L, reference range 0.5–2.2 mmol/L) and aldolase (6.4 U/L, reference range 1.2–7.6 U/L) were within normal limits. Her electromyography/nerve conduction study showed fibrillations and positive sharp waves, suggesting an axonal motor neuropathy. Whole exome sequencing showed a de novo pathogenic variant in the C19orf12 gene that has been shown to produce autosomal dominant MPAN. Daily CoQ10 supplementation and physical therapy were initiated. Into her teenage years, the patient could exercise regularly but she started to experience worsening gait, stiffness, spasticity, falls, and mild dysphagia. The patient was enrolled into the Expanded Access Program (SPIES-006: Elamipretide for Subcutaneous [SC] Injection in Patients with Genetically Confirmed Rare Diseases with Known Mitochondrial Dysfunction; Stealth BioTherapeutics) at the age of 21. Elamipretide was initiated at a dose of 40 mg per day, subcutaneously. After 3 months of treatment, improvements were noted in the patient's dysarthria, dysphagia, gait, and ability to complete her activities of daily living. Her 6-minute walk test distance improved by nearly 10 meters and she no longer needed to use the walls to steady herself. Her 5-times sit-to-stand test improved by 0.5 second, but the patient remained unable to complete the test without using her arms to assist herself out of the chair. Her score on the EQ-5D-5L Health Questionnaire improved from 72 to 107 in the 3 months on elamipretide. Stealth BioTherapeutics provided the support in supplying elamipretide for the patient and publishing the case report; however, the authors confirmed they were independent from the sponsor in that the content of the case report was not influenced by the sponsor.

Human research to suggest benefits to patients with dementia:

There have been no studies of elamipretide in patients with dementia to date.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

SS-31 is rapidly absorbed after subcutaneous administration and concentrates in the kidney, but is also taken up by the heart, liver, skeletal muscle, and lungs (Birk et al., 2013). Brain concentrations are low compared to plasma, but it does cross the blood-brain barrier (Yang et al., 2009).

Models of cognitive impairment: A study examined the effects of SS-31 in aged mice exposed to anesthesia. Isoflurane exposure induced cognitive deficits and mitochondrial dysfunction (e.g., decreased activity of complex I) in the mouse hippocampus (Wu et al., 2016). These mice exhibited increased reactive oxygen species, decreased ATP production, decreased mitochondrial membrane potential, and opening of the mitochondrial permeability transition pore. SS-31 treatment (5.0 mg/kg, i.p.) protected cognitive function and mitochondrial function (complex I activity, ATP production) in these mice and prevented the opening of the mitochondrial permeability transition pore. SS-31 also promoted synaptic plasticity by facilitating BDNF signaling.

In young rats exposed to anesthesia (isoflurane)-induced cognitive impairment, pretreatment with SS-31 (5 mg/kg, i.p.) provided protective effects against oxidative stress and mitochondrial damages while also attenuating cognitive deficits (Wu et al., 2017). SS-31-treated isoflurane-exposed rats had cognitive functions comparable to controls not exposed to isoflurane. However, when SS-31 is given to control rats, their cognitive function is not significantly improved, likely due to a ceiling effect. SS-31 is not likely to produce benefits in the absence of mitochondrial dysfunction.

In a mouse model of anesthesia-induced cognitive impairment (exploratory laparotomy in aged mice under isoflurane anesthesia), SS-31 treatment (5 mg/kg, i.p.) 30 minutes before isoflurane and once daily for 3 days thereafter had protective effects against mitochondrial dysfunction but also attenuated surgery-induced pyroptosis (inflammatory form of programmed cell death) and cognitive deficits as measured by fear conditioning (Zuo et al., 2020). Pyroptosis is thought to be involved in the pathogenesis of perioperative neurocognitive disorders, and surgery with anesthesia causes mitochondrial dysfunction and abnormal morphology. SS-31 treatment restored ATP and mitochondrial membrane potential levels to those of control mice, and reduced reactive oxygen species levels and abnormal mitochondria to levels comparable to control mice. Protein levels of NLRP3 and cleaved caspase 1 were elevated with surgery but restored to control levels with SS-31 pretreatment. Inflammatory biomarkers (IL-1β and IL-18 levels) were also increased with surgery, but this increase was mostly prevented with SS-31 pretreatment. SS-31 treatment also restored synaptic proteins (synapsin 1, PSD-95) to levels comparable to control mice. Thus, SS-31 appeared to exert neuroprotective properties under surgery/anesthesia induction by protecting the mitochondria, attenuating neuroinflammation and neuronal pyroptosis, and improving synaptic integrity.

In a mouse model of memory impairment (LPS-induced), SS-31 treatment (5 mg/kg, i.p.) started 30 minutes before LPS and continued daily for 3 days thereafter significantly ameliorated LPS-induced learning and memory impairment during behavioral tests (Zhao et al, 2019). SS-31 provided protective effects against mitochondrial dysfunction by maintaining mitochondrial membrane potential and ATP levels and protected against oxidative stress (decreased MDA, increased SOD) and inflammation (as measured by decreased IL-6 and TNF-α). SS-31 treatment also facilitated the signaling of the neurotrophic factor BDNF, including restoration of synaptic proteins (PSD-95 and synaptophysin) and increased synaptic structural complexity (increased spine density).

An *in vitro* study reported that SS-31 treatment protected microglia (BV2 cell culture) from LPS by preserving mitochondrial ultrastructure by reducing the mitochondrial fission protein (Fis1) expression (Mo et al., 2019).

Alzheimer's models: Mitochondria are central to proper neuronal and synaptic activity, and decreased mitochondrial transport is an early event in neurodegeneration (Calkins et al., 2012).

In a mouse model of Alzheimer's (Tg2576 mice), SS-31 treatment (5 mg/kg, i.p. twice a week) for 6 weeks significantly reduced mRNA and protein levels of mitochondrial fission genes (Drp1, Fis1), and significantly increased mRNA and protein levels of mitochondrial fusion genes (Mfn 1, 2), mitochondrial biogenesis genes (PGC1α, Nrf1, Nrf2, TFAM), and synaptic genes (PSD95, synaptophysin)(Reddy et al., 2017). SS-31-treated mice also had lower levels of soluble and insoluble Aβ. SS-31 treatment had protective effects against mitochondrial and synaptic toxicities by improving mitochondrial dynamics, mitochondrial biogenesis, and synaptic functions in this mouse model.

In neuronal cultures from AD mice (Tg2576), SS-31 restored synaptic viability, mitochondrial motility, and mitochondrial transport, suggesting that it may protect synapses and mitochondria from Aβ toxicity (Calkins et al., 2011). Another study examined the effects of SS-31 against oxidant-induced mitochondrial dysfunction and apoptosis in 2 neuronal cell lines. Treatment with SS-31 significantly decreased intracellular reactive oxygen species, increased mitochondrial potential, and prevented apoptosis (Zhao et al., 2005). SS-31 was 5000 times more concentrated in mitochondria compared to other parts of the cell.

Parkinson's models: In a mouse model of Parkinson's disease (MPTP exposure), SS-31 administration (1 mg/kg) attenuated dopamine depletion and protected dopaminergic neurons in the brain (Yang et al.,

2009). SS-31 also promoted oxygen consumption and ATP production while preventing mitochondrial swelling.

Models of brain injury: In a rat model of subarachnoid hemorrhage, SS-31 treatment (2, 5, or 10 mg/kg, i.p.) initiated 30 minutes post hemorrhage significantly reduced oxidative stress (MDA levels), increased antioxidant enzymes (increased activities of GPx and SOD), and reduced apoptosis (suppressed Bax translocation and cytochrome c release) when compared with the vehicle-treated group (Shen et al., 2020). SS-31 treatment also ameliorated brain edema and Evans blue dye extravasation, improved neurological deficits, and decreased neuronal apoptosis. These findings suggest that SS-31 may exert neuroprotective effects in brain injury by preventing secondary brain insult.

In hypertensive rats subjected to mild traumatic brain injury, SS-31 treatment (5.7 mg/kg/day, i.p.) for 14 days after injury decreased the cytoplasmic and mitochondrial superoxide production and normalized levels of Nox4, a protein localized to the mitochondrial membrane that can be activated by mechanical forces and associated with mitochondrial oxidative stress (Czigler et al., 2019).

