

RESEARCH MONOGRAPH . COMPOUND PROFILE

SBT-272

A next-generation cardiolipin-binding peptidomimetic developed by Stealth BioTherapeutics as a brain-penetrant successor to elamipretide (SS-31), designed to restore mitochondrial structure and function in neurodegenerative disease with demonstrated preclinical neuroprotection in models of amyotrophic lateral sclerosis, frontotemporal dementia, Parkinson's disease, Huntington's disease, and ischemic stroke.

DOCUMENT	KDC-MN-1604
ISSUED	2026-05-20
REVISION	1.0
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COMPOUND CLASS	Mitochondria-targeted cardiolipin-stabilizing peptidomimetic with enhanced central nervous system penetration

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ABSTRACT

SBT-272, also designated bevemipretide (International Nonproprietary Name), is a clinical-stage mitochondria-targeted peptidomimetic small molecule developed by Stealth BioTherapeutics as a structurally optimized successor to elamipretide (SS-31, MTP-131, Bendavia). The compound selectively binds cardiolipin, a diphosphatidylglycerol lipid exclusively localized to the inner mitochondrial membrane, where it stabilizes the organization of electron transport chain complexes into supercomplexes (respirasomes), promotes efficient oxidative phosphorylation, reduces mitochondrial reactive oxygen species generation, and prevents the cytochrome c/cardiolipin peroxidase activity that initiates apoptotic signaling. Relative to the first-generation elamipretide scaffold, SBT-272 demonstrates higher mitochondrial uptake, greater brain accumulation following subcutaneous administration, and improved systemic bioavailability in preclinical species, properties that position the compound for neurodegenerative disease indications where central nervous system exposure is a critical determinant of therapeutic effect.

The preclinical pharmacology of SBT-272 encompasses multiple neurodegenerative disease models. In TDP-43 mutant upper motor neuron cultures derived from the prpTDP-43(A315T) transgenic mouse, SBT-272 restored mitochondrial structural integrity, recovered mitochondrial motility in a dose-dependent manner, and improved axon outgrowth, a functional indicator of neuronal health, with effects superior to those of edaravone and AMX0035 in the same system [1]. Chronic in vivo treatment for

sixty days in the same model significantly reduced astrogliosis, microgliosis, and TDP-43 pathology in the motor cortex [1]. In the SOD1(G93A) transgenic mouse model of amyotrophic lateral sclerosis, high-dose SBT-272 (5.0 mg/kg/day intraperitoneal) delayed neurological symptom onset and significantly extended lifespan in male mice [2]. In an alpha-synucleinopathy mouse model of Parkinson's disease, daily subcutaneous SBT-272 attenuated dopaminergic neuron loss, reduced pathological alpha-synuclein burden, and suppressed neuroinflammatory markers [3]. Additional preclinical neuroprotective activity has been reported in models of frontotemporal lobar dementia, Huntington's disease, and ischemic stroke [4].

Clinical development has advanced through a Phase 1 double-blind, placebo-controlled study in healthy volunteers evaluating subcutaneous SBT-272 at single ascending doses of 5 to 60 mg and multiple ascending doses of 20, 40, and 60 mg daily for 7 days [5]. Interim results demonstrated a pharmacokinetic profile consistent with preclinical allometric scaling predictions, plasma and projected brain exposures at doses anticipated to reach therapeutic concentrations based on preclinical efficacy thresholds, and a safety profile in which the most commonly reported adverse event was mild-to-moderate injection site reaction resolving within approximately 4 hours of dosing [5]. The United States Food and Drug Administration granted Orphan Drug Designation for SBT-272 for the treatment of amyotrophic lateral sclerosis in 2022 [4]. A separate development program for topical ocular bevemipretide (eye drops) in dry age-related macular degeneration has advanced through preclinical studies demonstrating approximately 4- to 6-fold higher retinal tissue concentrations compared to elamipretide, with a 13-week GLP toxicology study informing Phase 1 trial design [6, 7].

This monograph reviews the chemistry, structural class, and synthesis of SBT-272; the cardiolipin-stabilization mechanism at the inner mitochondrial membrane; the pharmacokinetic profile including brain penetration; the preclinical pharmacology across ALS, Parkinson's disease, and additional neurodegenerative models; the Phase 1 clinical evidence base; sourcing and quality verification considerations; reconstitution and handling; stack-interaction implications; adverse-event signal; and a comparative assessment of five mitochondria-targeted or neuroprotective candidates against SBT-272 on five competency standards (novelty, effect size, promising potential, side-effect profile, and overall validation).

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Bevemipretide.

Development code: SBT-272 (Stealth BioTherapeutics). The development code is the canonical identifier in essentially all published preclinical and clinical literature; bevemipretide has not yet entered widespread pharmacopoeial or regulatory use as a primary identifier.

