



*Cognitive Vitality Reports<sup>®</sup> 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 (also known as Elamipretide<sup>®</sup>, Bendavia<sup>®</sup>, and MTP-131)

### Evidence Summary

Preclinical studies showed benefit in cognitive impairment, muscle aging, atherosclerosis, osteoarthritis, diabetes, glaucoma, etc., but clinical trials in heart failure and mitochondrial myopathy have failed.

**Neuroprotective Benefit:** In models of cognitive impairment, SS-31 improves cognitive functions by promoting mitochondrial and synaptic health and decreasing inflammation and pyroptosis. But these effects have not been confirmed in humans.

**Aging and related health concerns:** Preclinical studies suggest benefits in muscle aging, atherosclerosis, ischemia, osteoarthritis, diabetes, and glaucoma. But clinical trials in heart failure and primary mitochondrial myopathy have failed.

**Safety:** SS-31 treatment leads to a few adverse events, though mostly mild. The most common adverse event with SS-31 is injection site reaction. Treatments longer than 4 weeks have not been studied, so long-term safety of SS-31 is not established in humans.



<p><b>Availability:</b> In clinical development by Stealth Biotherapeutics using a clinical formulation named Elamipretide™ (or Bendavia™)</p>	<p><b>Dose:</b> Intravenous infusion over a wide dose range (0.01 mg/kg/h to 0.25 mg/kg/h over 4 hr) has been tested in humans.</p>	<p><b>Chemical formula:</b> C<sub>32</sub>H<sub>49</sub> N<sub>9</sub>O<sub>5</sub> <b>MW:</b> 639.80</p>
<p><b>Half life:</b> 4 hours in dogs with i.v. administration</p>	<p><b>BBB:</b> Permeable</p>	
<p><b>Clinical trials:</b> 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.</p>	<p><b>Observational studies:</b> None</p>	

**What is it?** SS-31 (also known as Bendavia, Elamipretide, and MTP-131) is a small peptide (D-Arg-dimethyl-Tyr-Lys-Phe-NH<sub>2</sub>) 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:** In models of cognitive impairment, SS-31 improves cognitive functions by promoting mitochondrial and synaptic health and decreasing inflammation and pyroptosis. But these effects have not been confirmed in humans.

Types of evidence:

- 0 clinical trials
- Numerous 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](#)).

**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-1 $\beta$  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- $\alpha$ ). 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 (PGC1 $\alpha$ , 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 $\beta$ . 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 A $\beta$  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.

**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), 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-1 $\alpha$ , 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.

**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:** Preclinical studies suggest benefits in muscle aging, atherosclerosis, ischemia, osteoarthritis, diabetes, and glaucoma. But clinical trials in heart failure and primary mitochondrial myopathy have failed.

Types of evidence:

- 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
- 2 double-blind randomized controlled trials, 1 in patients with atherosclerotic renal artery stenosis and 1 in heart failure
- 1 pilot clinical study in renovascular hypertensive patients undergoing renal revascularization
- Numerous preclinical studies



- 3 reviews on SS-31

**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](#)).

**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. A phase 2a clinical trial in renal artery atherosclerosis is described in a later section.

**Primary mitochondrial myopathy:** FAILED TO MEET PRIMARY ENDPOINTS IN PHASE 3 TRIAL.

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](#)). In addition, 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 ( $\pm$ 134.16) meters compared with 378.5 ( $\pm$ 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 initiation of MMPOWER-3, a 6-month long, phase 3 trial in 218 patients with genetically confirmed primary mitochondrial myopathy, which would have been followed by an open-label treatment extension. However, this trial testing SS-31 therapy (40 mg/day, s.c.) was terminated because the double-blind portion of the trial did not meet the primary endpoints ([NCT03323749](#)).

**Barth syndrome:** FAILED TO MEET PRIMARY ENDPOINTS IN PHASE 2/3 TRIAL. In a small phase 2/3 randomized controlled trial in 12 patients with Barth syndrome, a genetic disorder of mitochondrial cardiolipin metabolism, 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., 2020](#)). 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 (-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.

A larger, longer phase 2/3 randomized double-blind controlled crossover trial is testing the safety, tolerability, and efficacy of SS-31 in 180 subjects with Barth Syndrome (TAZPOWER)([NCT03098797](#)). This study is testing a SS-31 treatment (40 mg daily subcutaneous injections) for 12 weeks followed by or preceded by 12 weeks of placebo injections, followed by a 168-week open-label extension. This trial is scheduled to be completed in June 2021.

**Ischemic brain injury:** POTENTIAL BENEFIT IN PRECLINICAL MODEL. 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 PRECLINICAL MODEL. 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.

**Muscle aging:** POTENTIAL BENEFIT IN PRECLINICAL MODELS. 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.

**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).

**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 NFκB 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 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 H<sub>2</sub>O<sub>2</sub>, 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](#)).



**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, TGF $\beta$ , and TNF $\alpha$ ) markers, and attenuated only senescence-associated  $\beta$ -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.

**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-1 $\beta$  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, TNF $\alpha$ , 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).

***Mitochondria:*** POTENTIAL BENEFIT. 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 treatment leads to a few adverse events, though mostly mild. The most common adverse event with SS-31 is injection site reaction. Treatments longer than 4 weeks have not been studied, so long-term safety of SS-31 is not established in humans.

*Types of evidence:*

- 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 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

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.

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 per cent 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.

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.

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.

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.

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 2010, SS-31 entered into clinical development with Stealth Biotherapeutics (formerly Stealth Peptides Inc., Newton, MA) using clinical formulations named Elamipretide™ and 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 of 4 and 40 mg once daily (s.c.) were tested in a phase 2 double-blind randomized controlled trial in heart failure ([Butler et al., 2020](#)). A dose of 40 mg/day (s.c.) was tested in the phase 3 MMPOWER-3 trial in patients with genetically confirmed primary mitochondrial myopathy, though this study was terminated because the double-blind portion of the trial did not meet the primary endpoints ([NCT03323749](#)).

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](#)).

In December 2020, StealthBiotherapeutics started an Expanded Access Program towards an intermediate-size population ([NCT04689360](#)). This program is available to people with genetically confirmed rare diseases with known mitochondrial dysfunction, or to people without genetic confirmation of a rare disease but exhibit serious or life-threatening clinical manifestations of mitochondrial dysfunction. The treating physician must contact StealthBiotherapeutics through this program and elamipretide can be made available after careful review of each request.

**Research underway:** 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 (elamipretide) was also 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.

A phase 2/3 randomized double-blind controlled crossover trial is testing the safety, tolerability, and efficacy of SS-31 in subjects with Barth Syndrome (TAZPOWER)([NCT03098797](#)). This study is testing a SS-31 treatment (40 mg daily subcutaneous injections) for 12 weeks followed by or preceded by 12 weeks of placebo injections, followed by a 168-week open-label extension. This trial is finished recruiting subjects and is scheduled to be completed in June 2021.

A phase 2 randomized, double-masked, placebo-controlled clinical trial (named ReCLAIM-2 study) is studying the safety, efficacy, and pharmacokinetics of SS-31 in subjects with age-related macular degeneration with non-central geographic atrophy ([NCT03891875](#)).

#### 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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