In a mouse model of traumatic brain injury (Marmarou weight-drop model), SS-31 treatment (5 mg/kg, i.p.) administered 30 minutes after injury significantly reversed mitochondrial dysfunction and ameliorated secondary brain injury (Zhu et al., 2018). SS-31 decreased reactive oxygen species, restored the activity of superoxide dismutase (SOD), and decreased the level of malondialdehyde (MDA) and the release of cytochrome c, while attenuating neurological deficits (e.g., grip test score), brain water content, DNA damage, and neural apoptosis (the apoptosis index in the cortex reduced by half, increased Bcl-2, and decreased cleaved caspase 3 levels). SS-31 also restored the expression of SIRT1 and upregulated the nuclear translocation of PGC-1α, a transcriptional coactivator that acts as a molecular switch in a variety of metabolic pathways, while directly linking external stress to the regulation of mitochondrial biogenesis and function. This study suggested that SS-31 improved mitochondrial function in traumatic brain injury through enhanced mitochondrial biogenesis.

In a mouse model of ischemic brain injury, SS-31 (2 or 5 mg/kg, i.p.) administration significantly attenuated antioxidant (glutathione) depletion and reduced infarct size (Cho et al., 2007).

Neurovascular function: In aged mice, treatment with SS-31 (10 mg/kg/day, i.p.) significantly improved neurovascular coupling responses by increasing NO-mediated cerebromicrovascular dilation, which was associated with significantly improved spatial working memory, motor skill learning, and gait

coordination (Tarantini et al., 2018). SS-31 may be promising for microvascular protection in prevention/treatment of age-related vascular cognitive impairment (VCI).

In a cell culture study with human brain microvascular endothelial cells, pre-treatment with SS-31 before oxygen glucose deprivation prevented cell death and reduced caspase 3/7 activity while promoting mitochondrial functions (Imai et al., 2017). The details of this study could not be evaluated as the full text of this paper was inaccessible.

***APOE4 interactions**:* Unknown.

Aging and related health concerns: Elamipretide is approved for Barth syndrome. Benefits in some outcomes have been observed in select subgroups of primary mitochondrial myopathy and age-related macular degeneration. Confirmatory trials are ongoing.

Types of evidence:

- a 168-week open-label extension of phase 2/3 trial in Barth syndrome
- 1 phase 3 double-blind randomized controlled trial in primary mitochondrial myopathy
- 1 phase 2/3 randomized controlled trial in Barth syndrome patients
- 1 double-blind phase 2 RCT in patients with heart failure
- 1 double-blind phase 2 RCT in patients with primary mitochondrial myopathy
- 1 double-blind phase 1/2 RCT in patients with primary mitochondrial myopathy
- 1 double-blind phase 2a RCT in patients with myocardial infarction
- 1 double-blind randomized placebo-controlled phase 2 trial in patients with age-related macular degeneration with noncentral geographic atrophy
- 1 double-blind randomized placebo-controlled trial in patients with Leber hereditary optic neuropathy
- 3 double-blind randomized controlled trials, 1 in patients with atherosclerotic renal artery stenosis, 1 in heart failure, and 1 in healthy older adults
- 1 pilot clinical study in renovascular hypertensive patients undergoing renal revascularization
- 2 phase 1 open-label studies in age-related macular degeneration
- Numerous case reports and case series
- Numerous preclinical studies
- Numerous review articles

***Heart failure**:* MIXED/INCONCLUSIVE.

In a phase 2 double-blind randomized controlled trial enrolling 71 patients with heart failure (reduced ejection fraction, <40%), SS-31 treatment (4 or 40 mg, once daily, s.c.) for 28 days did not significantly alter the left ventricular end systolic volume from baseline to week 4 when compared to placebo (Butler et al., 2020).

In a double-blind phase 2a RCT in 118 patients with myocardial infarction who underwent a coronary intervention, SS-31 was not associated with a decrease in myocardial infarct size (Gibson et al., 2016). However, congestive heart failure within 24 hours of the coronary intervention tended to be reduced with SS-31 treatment. Preclinical studies had shown greater promise, with SS-31 pretreatment (3 mg/kg) producing significantly reduced myocardial lipid peroxidation and infarct size in rats undergoing myocardial infarction (Cho et al., 2007).

In a follow-up study of the phase 2a trial described above, serum levels of high-temperature requirement serine peptidase 2 (HtrA2) was significantly increased in patients with myocardial infarction who underwent coronary intervention, whereas levels were significantly decreased in patients who were treated with SS-31 (0.05 mg/kg/hr)(Hortmann et al., 2017). HtrA2 is present in the mitochondria, but when it is translocated to the cytosol, it induces a protease activity-dependent apoptosis that is mediated by caspases. HtrA2 may be a good biomarker for mitochondria-induced cardiomyocyte apoptosis, though this possibility needs to be validated in a larger study.

A double-blind randomized controlled trial (phase I) enrolling 36 heart failure patients (77% of whom had ischemic cardiomyopathy) reported that a 4-hour infusion of high dose SS-31 (0.25 mg/kg/hr) resulted in favorable changes, including significant reductions in left ventricular volumes (Daubert et al., 2017). These effects were seen among patients who were already receiving optimal guideline-based heart failure treatment. However, cardiac biomarkers (NT-proBNP and high-sensitivity C-reactive protein) did not significantly differ between SS-31 or placebo groups. Blood pressure and heart rate remained stable in all groups (placebo, 0.005, 0.05, or 0.25 mg/kg/hr).

In an *ex vivo* study of failing human hearts, SS-31 treatment improved mitochondrial function, including mitochondrial oxygen flux, complex I and IV activities, supercomplex-associated complex IV activity (Chatfield et al., 2019).

In a dog model of heart failure (chronic intracoronary microembolization-induced heart failure), SS-31 treatment (0.5 mg/kg, s.c.) for 3 months significantly restored fiber-type composition in skeletal muscle while improving mitochondrial respiration, mitochondrial membrane potential, mitochondrial permeability transition pore, and cytochrome c oxidase activity (Sabbah et al., 2019). The authors argued that the observed improvements in skeletal muscle morphology and metabolism could potentially lead to an improvement in exercise tolerance, a key issue with heart failure. These benefits in mitochondrial metrics were not observed in healthy dogs without heart failure receiving SS-31.

In old mice with cardiac dysfunction, SS-31 treatment (3 mg/kg/day via minipumps) for 8 weeks significantly reversed the diastolic dysfunction prominent in cardiac aging and decreased cardiac hypertrophy, while normalizing the increase in proton leak, reducing protein oxidation and mitochondrial reactive oxygen species in cardiomyocytes (Chiao et al., 2020).

In mice, chronic elamipretide treatment (3 mg/kg, s.c., 5 days per week) for 10 months improved diastolic function in both males and females, but to a greater extent in males (Nickel et al., 2022).

Primary mitochondrial myopathy: INCONCLUSIVE; THERE MAY BE BENEFITS IN SPECIFIC GENETIC SUBTYPES.

Primary mitochondrial myopathies are a group of genetically confirmed disorders of the mitochondria that predominantly affect skeletal muscle. Symptoms include muscle weakness, muscle atrophy, limited exercise capacity, fatigue, and pain (Arena et al., 2022).

In a phase I/II double-blind randomized controlled trial (MMPOWER) enrolling 36 participants with genetically confirmed primary mitochondrial myopathy, participants who received the highest dose of SS-31 (0.25 mg/kg/hour, i.v. for 2 hours) walked a mean of 64.5 meters farther on day 5 compared to a change of 20.4 meters in the placebo group ($p = 0.053$) (Karaa et al., 2018). There was a dose-dependent increase in distance walked on the 6-minute walk test (6MWT) with SS-31 treatment ($p = 0.014$).

This study was followed by the MMPOWER-2 study, also a double-blind randomized controlled study (Karaa et al., 2020). MMPOWER-2 was a phase 2 study that enrolled 30 patients with genetically confirmed primary mitochondrial myopathy and SS-31 (40 mg/day, s.c.) was administered for 4 weeks followed by 4 weeks of placebo (or the opposite sequence). The distance walked on the 6MWT in SS-31-treated patients was 398.3 (±134.16) meters compared with 378.5 (±125.10) meters in the placebo-treated group, a difference of 19.8 m (95% CI, -2.8 to 42.5; p=0.0833). The results of the Primary

Mitochondrial Myopathy Symptom Assessment (PMMSA) Total Fatigue and Total Fatigue During Activities scores showed that participants treated with SS-31 reported less fatigue and muscle complaints compared with placebo (p=0.0006 and p=0.0018, respectively), though the treatment benefit was not sustained upon discontinuation of SS-31 therapy, and subjects returned to pre-therapy severity 2 weeks after the end of treatment. While receiving SS-31, participants reported improvements in individual myopathy-related symptoms on the PMMSA: tiredness at rest (p=0.0008), tiredness during activities (p=0.0046), muscle weakness at rest (p=0.0007), muscle weakness during activities (p=0.0019), and muscle pain (p=0.0079), but no statistically significant treatment differences for balance problems, vision problems, abdominal discomfort, numbness, or headache. Findings for these exploratory endpoints were not corrected for multiple comparisons and there is potential for Type 1 error. Additionally, the Neuro-QoL Fatigue Short Form and Patient Global Assessment showed reductions in symptoms (p=0.0115 and p=0.0421, respectively). During the treatment period, no statistically significant changes were observed in the Physician Global Assessment (p=0.0636), the Triple Timed Up and Go (p=0.8423) test, and wrist/hip accelerometry (p=0.9345 and p=0.7326, respectively). There were no treatment differences observed in exploratory biomarkers (levels of serum GDF-15, FGF-21, and glutathione).

