

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.

SS-31 (Elamipretide, Bendavia, and MTP-131)

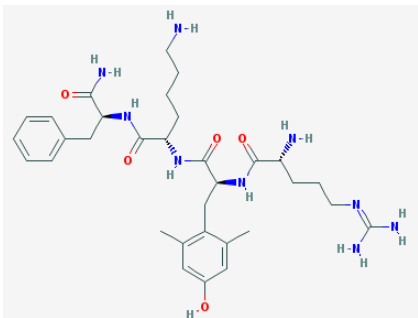
Evidence Summary

SS-31 has therapeutic potential for neurodegenerative diseases, heart failure, ischemia, and muscle aging—we will know more when results from the ongoing clinical trials are published.

Neuroprotective Benefit: SS-31 prevents anesthesia-induced cognitive impairment and promotes mitochondrial and synaptic health in AD mice, but no studies have tested its neuroprotective effects in humans.

Aging and related health concerns: Preliminary findings from short-term phase I/II clinical trials suggest potential benefit of SS-31 in patients with heart failure, though long-term studies are needed to confirm these trends.

Safety: SS-31 has been used extensively in many species and appears to be safe in people too when given acutely—more safety information will be available when results from the ongoing clinical trials are published.

Availability: In clinical development with Stealth Biotherapeutics using a clinical formulation named Elamipretide™ (or Bendavia™)	Dose: Intravenous infusion over a wide dose range (0.01 mg/kg/h to 0.25 mg/kg/h over 4 hr) in humans.	Chemical formula: C ₃₂ H ₄₉ N ₉ O ₅ MW: 639.80 
Half life: 4 hours in dogs with i.v. administration	BBB: Permeable	Source: PubChem
Clinical trials: Two phase 2a trials and one phase 1 trial, with a total of 156 subjects	Observational studies: None	

What is it? SS-31 (also known as Bendavia, Elamipretide, 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.

Neuroprotective Benefit: SS-31 prevents anesthesia-induced cognitive impairment and promotes mitochondrial and synaptic health in AD mice, but no studies have tested its neuroprotective effects in humans.

Types of evidence: (bullet points)

- o clinical trials

- 3 laboratory studies
- 1 review

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?: None available.

Human research to suggest benefits to patients with dementia: None available.

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](#)).

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.

Mitochondria are central to proper neuronal and synaptic activity, and decreased mitochondrial transport is an early event in neurodegeneration ([Calkins et al., 2012](#)). 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 A β 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.

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 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 (PGC1 α , Nrf1, Nrf2, TFAM), and synaptic genes (PSD95, synaptophysin)([Reddy et al., 2017](#)). SS-31-treated mice also had lower levels of soluble and insoluble A β . SS-31 treatment had protective effects against mitochondrial and synaptic toxicities by improving mitochondrial dynamics, mitochondrial biogenesis, and synaptic functions in this mouse model.

APOE4 interactions: Unknown.

Aging and related health concerns: Preliminary findings from short-term phase I/II clinical trials suggest potential benefit of SS-31 in patients with heart failure, though long-term studies are needed to confirm these trends.

Types of evidence:

- 1 double-blind phase 2a RCT in patients with myocardial infarction
- 2 double-blind randomized controlled trials, 1 in patients with atherosclerotic renal artery stenosis and 1 in heart failure
- 11 laboratory studies, 1 on myocardial infarction, 1 on ischemic brain injury, 1 on a Parkinson's disease model, 1 on neurovascular function, 1 on skeletal muscle aging, 2 on renal ischemia, 1 on ATP synthesis, 1 on diabetic mice, 1 on pulmonary arterial hypertension, and 1 on glaucoma
- 7 additional preclinical studies
- 3 reviews on SS-31

Heart failure: BENEFIT/MIXED. 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).

Atherosclerosis: POTENTIAL BENEFIT BASED IN MICE. 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. A phase 2a clinical trial in renal artery arteriosclerosis is described below.

Ischemic brain injury: POTENTIAL BENEFIT IN MICE. 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](#)).

Parkinson's disease: POTENTIAL BENEFIT. 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.



Neurovascular function: POTENTIAL BENEFIT. In aged mice, SS-31 treatment (10 mg/kg/day, s.c.) for 2 weeks improved neurovascular function. The 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 full text of this paper was not accessible.

Muscle aging: POTENTIAL BENEFIT IN MICE. 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.

Osteoarthritis: POTENTIAL BENEFIT IN PRECLINICAL MODELS. 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 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).

Inflammation: POTENTIAL BENEFIT IN MICE. 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).

Diabetes/Kidneys: POTENTIAL BENEFIT IN MICE. 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 the antiapoptotic protein Bcl2. SS-31 appears to be protective against diabetic nephropathy.