The results of MMPOWER-2 provided an efficacy signal and data (while not statistically significant) to support the MMPOWER-3 trial. In the pivotal phase 3 double-blind randomized placebo-controlled trial (MMPOWER-3) of 218 patients with genetically confirmed primary mitochondrial myopathy, elamipretide treatment (40 mg/day, s.c.) for 24 weeks failed to significantly improve the coprimary endpoints of the 6-minute walk test (p=0.69) and 'total fatigue' on the Primary Mitochondrial Myopathy Symptom Assessment (PMMSA; p=0.37)(Karaa et al., 2023). However, subgroup analysis (post hoc) for participants with nuclear DNA alteration showed that elamipretide treatment led to a 6-minute walk test change from baseline of 25.5 meters compared to 0.3 meters for placebo, favoring elamipretide (95% CI, 3.1-47.3 meters; p=0.03). Subgroup analysis for participants with mtDNA alteration showed a numerically (but not statistically) worse change from baseline with elamipretide on the 6-minute walk test (14.0 meters) compared to the placebo group (25.0 meters; p=0.21). With regards to fatigue, while not statistically significant, participants treated with elamipretide reported slightly less total fatigue at the end of the treatment. In another post hoc analysis of MMPOWER-3 trial, subjects with pathogenic variants in genes required for mtDNA maintenance (mtDNA replisome) displayed a numeric improvement on the 6-minute walk test with elamipretide treatment (by 25.2 ± 8.7 meters) compared to the placebo group (by 2.0 ± 8.6 meters; p=0.06)(Karaa et al., 2024). Of the subjects with mtDNA replisome variants, those who had chronic progressive external ophthalmoplegia (CPEO) showed a significant improvement in the 6-minute walk test with elamipretide (by 37.3 ± 9.5 meters) compared to

placebo (-8.0 ± 10.7 meters; p=0.0024). People with CPEO experience ptosis, ophthalmoplegia, fatigue, and some patients had proximal muscle weakness. Together, these findings suggest that specific genetic subtypes of primary mitochondrial myopathy may differentially benefit from elamipretide treatment.

In a case report of a 67-year-old male with CPEO (e.g., ptosis), hearing loss, abnormal gait, lower extremity weakness, muscle atrophy, dysphagia, extreme fatigue, cognitive decline, speech problems, and Parkinsonism, treatment with elamipretide initiated at a dose of 40 mg/day (s.c.) significantly improved his eye symptoms (Ansari and Koenig, 2024). The patient's CPEO was secondary to a pathogenic genetic variant in the POLG, a gene that encodes the catalytic subunit of DNA polymerase gamma that replicates and repairs mtDNA. The patient had a history of bilateral ptosis and progressive ophthalmoplegia in his early teenage years and his eye issues worsened subsequently. He underwent strabismus surgery and two ptosis surgeries between the ages of 25 and 42 years. Upon his first elamipretide treatment, the patient reported an immediate sensation in his leg that radiated throughout his body and tension in his eyes as if they were regaining motion. After only 2 weeks of treatment, the patient could raise his eyebrows and look upward, ambulated more quickly, and experienced fewer head tremors. Within 1 month of beginning elamipretide, the patient and his family reported significant improvement in stamina, muscle strength, balance, posture, and stability. He was able to stand without assistance, and his eyes were no longer fixed in place. The patient reported walking and riding his bicycle weekly as well as lifting heavier weights at the gym. After about 3 months of daily elamipretide therapy, the patient went cross-country skiing at 9400 ft elevation, an activity he was unable to perform in over 5 years. After 5 months of elamipretide therapy, the patient hiked over 6 miles at high elevation in the Yosemite National Park. The patient continued to improve after 1 year on elamipretide therapy. After 18 months of elamipretide therapy, the patient continued to report drastic improvements in his strength, endurance, and overall quality of life. He was able to ride his bike for 20 miles weekly, lift heavier weights, and walk 5 miles. His dysphagia persisted.

Neuropathy Ataxia and Retinitis Pigmentosa (NARP) syndrome is a rare mitochondrial disorder that causes sensory neuropathy, ataxia, and vision loss due to retinitis pigmentosa. In a case report of a 40-year-old male with primary diagnosis of NARP syndrome with retinitis pigmentosa, sensorineural hearing loss, progressive cerebellar ataxia, cognitive impairment, and proximal myopathy, treatment with elamipretide (40 mg/day, s.c.) significantly improved his ability to work, socialize, exercise, and balance (Ansari and Koenig, 2024). The patient's vision was compromised prior to 2 years of age and the patient had been legally blind since 14 years of age when he was diagnosed with NARP syndrome. He developed sensorineural hearing loss at 20 years of age and used hearing aids. The patient initially received elamipretide therapy through participation in a clinical trial (SPIMM-301). Within the first

6 months of elamipretide treatment, his walking capacity on the 6-minute walk test improved from 120 to 259 m. The patient also showed improved fatigue and quality of life scores. After the clinical trial ended, the patient and his family reported loss of improvements made during treatment (e.g., worsened balance, orientation, mobility, weakness, lethargy, and confusion). He was unable to walk or hold his head up. Several months later, the patient was enrolled into the Expanded Access Program for elamipretide and reinitiated treatment with elamipretide (40 mg/day, s.c.). After about 1 year on elamipretide treatment, the daily dose was increased to 60 mg/day, s.c. The patient's family reported decreased ataxia (poor muscle control) and increased walking distance (up to 50 yards) after 3 months of treatment. They also reported reduced dysarthria (motor speech disorder), improved ability to perform activities of daily living, and increased independence. Physical examination revealed improved strength and ambulation, such that the patient stood easily from the chair and ambulated steadily with minimal assistance. Ataxia remained. When the daily dose was increased to 60 mg/day, s.c., after about 1 year in the Expanded Access Program, a dramatic improvement in his condition was observed within 6 months and included resolution of previous walking problems, return of long-term memory, and improvement in quality of life scores. The patient and his family reported increased energy, stamina, walking ability, walking distance, hearing, speech clarity, balance, strength, and endurance. After 18 months at the 60 mg/day dose, the patient reported some return of vision (e.g., seeing colors). No other medication changes were made.

Barth syndrome: ACCELERATED APPROVAL BY FDA; IMPROVES MUSCLE STRENGTH

Barth syndrome is a very rare, life-shortening genetic disorder caused by defects in the TAFAZZIN gene which encodes an acyltransferase involved in the remodeling and maturation of cardiolipin (Ferreira et al., 2026). TAFAZZIN deficiency causes abnormal cardiolipin content, including accumulation of monolysocardiolipin and lower mature cardiolipin levels, leading to mitochondrial dysfunction. The disease is characterized by skeletal muscle weakness, abnormal growth, neutropenia, and early-onset cardiomyopathy. Barth syndrome is not an age-related disease, per se, but is a disease that significantly shortens one's life expectancy. In September 2025, the US FDA granted accelerated approval of elamipretide (marketed as Forzinity) to improve muscle strength in adult and pediatric patients with Barth syndrome weighing at least 30 kg (~66 lbs)(Shirley, 2026).

In a phase 2/3 randomized controlled trial (TAZPOWER) in 12 patients with Barth syndrome, SS-31 treatment (40 mg/day) for 12 weeks failed to meet the primary endpoints (6-minute walk test and improvement on a Barth syndrome Symptom Assessment scale)(Thompson et al., 2021). However, at 36 weeks in the open-label extension phase of the trial, there were significant improvements in the 6-

minute walk test (+95.9 meters, p=0.024) and Barth syndrome Symptom Assessment scale (BTHS-SA; -2.1 points; p=0.031). There were also significant improvements in secondary endpoints including knee extensor strength, patient global impression of symptoms, and some cardiac parameters.

The 168-week open-label extension study of the TAZPOWER trial in 10 patients with Barth syndrome reported significant improvements from baseline on the 6-minute walk test at all open-label extension timepoints, with a cumulative improvement of 96.1 meters of improvement at week 168 (p=0.003)(Thompson et al., 2024). Baseline 6-minute walk test mean distance was 382 meters and the distances for open-label time points ranged from 478 to 489 meters. BTHS-SA total fatigue scores were numerically (but not statistically) improved from baseline at all open-label extension time points (-1.21; p=0.21). Significant improvements from baseline were observed for all patients on the mean muscle strength measured by hand-held dynamometry at all visits (p<0.05), with improvements ranging from 37.9 to 60.3 newtons. Mean baseline values were 132 newtons and open-label extension values ranged from 175 to 192 newtons. A significant improvement in mean SWAY balance score was observed at weeks 72 and 168 (p<0.05). Time to complete the 5 times sit-to-stand test improved from baseline at all time points (range, -1.6 to -2.2 seconds); however, the mean difference did not reach statistical significance.

Mean Clinical Global Impression of Symptom Severity (CGI-S) scores improved from baseline, with statistically significant differences observed at week 24 (p=0.02), week 48 (p=0.02), week 72 (p=0.006), week 96 (p=0.02), week 120 (p=0.002), week 144 (p=0.006), and week 168 (p=0.007)(Thompson et al., 2024). An improvement from baseline in the Patient Global Impression of Symptom Severity (PGI-S) scores was also observed with a statistically significant difference observed on week 36 (p=0.05) and week 168 (p=0.05).

Eight patients had cardiac evaluations through week 168. A mean, nominally significant 24.42 mL/m2 increase from baseline in left ventricular end-diastolic volume index was seen at week 168 (p=0.003) (Thompson et al., 2024). There was also a nominally significant 10.04 mL/m2 increase in left ventricular end-systolic volume index at week 168 (p=0.0008). Progressive improvement from baseline in left ventricular stroke volume index was observed at all open-label extension timepoints. With longer duration elamipretide therapy, left ventricular stroke volume index continued to improve, with a greater than 45% improvement (by 14.4 mL/m2; p=0.007) from baseline (~30 mL) at week 168 (~45 mL).

The monolysocardiolipin (immature) to cardiolipin (mature) ratios showed improvement at week 168 compared to baseline (Thompson et al., 2024).

Authors speculated that the delayed clinical and functional benefits with elamipretide in Barth syndrome patients were due to a period of restructuring in both skeletal and cardiac muscles, which may have been required before observable improvements in function.

Several case reports of infants with Barth syndrome have described benefits of elamipretide; these infants were enrolled into the Expanded Access Program for elamipretide. Cardiomyopathy is the most common clinical manifestation of Barth syndrome and occurs in 90% of patients, with 70% diagnosed in infancy. The first case study described a newborn receiving elamipretide treatment initiated shortly after birth, which led to significant and sustained improvement in the Barth syndrome-related severe left ventricle non-compaction cardiomyopathy (Jacob et al., 2025). The improvement resulted in an inactive status on the heart transplant list with eventual anticipated delisting. The mother had two other sons diagnosed with Barth syndrome and the newborn was diagnosed prenatally. In another infant diagnosed in utero with Barth syndrome with a left ventricular ejection fraction of 20% at birth, elamipretide treatment started on day of life 34 (0.25 mg/kg increased to 0.5 mg/kg on day of life 39) along with standard-of-care oral heart failure medications resulted in improved left ventricular ejection fraction to near-normal levels (Ortmann et al., 2025). He was weaned off of oxygen on day of life 49 and discharged home on day of life 61, continuing daily subcutaneous elamipretide 0.5 mg/kg and oral heart failure medications. Subsequent echocardiogram (on day of life 88) showed improvement of left ventricular ejection fraction to 60%. Given this infant's improvement, the patient was never placed on the heart transplant list and did not require mechanical circulatory support. In an 11-month-old boy with a maternally inherited pathogenic variant of TAFAZZIN, elamipretide treatment initiated at 5 mg/day, subcutaneously, along with daily citrulline and coenzyme Q10, heart failure medications (enalapril, carvedilol, and spironolactone), and implantation of left ventricular assist device (LVAD) resulted in a left ventricular ejection fraction of 54%, 5 months later, and because of this improvement, he underwent cardiac catheterization (Goldstein et al., 2024). Before the LVAD was implanted, the left ventricular ejection fraction was at 18%. At 23 months old, the patient had a left ventricular ejection fraction of 67% and was crawling, standing, walking with assistance, and babbling. Because of the observational nature of these case reports, it is not possible to determine the relative roles of elamipretide, heart failure medications, LVAD, and cardiac catheterization on heart function improvement.

Age-related macular degeneration: POTENTIAL BENEFIT IN LOW-LUMINANCE

Age-related macular degeneration is the leading cause of vision loss in people over 65 years old. Drusen are small yellow deposits of extracellular waste that accumulate under the retina, often in people over

the age of 50. People with high-risk drusen have a significantly increased risk of developing vision-threatening dry or wet age-related macular degeneration, and some people experience difficulties with activities of daily living (despite preserved best-corrected visual acuity). Some evidence suggests that mitochondrial dysfunction plays a major role in the pathobiology of age-related macular degeneration (Chen et al., 2026).

In a phase 1 open-label study of 18 patients with intermediate age-related macular degeneration and high-risk drusen (ReCLAIM High-Risk Drusen Study), elamipretide treatment (40 mg/day, s.c.) for 24 weeks significantly improved visual acuity (Allingham et al., 2021). Compared with baseline, normal best-corrected visual acuity (BCVA) was improved by +3.6 letters (from 79.4 ± 7.4 letters to 82.0 ± 6.9 letters; p=0.014) and low-luminance best-corrected visual acuity (LLVA) was improved by +5.6 letters (from 63.8 ± 10.0 letters to 68.4 ± 11.5 letters; p=0.004). BCVA was increased in 14 out of 18 patients, with 5 of them (26.3%) achieving more than a 5-letter improvement and 2 of them (10.5%) achieving more than a 10-letter increase. No participant showed a greater than 5-letter decrease in BCVA. LLVA improvement was noted at all time points, with 9 of 19 participants (50%) achieving greater than a 5-letter improvement, and 3 out of 18 participants (16.7%) achieving more than a 10-letter improvement. One participant showed a decline of more than 5 letters in LLVA. Compared with baseline, normal-luminance binocular reading acuity (NLRA; p=0.001) and low-luminance binocular reading acuity (LLRA) improved (p<0.0001). Improvements in NLRA and LLRA were evident by week 4 and maintained at weeks 8 through 24. Significant improvements with elamipretide treatment were seen in 6 out of 7 subscales of the Low-Luminance Questionnaire (p<0.0015; dim-light reading, driving or riding in car, general dim-light vision, light transitions and glare, other activities of daily living, and peripheral vision). Some of these significant changes from baseline could be due to a placebo or practice effect given the open-label study design. No significant changes were observed for retinal pigment epithelium (RPE)-drusen complex (DC) volume, fundus autofluorescence, mesopic microperimetry, or dark adaptation.

Noncentral geographic atrophy is an advanced, progressive form of dry age-related macular degeneration, where tissue death occurs in the retina outside the fovea. While initially sparing the center, these lesions typically expand and eventually involve the fovea, leading to significant loss of central vision. Low-luminance vision impairment affects up to 50% of people with noncentral geographic atrophy. In a phase 1 open-label study of 15 patients with intermediate age-related macular degeneration and noncentral geographic atrophy (ReCLAIM NCGA Study), elamipretide treatment (40 mg/day, s.c.) for 24 weeks significantly improved visual acuity (Mettu et al., 2021). Compared with baseline, normal BCVA was improved by +4.6 letters (from 73.7 ± 9.5 letters to 77.9 ± 12.7 letters; p=0.0032) and LLVA was improved by +5.4 letters (from 44.0 ± 19.8 letters to 51.5 ± 21.8 letters;

p=0.0245). Six of the 15 participants (40%) achieved at least a 6-letter increase in BCVA at week 24, and 2 out of 15 participants (13.3%) achieved a greater than 10-letter increase. No participants showed a greater than 5-letter decrease in BCVA. Eight out of 15 participants (53.3%) achieved at least a 6-letter increase in LLVA and 5 out of 15 participants (33.3%) achieved a more than 10-letter increase in LLVA. Two out of 15 participants (13.3%) showed at least a 6-letter decrease in LLVA. As is true in the high-risk drusen phase I study described above, some of the significant changes from baseline in the NCGA cohort could be due to a placebo or practice effect given the open-label study design. The investigators adjusted analyses for multiple comparisons to determine appropriate thresholds for statistical significance, after which the observed changes from baseline to week 24 for BCVA and LLVA remained statistically significant.

In a phase 2 double-blind randomized placebo-controlled trial of 176 patients with dry age-related macular degeneration with noncentral geographic atrophy (ReCLAIM-2), elamipretide treatment (40 mg/day, s.c.) for 48 weeks did not meet statistical significance for the primary end points, which were change from baseline in LLVA and mean change in square root converted geographic atrophy area (Ehlers et al., 2024). There were also no significant differences between elamipretide and placebo groups for low-luminance reading acuity or change in geographic atrophy area. However, elamipretide treatment resulted in a 43% reduction in the mean progression from baseline in a measure of progressive photoreceptor degeneration (macular percentage of total ellipsoid zone loss) and 47% reduction in the mean progression of macular percentage of partial ellipsoid zone loss compared to placebo. These findings suggest that elamipretide treatment preserved photoreceptors. Elamipretide treatment was also associated with more patients experiencing a ≥10 letter gain in LLVA (14.6% vs. 2.1%; nominal p=0.0404) than placebo.