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.

Renal ischemia: POTENTIAL BENEFIT. 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-1 β expression.

Pulmonary hypertension: POTENTIAL BENEFIT IN MICE. In a mouse model of pulmonary arterial hypertension, SS-31 administration suppressed blood pressure elevation, oxidative stress proteins, markers of inflammation (MMP9, TNF α , iNOS), proapoptotic proteins (Bax, caspase 3), DNA damage, and lung injury score ([Lu et al., 2016](#)).

Liver cancer: POTENTIAL HARM IN MICE. 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 SS31 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: UNKNOWN. 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](#)).

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](#)).

Safety: SS-31 has been used extensively in many species and appears to be safe in people too when given acutely—more safety information will be available when results from ongoing clinical trials are published.

Types of evidence:

- 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 I RCT in patients with heart failure
- Several phase I studies on safety, tolerability, and pharmacokinetics
- Numerous laboratory studies in mice, rats, rabbits, sheep, and dogs

Details. 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](#)). 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. Oral SS-31 appeared to also be safe in people and was well-tolerated with no serious adverse effects across a broad dose range. However, all studies in humans thus far have only tested its acute effects. It is not known whether SS-31 accumulates in mitochondria over time and whether that is helpful or harmful.

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.

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. Further studies of SS-31 are needed to determine long-term safety and efficacy.

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 are unknown.

Sources and dosing: In 2010, SS-31 entered into clinical development with Stealth Biotherapeutics (formerly Stealth Peptides Inc., Newton, MA) using a clinical formulation named Elamipretide™ (or Bendavia™). SS-31 is well-tolerated as an intravenous infusion over a wide dose range (0.01 mg/kg/h to 0.25 mg/kg/h over 4 hr) in humans ([Szeto, 2014](#)). Oral SS-31 appears to also be safe and well-tolerated with no serious adverse effects. A dose of 0.05 mg/kg/hr for 1 hour was used in the phase 2a clinical trial in patients with acute myocardial infarction with percutaneous coronary intervention ([Gibson et al., 2016](#)). Doses used in preclinical studies ranged from 0.5-10.0 mg/kg (s.c., i.v., or i.p.) for rats and mice, 0.05-0.1 mg/kg (i.v.) for rabbits, and 0.05 mg/kg/hr (i.v.) for pigs, sheep, and dogs ([Szeto, 2014](#)).

Research underway: Clinical trials are testing whether SS-31 is effective in treating people with heart failure ([NCT02814097](#), [NCT02914665](#), and [NCT02788747](#)), mitochondrial disease ([NCT02805790](#)), age-related macular degeneration ([NCT02848313](#)), age-related skeletal muscle mitochondrial dysfunction ([NCT02245620](#)), and Leber's hereditary optic neuropathy ([NCT02693119](#)). Most of these trials were scheduled to be completed in 2017.

A phase 3 randomized double-blind controlled trial is evaluating the safety and efficacy of SS-31 (elamipretide) in 202 subjects with mitochondrial myopathy—this study is followed by an open-label extension (MMPOWER-3) ([NCT03323749](#)). The dose is daily 40 mg (0.5 mL) subcutaneous injections for 24 weeks. This trial is scheduled to be completed in December 2020.

A phase 2/3 randomized double-blind controlled trial is testing the safety, tolerability, and efficacy of SS-31 in subjects with Barth Syndrome (TAZPOWER)([NCT03098797](#)). This study is also using the same dose of 40 mg daily subcutaneous injections for 12 weeks. This trial is scheduled to be completed in August 2018.

An open-label extension trial is evaluating the long-term safety and tolerability of SS-31 (daily 40 mg s.c. injections) in subjects with genetically confirmed primary mitochondrial disease ([NCT02976038](#)). Treatment continues for 260 weeks. The trial is scheduled to be completed in December 2021.

On the other hand, a study to assess the effects of i.v. SS-31 in patients undergoing percutaneous transluminal angioplasty of the renal artery has been terminated ([NCT01755858](#)). It is unclear how this study that started in 2012 is different from the phase 2a study published in 2017 ([Saad et al., 2017](#)).

In January 2016, SS-31 (Elamipretide) was granted [fast track designation for the treatment of primary mitochondrial myopathy](#) in patients with genetic mitochondrial diseases, for which there are currently no approved treatments. SS-31 has also been granted [orphan drug designation for the treatment of patients with primary mitochondrial myopathy](#) in October 2017, [fast track designation for the treatment of Barth Syndrome](#) in November 2017, and [fast track designation for the treatment of Leber's Hereditary Optic Neuropathy](#) in December 2017.

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

Clinicaltrials.gov:

- SS-31, Bendavia, Elamipretide, MTP-131, Stealth Biotherapeutics

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