Phase 3 trials, ReNEW (NCT06373731) and ReGAIN, are ongoing in dry age-related macular degeneration patients, as of May 2026.

Optic neuropathy: POTENTIAL BENEFIT IN SELECT MEASURES

Leber hereditary optic neuropathy (LHON) is the most common hereditary optic neuropathy and is characterized by rapid and severe central vision loss due to degeneration of retinal ganglion cells. Genetic variants associated with LHON alter complex I of the mitochondrial electron transport chain (Ji et al., 2020). Improving the efficiency of the electron transport chain and reducing the production of reactive oxygen species are promising strategies for the treatment of LHON. In a phase 2 double-blind randomized controlled trial of 12 patients with LHON, elamipretide treatment (1% topical ophthalmic

solution) for 52 weeks did not significantly improve the primary outcome, which was the change from baseline in BCVA compared to vehicle-treated eyes (Karanjia et al., 2024). Patients received either elamipretide in both eyes or elamipretide in one eye (and vehicle in the other eye). The double-blind portion of the study was followed by an up to 108 weeks of open-label extension. At the end of the double-blind period (52 weeks), 4 out of 12 patients (6 eyes total) met the criteria for 'clinically relevant benefit', and at the last visit in the open-label extension (160 weeks), 6 out of 12 subjects (8 eyes total) met the criteria for clinically relevant benefit. Patients described a meaningful improvement in their quality of life as a result of their improved visual function. The authors noted that these types of improvement/benefit would not be expected based on the natural history and disease progression of LHON (particularly in participants having experienced more than 3 years of vision loss prior to study entry). In a post hoc analysis, the change from baseline in mean deviation in the central visual field was significantly greater in elamipretide-treated eyes (signifying greater improvement) than in the vehicle-treated eyes when the least squares mean differences were averaged over all double-masked time points (1.8 dB; $p<0.0001$). No significant differences from baseline in OCT parameters were observed between elamipretide- and vehicle-treated eyes (retinal nerve fiber layer thickness and retinal ganglion cell layer thickness) on week 52.

Atherosclerotic renal artery stenosis: POTENTIAL BENEFIT.

A phase 2a double-blind randomized controlled trial enrolling 14 patients with severe atherosclerotic renal artery stenosis reported that SS-31 administration (0.05 mg/kg/hr for 3 hours) before and during percutaneous transluminal renal angioplasty resulted in attenuated post-procedural hypoxia, increased renal blood flow, and improved kidney function (Saad et al., 2017). Changes in the SS-31 group were associated with reductions in systolic blood pressure and greater increase in total glomerular flow rate. These data suggest that protecting mitochondrial health may minimize procedure-associated ischemic injury and improve revascularization for atherosclerotic renal artery stenosis.

In pigs subjected to unilateral atherosclerotic renal artery stenosis, SS-31 treatment (0.1 mg/kg, s.c., once daily, 5 days/week) for 4 weeks normalized the stenotic kidney renal blood flow and glomerular filtration rate, alleviated fibrosis and oxidative stress, and restored mitochondrial cardiolipin, biogenesis, and mitophagy (Kim et al., 2019). SS-31 treatment, however, did not change senescence-associated secretory phenotype (SASP; PAI-1, MCP-1, TGFβ, and TNFα) markers, and attenuated only senescence-associated β-galactosidase activity and p53 gene expression. The authors argued that while mitochondrial protection improved renal function and alleviated tissue fibrosis, SS-31 treatment only partly mitigated the atherosclerotic renal artery stenosis-induced cellular senescence. Mitochondrial

dysfunction may not be the chief inducer of cellular senescence in this condition, possibly due to the multiple injurious pathways involved.

Renovascular hypertension: POTENTIAL BENEFIT BASED ON PILOT STUDY.

In a pilot clinical study of 14 patients with renovascular hypertension undergoing renal revascularization (percutaneous transluminal renal angioplasty), cotreatment with SS-31 (0.05 mg/kg/hour, i.v. infusion) blunted the increase in urinary mitochondria DNA (COX3 and ND1) levels 24 hours after the renal angioplasty (Eirin et al., 2019). Furthermore, 3 months after the angioplasty, systolic blood pressure decreased and estimated glomerular filtration rate increased only in SS-31-treated patients and not the vehicle-treated patients. In a pig model of renovascular hypertension, mitochondrial damage was observed in tubular cells and elevated urinary mtDNA levels inversely correlated with renal mitochondrial density.

Atherosclerosis: POTENTIAL BENEFIT IN RODENT MODEL.

In a mouse model of atherosclerosis (ApoE knockout mice fed a Western diet), SS-31 treatment (1 or 3 mg/kg/day, s.c.) for 12 weeks reduced the area and sizes of atherosclerotic plaques and changed the composition of the plaques (Zhang et al., 2017). Chronic SS-31 treatment led to suppression of oxidative stress, increased antioxidant (SOD) activity, and decreased systemic inflammation (decreased serum ICAM-1, MCP-1, and IL-6 levels). Notably, SS-31 administration inhibited cholesterol influx by down-regulating expression of CD36 and LOX-1 to prevent lipid accumulation to further suppress the foam cell formation and atherosclerotic progression. SS-31 may be promising in preventing atherosclerotic progression.

Muscle aging and athletic performance: INCONCLUSIVE.

Social media has promoted gray market SS-31 for improving physical endurance and recovery; however, evidence in humans regarding the safety and efficacy of SS-31 for performance enhancement or injury recovery is limited (Mendias et al., 2026).

In a double-blind placebo-controlled randomized clinical trial of 39 healthy older subjects (60-85 years old), a single 2-hour infusion of elamipretide increased mitochondrial energetic capacity (change in ATPmax) in the first dorsal interosseous muscle (muscle between the thumb and index finger), measured using MRS-optical spectroscopy (Roshanravan et al., 2021). However, no difference was found

on day 7 after treatment (which is expected given its short half-life). There were also no significant changes observed in resting muscle mitochondrial coupling or fatigue resistance in the muscle.

In aged mice, SS-31 reversed the age-related declines in mitochondrial function (ATP production, coupling of oxidative phosphorylation, and cell energy state) in skeletal muscle (Siegel et al., 2013). Acute SS-31 treatment in aged mice improved fatigue-resistance. Treatment (3 mg/kg, i.p.) for 8 days increased whole-animal endurance capacity. Interestingly, SS-31 had no observable effects on muscle in young mice.

In aged mice with exercise tolerance issues, SS-31 treatment (3 mg/kg/day, osmotic minipumps) for 8 weeks increased exercise tolerance while reversing age-related decline in maximum mitochondrial ATP production, improving coupling of oxidative phosphorylation, and restoring redox homeostasis in the skeletal muscle (Campbell et al., 2019). There was no change in mitochondrial content. The gastrocnemius in the aged SS-31-treated mice was more fatigue resistant with significantly greater mass compared to aged controls, leading to a significant increase in treadmill endurance compared to both pretreatment and untreated control values. In contrast, young mice treated with SS-31 did not show changes in ATP, oxidative phosphorylation, running distance, or other metrics.

In aged female mice, elamipretide treatment (3 mg/kg, i.p.) twice weekly for 8 months preserved exercise tolerance measured by treadmill running time and left ventricular mass (Campbell et al., 2023). Elamipretide treatment also partly protected diastolic function and skeletal muscle force production. Elamipretide did not protect kidney function or increase the probability of survival.

Osteoarthritis: POTENTIAL BENEFIT IN PRECLINICAL STUDIES.

In an ex vivo study, cartilage harvested from bovine knee joints was subjected to acute injury. SS-31 treatment immediately post-impact or at 1, 6, or 12 hours post-injury resulted in chondrocyte viability similar to that of uninjured controls (Delco et al., 2018). This protective effect was sustained for up to a week in culture. Specifically, SS-31 prevented impact-induced chondrocyte apoptosis, cell membrane damage, and cartilage matrix degeneration. These results are promising and suggest that SS-31 may be protective in posttraumatic osteoarthritis even when the treatment is delayed (by up to 12 hours in this ex vivo model).

Diabetes/Kidneys: POTENTIAL BENEFIT IN PRECLINICAL STUDIES.

In a mouse model of diabetes, SS-31 prevented apoptosis of kidney cells (Hou et al., 2016). SS-31 inhibited expressions of proapoptotic protein Bax and a cytokine (TGFβ1), while promoting expression of antiapoptotic protein Bcl2. SS-31 appears to be protective against diabetic nephropathy.

In leukocytes from type 2 diabetes patients, SS-31 treatment decreased mitochondrial ROS production, increased mitochondrial membrane potential, glutathione content, SIRT1 levels, and leukocyte rolling velocity (Escribano-Lopez et al., 2018). NFκB-p65 and TNF-α, which were increased in leukocytes of diabetic patients, were also reduced by SS-31 treatment.

In a mouse model of type 2 diabetes mellitus and diabetic kidney disease (db/db mice), SS-31 treatment (3 mg/kg, s.c.) for 12 weeks significantly inhibited increases in albuminuria, urinary H2O2, and mesangial matrix accumulation while fully preserving levels of renal superoxide production (Miyamoto et al., 2020). SS-31 treatment also slightly reduced perigonadal adipocyte size, preserved renal superoxide production, regulated immature cardiolipins and long-chain mature cardiolipins, and regulated the mitochondrial fusion machinery in the kidneys.

In the same mouse model (db/db), SS-31 treatment (3 mg/kg/day, i.p.) for 12 weeks alleviated proteinuria, glomerular hypertrophy, and tubular injury, suppressed the levels of oxidative stress, NADPH oxidase subunits, CD36, and NF-κB p65, and increased antioxidant defense (activated MnSOD and catalase)(Hou et al., 2018).

In a rat model of diabetic retinopathy (induced by high fat diet and streptozotocin), eyedrops of SS-31 (0.03 M) for 7 weeks restored vision while reducing the % area of oxidative protein damage in the retina compared to the untreated eye (Daniel et al., 2021).

Renal ischemia: POTENTIAL BENEFIT IN PRECLINICAL MODELS.

In a rat model of renal ischemia, SS-31 treatment (2 mg/kg/day, s.c. osmotic pump) started 1 month after ischemia and continued for 6 weeks was beneficial in restoring glomerular capillaries and podocyte structure, and arresting glomerulosclerosis and interstitial fibrosis (Szeto et al., 2017). SS-31 treatment also reversed ischemia-induced mitochondrial damage in podocytes and expression of inflammatory markers. In fact, the protection with SS-31 was sustained for over 6 months after treatment ended, with normalization of IL-18 and IL-1β expression.

Pulmonary hypertension: POTENTIAL BENEFIT IN RODENTS.

In a mouse model of pulmonary arterial hypertension, SS-31 administration suppressed blood pressure elevation, oxidative stress proteins, markers of inflammation (MMP9, TNFα, iNOS), proapoptotic proteins (Bax, caspase 3), DNA damage, and lung injury score (Lu et al., 2016).

Liver cancer: POTENTIAL HARM BASED ON PRECLINICAL STUDIES.

In a mouse model of liver cancer (injected with diethylnitrosamine), N-acetylcysteine (NAC) and the soluble vitamin E analog Trolox prevented tumorigenesis, whereas mitochondria-targeted antioxidants SS-31 and Mito-Q (derivative of ubiquinone) facilitated tumorigenesis (Wang et al., 2017). NAC and Trolox reduced tumor number and size while SS-31 and MitoQ increased them. NAC and Trolox alleviated DNA damage by activating DNA repair (ataxia-telangiectasia mutated (ATM)/ATM and Rad3-related (ATR)), whereas SS-31 and Mito-Q aggravated damage by inactivating DNA repair and accelerating hepatocarcinogenesis. It is not possible to directly extrapolate this data to other models of liver cancer, other cancers, or cancers in humans. However, because SS-31 is likely to promote oxidative phosphorylation in all mitochondria including those in cancer cells, theoretically, it could accelerate cancer growth.

Glaucoma: POTENTIAL BENEFIT IN PRECLINICAL STUDIES.

A review on glaucoma suggests that SS-31 is an attractive drug that may prevent oxidative damage against retinal ganglion cells (Pang et al., 2015).

In a rat model of glaucoma (intracameral injection of polystyrene microspheres to induce elevated intraocular pressure), SS-31 treatment (3 mg/kg/day, i.p.) ameliorated the reductions in the a- and b-wave amplitudes on electroretinography and the flash visual-evoked potential amplitude (Wu et al., 2019). SS-31 treatment also preserved ganglion cell complex thickness, decreased TUNEL-positive cells in the retina, reduced oxidative stress (decreased MDA levels and increased SOD2 levels), and significantly reduced apoptosis (as measured by decreased cytochrome c release, increased Bcl-2, and downregulation of Bax).

Spinal cord injury: POTENTIAL BENEFIT IN PRECLINICAL MODELS.

In a mouse model of spinal cord injury (spinal laminectomy followed by crush injury), elamipretide treatment (5 mg/kg/day, i.p.) started immediately after injury and continued for 3 days improved

locomotor functional recovery and reduced motor neuron loss (Jiang et al., 2023). Elamipretide treatment also inhibited NLRP3 inflammasome activation, decreased pro-inflammatory cytokine levels (e.g., IL-1β, IL-18), and pyroptosis (proinflammatory programmed cell death).

In another study of mice with spinal cord injury (spinal cord contusion injury model), elamipretide treatment (5 mg/kg/day, i.p.) 30 minutes prior to injury and for 3 days following injury promoted functional recovery while inhibiting pyroptosis, enhancing autophagy, and attenuating lysosomal membrane permeabilization (Zhang et al., 2023). Elamipretide's effects were in part through inhibition of the phosphorylation of cPLA2, resulting in restoration of autophagic flux and attenuation of pyroptosis.

In another study of mice with contusive spinal cord injury, treatment with SS-31 attenuated the reduction in cardiolipin in a dose-dependent manner, while improving behavioral recovery (Ravenscraft et al., 2025). SS-31 treatment, however, did not have any significant effects on tissue damage.

In a different mouse model of spinal cord injury (thoracic contusion model), SS-31 treatment (10 mg/kg/day, i.p.) started 2 hours after injury and continued for 7 days significantly enhanced locomotor recovery and gait performance, while reducing lesion pathology and preserving neurons in the spinal cord (Song et al., 2026). Early after spinal cord injury, SS-31 attenuated apoptosis signaling (measured by reduced cleaved caspase-3 and Bax and increased Bcl-2). In the later phases, SS-31 decreased astrogliosis and enhanced markers of axonal (GAP43) and synaptic remodeling (Synapsin 1).

Mitochondria: POTENTIAL BENEFIT IN PRECLINICAL MODELS.

In multiple in vitro and rodent models, SS-31 protected mitochondrial health and function. In an ischemia model, SS-31 prevented mitochondrial swelling and protected cristae membrane integrity (Liu et al., 2014; Birk et al., 2013). In vitro models show that SS-31 selectively interacts with cardiolipin and promotes oxygen consumption, ATP synthesis, and optimal mitochondrial electron transport (Birk et al., 2014).

Inflammation: POTENTIAL BENEFIT IN RODENT MODEL.

In senescence accelerated mice (SAMP8), SS-31 treatment (5 mg/kg/day, i.p.) for 8 weeks inhibited the increase in NFkB expression seen with aging (Hao et al., 2017). SS-31 treatment also activated the

transcription factor, nuclear factor erythroid 2-related factor 2 (Nrf2), which upregulates genes to guard against oxidative stress (e.g., heme oxygenase-1).

Lifespan: NO BENEFIT IN MICE

In aged female mice, elamipretide treatment (3 mg/kg, i.p.) twice weekly for 8 months did not increase the probability of survival compared to vehicle (saline)(Campbell et al., 2023).

Safety: The most common adverse event with elamipretide is injection site reaction, occurring in most patients. Other adverse events include dizziness, nausea, and increased eosinophil counts (without clinical manifestations).

Types of evidence:

- a 168-week open-label extension of phase 2/3 trial in Barth syndrome
- 1 double-blind phase 2 RCT in patients with heart failure
- 1 double-blind phase 2 RCT in patients with primary mitochondrial myopathy
- 1 double-blind phase 2a RCT in patients with myocardial infarction
- 1 double-blind phase 2a RCT in patients with atherosclerotic renal artery stenosis
- 1 double-blind phase 1/II RCT in patients with primary mitochondrial myopathy
- 1 double-blind randomized placebo-controlled phase 2 trial in patients with age-related macular degeneration with noncentral geographic atrophy
- 1 double-blind randomized placebo-controlled trial in patients with Leber hereditary optic neuropathy
- 3 double-blind randomized controlled trials, 1 in patients with atherosclerotic renal artery stenosis, 1 in heart failure, and 1 in healthy older adults
- 1 pilot clinical study in renovascular hypertensive patients undergoing renal revascularization
- 2 phase 1 open-label studies in age-related macular degeneration
- 1 double-blind phase I RCT in patients with heart failure
- Numerous laboratory studies in mice, rats, rabbits, sheep, and dogs

The most common treatment-emergent adverse events reported in patients treated with subcutaneous elamipretide in clinical trials were injection-site reactions, including injection-site erythema, pain, induration, pruritus (itchiness), bruising, and urticaria (itchy raised welt) (Forzinity prescribing information; Shirley, 2026; Thompson et al., 2024; Karaa et al., 2023; Ehlers et al., 2024).

Increases in absolute eosinophil counts were observed in clinical trials where elamipretide was administered for 30 days or longer (Forzinity prescribing information), including in 6.0% of age-related macular degeneration patients in the ReCLAIM-2 trial (Ehlers et al., 2024) and 6.4% of primary mitochondrial myopathy patients in the MMPOWER-3 trial (Karaa et al., 2023). No patients receiving placebo experienced this increase. Peak eosinophil counts generally occurred about 90 days after elamipretide initiation, with counts returning to baseline levels after 6-12 months of elamipretide treatment or after discontinuation. The increases in eosinophil counts were not associated with clinical manifestations.

Hypersensitivity reactions have been reported in patients receiving elamipretide, some of which were serious (Forzinity prescribing information). Reactions occur within minutes to months after elamipretide initiation and include skin manifestations as well as respiratory symptoms. If a serious hypersensitivity reaction occurs, permanent discontinuation of elamipretide is recommended. Elamipretide is contraindicated in patients with a history of hypersensitivity to elamipretide or any of its excipients.

Elamipretide has an absolute bioavailability of approximately 92% (Shirley, 2026). There is minimal accumulation with once-daily subcutaneous administration at doses ranging from 2 to 80 mg. Elamipretide metabolism occurs via the urine. Elamipretide exposure increases in people with impaired renal function, and therefore, elamipretide dose reduction is recommended in adult patients with severe renal impairment (estimated glomerular filtration rate < 30 mL/min).

Barth syndrome patients: The 168-week open-label extension study of the phase 2/3 TAZPOWER trial in 10 patients with Barth syndrome reported injection-site reactions as the most common treatment-emergent adverse events (Thompson et al., 2024). Erythema and pruritus both occurred in 80% (8 out of 10) patients and injection-site pain occurred in 70% of patients (7 out of 10). Other treatment-emergent adverse events included dizziness (40%) and nausea (30%). Three patients had 5 serious adverse events of pneumothorax, mucosal inflammation, costochondritis, subcutaneous abscess, and gastroenteritis, which were all assessed as either 'unlikely related' or 'unrelated' to study treatment. Two patients discontinued from the study during the open-label extension because of an adverse event by the week 36 visit (during the open-label extension): one due to moderate injection-site urticaria and the other due to mild adverse event of urticaria and drug eruption. One patient discontinued study treatment during the open-label extension at week 72 for personal reasons unrelated to the study drug. No deaths were reported in the open-label extension. Laboratory values, vital signs, physical examinations, and electrocardiogram parameters remained stable overall through the open-label extension for all

participants. Except for the percent increase in eosinophils (of total leukocytes), there were no remarkable or consistent changes from baseline in hematology parameters over time. Mean eosinophils/leukocytes ratios were outside the normal range (0 to 4) at week 12 (7.14), week 24 (4.90), week 36 (4.21), week 120 (5.10), and week 192 (7.30). Mean hemoglobin levels were outside the normal range (11.0 to 14.5 mg/dL) at all study visits from week 72 to week 144, with patient means ranging from 14.62 to 15.16 mg/dL. There were no clinically meaningful changes observed in heart rate, blood pressure, or ejection fraction observed throughout the open-label extension. There were no clinically meaningful changes observed in heart rhythm in the open-label extension as assessed by 12-lead ECG.

Heart failure patients: In a phase 2 double-blind randomized controlled trial enrolling 71 patients with heart failure (with reduced ejection fraction, <40%), SS-31 treatment (4 or 40 mg, once daily, s.c.) for 28 days was well-tolerated, however a few adverse events were reported (Butler et al., 2020). One patient (SS-31, 4 mg dose) had a treatment-related adverse event (nausea and fatigue) leading to discontinuation of study participation. And 1 patient (SS-31, 40 mg dose) had a serious treatment-emergent adverse event. Rates of treatment-emergent adverse events were similar in the 3 groups. The most common adverse event was injection-site reactions in the SS-31 40 mg arm. There were no significant changes in blood pressure, heart rate, or ECG intervals in any of the groups.

A phase I double-blind randomized controlled trial enrolling 36 heart failure patients reported that a 4-hour infusion of SS-31 (0.005, 0.05, or 0.25 mg/kg/hr) did not result in any serious adverse events and was well-tolerated (Daubert et al., 2017). Blood pressure and heart rate remained stable in all cohorts. Changes in ECG intervals were small and transient and not clinically significant. Three adverse events were observed (1 in low-dose and 2 in intermediate-dose--none in high-dose); 1 patient with a history of chronic kidney disease experienced worsening of preexisting renal dysfunction (that did not affect study participation), 1 patient experienced dyspnea and tachycardia leading to study discontinuation, and 1 patient had a hemoglobin decrease that did not impact participation.

A phase 2a RCT in 118 patients with myocardial infarction also reported that MTP-131 (an acetate salt form of SS-31) at 0.05 mg/kg/hr for 1 hour was safe and well-tolerated (Gibson et al., 2016). At higher doses, changes in serum sodium levels were observed, with minimal changes in other serum electrolytes.

Mitochondrial myopathy patients: In the pivotal phase 3 double-blind randomized placebo-controlled trial (MMPOWER-3) of 218 patients with genetically confirmed primary mitochondrial myopathy, elamipretide treatment (40 mg/day, s.c.) for 24 weeks was well-tolerated with most adverse events

being mild to moderate in severity (Karaa et al., 2023). Thirteen randomized participants (6.0%) discontinued treatment (main reason was participant decision; n=9). Adverse events during the treatment period were reported by a higher percentage of elamipretide-treated participants (98.2%) than placebo-treated participants (76.1%). Most adverse events in the elamipretide group (97.2%) and half of the adverse events in the placebo group (51.4%) were reported as treatment-related adverse events. The most commonly reported adverse events for participants receiving elamipretide (frequency >10%) were injection site reactions, including erythema, pruritus, pain, swelling, induration, bruising, hemorrhage, urticaria, and injection site nodules and masses. A low percentage of serious adverse events were reported for participants in the elamipretide (5 out of 109 patients; 4.6%) and the placebo groups (3 out of 109 patients; 2.8%) and were not judged to be treatment-related. The incidence of adverse events leading to discontinuation was higher in the elamipretide group (8 out of 109 patients for elamipretide; 2 out of 109 patients for placebo). No participants had an adverse even with an outcome of death or hospitalization.

In a phase 2 double-blind crossover, randomized controlled trial (MMPOWER-2) enrolling 30 patients with genetically confirmed primary mitochondrial myopathy, SS-31 treatment (40 mg/day s.c.) for 4 weeks led to some adverse events, though the majority of these were mild (Karaa et al., 2020). Injection site reactions were the most commonly-reported adverse events with SS-31 (80%), and were most commonly characterized as erythema (57%), pruritus (47%), pain (20%), urticaria (20%), and irritation (10%). Of the participants experiencing injection site reactions with SS-31, the majority were reported to be mild, though moderate bruising, discomfort, erythema, induration, irritation, and/or pain were reported in a few participants. Injection site erythema, pain, bruising, and irritation were also reported with placebo, but at a lesser frequency (<10% each). No serious adverse events or deaths were reported. Sixty percent of subjects experienced only mild adverse events, and 40% experienced at least one adverse event of moderate severity. When excluding injection site reactions, the only adverse event reported in over 10% of subjects with SS-31 was dizziness (10%). Falls were the most commonly reported adverse event with placebo (10% vs. 3.3% in SS-31).

In a phase I/II double-blind randomized controlled trial (MMPOWER, the basis for the study above) enrolling 36 participants with genetically confirmed primary mitochondrial myopathy, SS-31 treatment (0.01, 0.1, and 0.25 mg/kg/hour, i.v. for 2 hours in a dose-escalating sequence) did not result in any deaths, serious adverse events, or adverse events leading to discontinuation of participation (Karaa et al., 2018). The most common adverse event was headache (6; 16.7% of participants), followed by dizziness (3; 8.3% of participants). For participants treated with the highest SS-31 dose or placebo, the

most common adverse event was headache (2; 22.2% of participants in each group). There were no differences in adverse events between the SS-31-treated and placebo groups.

Age-related macular degeneration patients: In a phase 1 open-label study of 18 patients with intermediate age-related macular degeneration and high-risk drusen, elamipretide treatment (40 mg/day, s.c.) for 24 weeks resulted in all participants experiencing 1 or more adverse events, but all were mild (57%) or moderate (43%), with the most common events related to injection site reactions (Allingham et al., 2021). No serious adverse events occurred. One participant discontinued due to an injection site reaction, 1 participant withdrew because they did not wish to continue study visits, and 1 participant withdrew after experiencing transient visual impairment. Eight participants experienced an adverse event in the study eye (2 participants each experienced 2 events): 1 participant showed conversion to neovascular age-related macular degeneration and retinal hemorrhage, 1 participant showed mild intraretinal hemorrhage, 1 participant showed reduced visual acuity and visual impairment, 1 participant showed borderline glaucoma, 1 participant showed eyelid pruritus, 1 participant showed meibomian gland dysfunction, 1 participant showed posterior capsular opacification, and 1 participant showed punctate keratopathy. Of the 2 participants who experienced retinal hemorrhage in the study eye, the first was a mild intraretinal hemorrhage outside the arcades that was attributed to longstanding hypertension. This was not considered related to the study drug. The second participant with intraretinal hemorrhage was diagnosed concurrently with new choroidal neovascularization resulting from neovascular age-related macular degeneration at the final week 28 study visit (4 weeks after having stopped study drug). Risk factors for the development of neovascular age-related macular degeneration in this participant included large drusen and pigmentary changes in the study eye and prior diagnosis of neovascular age-related macular degeneration in the other eye. This was not considered related to the study drug. One participant experienced 2 ocular adverse events of reduced visual acuity and visual impairment in the study eye at week 12. At week 12, some visual function measures were decreased compared with baseline, whereas others were stable or improved compared with baseline. No change in clinical examination or imaging findings was found. The participant voluntarily decided to withdraw from the study at the week 12 visit. At this participant's follow-up visit 1 month later, BCVA had recovered to baseline. These adverse events were considered mild and possibly related to the study drug.

In a phase 1 open-label study of 15 patients with intermediate age-related macular degeneration and noncentral geographic atrophy (ReCLAIM NCGA Study), elamipretide treatment (40 mg/day, s.c.) for 24 weeks resulted in all participants experiencing 1 or more nonocular adverse events, but all adverse events were mild (73.7%) or moderate (26.3%), with no serious adverse events (Mettu et al., 2021). Two

participants exited the study because of adverse events (one conversion to neovascular age-related macular degeneration and one intolerable injection site reaction), 1 participant discontinued because of self-perceived lack of efficacy, and 1 participant chose not to continue with study visits. Two treatment-emergent serious adverse events and no deaths occurred during the study. Both serious adverse events, (urinary tract infection and sepsis), occurred in the same participant, were of moderate intensity, and were not considered related to study drug. Both events resolved with full recovery of the participant. Two study participants experienced ocular adverse events in the study eye; conversion to neovascular age-related macular degeneration (moderate intensity) and vitreous floaters (mild intensity), but both events were not considered related to study drug. Two participants reported an ocular adverse event in the nonstudy eye, both of which were of mild intensity and were not related to the study drug.

In a phase 2 double-blind randomized placebo-controlled trial of 176 patients with dry age-related macular degeneration with noncentral geographic atrophy (ReCLAIM-2), elamipretide treatment (40 mg/day, s.c.) for 48 weeks resulted in adverse events in 86% of participants compared to 71% in those receiving placebo (Ehlers et al., 2024). As in other studies, injection site reactions were the most common, including pruritis, injection site pain, bruising, erythema, induration, injection site mass, hypertrophy, and swelling. The most common reasons for early discontinuation were withdrawal by subject (elamipretide, n=20; placebo, n=3) and adverse events (elamipretide, n=10; placebo, n=4). Some of the discontinuation was due to the challenges of study visits during the COVID-19 pandemic. There were no serious adverse events or deaths in either elamipretide or placebo groups that were considered related to study treatment.

Patients with Leber hereditary optic neuropathy: In a phase 2 double-blind randomized controlled trial of 12 patients with LHON, elamipretide treatment (1% topical ophthalmic solution) for 52 weeks was well tolerated with the majority of adverse events being mild to moderate and resolving spontaneously (Karanjia et al., 2024). No patients experienced a serious treatment-emergent adverse event and there were no treatment-emergent adverse events that led to discontinuation. The most common ocular treatment adverse events during the double-blind study period were conjunctival hyperemia (16.7%), superficial punctate keratitis (16.7%), other symptoms of dry eye (12.5%), eye irritation (12.5%), and eyelid irritation (12.5%). In the open-label extension, participants experienced mild adverse events consistent with those reported in the double-blind period with no serious treatment-emergent adverse events and no treatment-emergent adverse events leading to discontinuation of the study drug.

Patients with other conditions: A phase 2a double-blind randomized controlled trial enrolling 14 patients with severe atherosclerotic renal artery stenosis reported that SS-31 administration (0.05

mg/kg/hr for 3 hours) before and during percutaneous transluminal renal angioplasty was well-tolerated with no adverse clinical effects (Saad et al., 2017). Over the 24 hours after infusion of SS-31, there were no changes in serum creatinine or urine cytology.

Healthy people: Several phase I studies have assessed the safety, tolerability, and pharmacokinetics of SS-31 in healthy male and female subjects with i.v. and oral dosing (Szeto, 2014). SS-31 was well-tolerated as an i.v. infusion over a wide dose range (0.01 mg/kg/h to 0.25 mg/kg/h over 4 hr), achieving effective plasma levels at the lowest dose. Twelve healthy volunteers received 0.05 mg/kg/hr of SS-31 intravenously for 2 hours and there were no drug-related adverse events (Chakrabarti et al., 2013). Oral SS-31 appeared to also be safe in people and was well-tolerated with no serious adverse effects across a broad dose range.

Preclinical data: In a rat model of acute ischemia, SS-31 was effective in preserving mitochondria, ameliorating inflammatory responses, and protecting kidney structure and function even when treatment was initiated 1 month after the ischemia (Szeto et al., 2016). Also, the protection by SS-31 was sustained for over 6 months after treatment ended. SS-31 is water-soluble and excreted by the kidneys.

Drug interactions: Drug interactions with SS-31 have not been well-documented.

Sources and dosing:

In September 2025, the US FDA granted accelerated approval of elamipretide (marketed as Forzinity by Stealth BioTherapeutics) to improve muscle strength in adult and pediatric patients with Barth syndrome weighing at least 30 kg (~66 lbs)(Shirley, 2026). Continued approval for this indication may be contingent upon validation of clinical benefit in a confirmatory trial (Forzinity prescribing information). The recommended dose is 40 mg once daily, subcutaneously. The dose is given at the same time each day, with the injection in the abdomen (at least 2 inches away from the navel) or outer thigh, rotating the injection site daily. For adults with an estimated glomerular filtration rate (eGFR) under 30 mL/min and not on dialysis, the recommended dosage is elamipretide 20 mg once daily. There is insufficient information regarding the optimal dosage in pediatric patients with renal impairment or in adult patients with an eGFR < 30 mL/min and on dialysis.

Research underway:

Several ongoing clinical trials are testing SS-31 (Elamipretide™, Bendavia™).

ReNEW is a phase 3 randomized double-masked placebo-controlled clinical trial testing the efficacy, safety, and pharmacokinetics of subcutaneous injections of elamipretide in 313 people with dry age-related macular degeneration (NCT06373731). Participants will be randomized 2:1 to once daily subcutaneous doses of 40 mg elamipretide or placebo for 96 weeks. The primary outcome is the rate of change in the macular area of photoreceptor loss assessed at week 48. This study is scheduled to be completed in September 2027.

4TAZPower is a phase 3b/4 randomized double-blind placebo-controlled post-marketing trial in 48 patients with genetically confirmed Barth syndrome (BTHS) (NCT07531251). Participants will be randomized to once daily subcutaneous elamipretide or matching placebo for 72 weeks. The primary outcome is the change in the composite normalized score of 3 functional tests (6MWT, 3TUG, and 5XSST). This study is scheduled to be completed in November 2029.

SHAPE is an open-label single-arm phase 2a study enrolling 30 older adults with lower function (NCT07275424). The primary outcome is the safety and tolerability of daily subcutaneous injections of elamipretide for 4 weeks. Secondary outcomes include blood biomarkers (BDNF, VEGF, IGF-1, IL-6, TNF-α), 6-minute walk test, cognitive function (MoCA), and skeletal muscle strength. This study had an original estimated study completion of April 2026; the study's current status is "recruiting".

Search terms:

Pubmed, Google: SS-31 or Bendavia or Elamipretide or MTP-131

- + cognitive, + memory, + dementia, + Alzheimer's, + ischemia, +review, + ApoE4, + cardiovascular, + diabetes, + aging, + safety, + toxicity

Websites visited:

- Clinicaltrials.gov
- Drugs.com
- WebMD.com

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