Chemical Abstracts Service registry number: 2356106-71-1 (free base). The trihydrochloride salt form is listed in PubChem under CID 163361905.

International Union of Pure and Applied Chemistry name: D-arginyl-N-alpha-[(1S)-5-amino-1-(3-benzyl-1,2,4-oxadiazol-5-yl)pentyl]-2,6-dimethyl-L-tyrosinamide. The compound is a peptidomimetic incorporating a D-arginine residue, a modified dimethyltyrosine, and a C-terminal 1,2,4-oxadiazole heterocycle bearing a benzyl substituent at the 3-position.

Relationship to elamipretide: SBT-272 is a structural analog of elamipretide (SS-31, MTP-131, Bendavia), the first-in-class cardiolipin-binding tetrapeptide approved by the United States Food and Drug Administration in September 2025 under the trade name Forzinity for the treatment of Barth syndrome [8]. Both compounds share the core mechanism of selective cardiolipin binding at the inner mitochondrial membrane. SBT-272 was designed to retain the mitochondrial targeting pharmacophore while incorporating structural modifications that improve blood-brain barrier penetration, mitochondrial uptake, and systemic bioavailability relative to the parent elamipretide scaffold.

1.2 Structural class and chemistry

SBT-272 is a peptidomimetic small molecule belonging to the Szeto-Schiller (SS) peptide family of mitochondria-targeted compounds. The structural class is defined by an alternating aromatic-cationic motif that enables selective accumulation in the cardiolipin-rich inner mitochondrial membrane through electrostatic and hydrophobic interactions. Unlike the parent SS-31 tetrapeptide (D-Arg-Dmt-Lys-Phe-

NH₂, where Dmt is 2,6-dimethyltyrosine), SBT-272 replaces the C-terminal lysine-phenylalanine dipeptide with a lysine-oxadiazole(benzyl) moiety, conferring increased lipophilicity and improved membrane permeability.

Molecular formula: C₃₁H₄₅N₉O₄ (free base).

Exact mass: 607.3595 g/mol (free base, monoisotopic).

Molecular weight: 607.76 g/mol (free base).

Physical properties: The compound is supplied as a white to off-white solid (free base or hydrochloride salt). Solubility in aqueous media is facilitated by the guanidinium and amino groups; the compound is soluble in dimethyl sulfoxide and in acidified aqueous solutions.

Stereochemistry: SBT-272 contains defined stereocenters at the D-arginine residue (R-configuration) and at the modified tyrosine and lysine residues (S-configuration at the alpha-carbon). The compound is supplied as a single stereoisomer.

1.3 Synthesis

The synthesis of SBT-272 has not been disclosed in full in the peer-reviewed literature. Based on the structural class and the precedent of elamipretide synthesis, the compound is expected to be accessible by standard solid-phase or solution-phase peptide synthesis methods incorporating Fmoc-protected D-arginine, the 2,6-dimethyltyrosine building block (available from specialized amino acid suppliers or synthesized by Friedel-Crafts methylation of protected tyrosine), and a C-terminal lysine derivative bearing the 3-benzyl-1,2,4-oxadiazole heterocycle. The oxadiazole ring is typically constructed by cyclodehydration of an amidoxime with an activated carboxylic acid or by related heterocycle-forming reactions. Final global deprotection and purification by reverse-phase high-performance liquid chromatography yield the target compound. The hydrochloride salt is prepared by treatment with hydrogen chloride in an appropriate solvent system. Industrial-scale synthesis is performed by Stealth BioTherapeutics and contract manufacturing organizations; the compound is protected by patent claims covering the chemical matter and methods of use [9].

2. Abstract

SBT-272 (bevemipretide) is a next-generation mitochondria-targeted peptidomimetic developed by Stealth BioTherapeutics as a central nervous system-optimized analog of elamipretide (SS-31). The compound binds cardiolipin on the inner mitochondrial membrane, stabilizes electron transport chain supercomplex organization, restores oxidative phosphorylation efficiency, and reduces mitochondrial reactive oxygen species production [1, 10]. Compared to the parent elamipretide, SBT-272 achieves higher mitochondrial uptake, greater brain accumulation after subcutaneous dosing, and improved systemic bioavailability in preclinical species [2, 11].

The principal development indication is amyotrophic lateral sclerosis (ALS), for which the compound has received FDA Orphan Drug Designation [4]. Preclinical data in TDP-43 mutant upper motor neuron models demonstrate dose-dependent restoration of mitochondrial structural integrity, motility, and function, with improvements in axon outgrowth that were superior to edaravone and AMX0035 [1]. In the SOD1(G93A) transgenic mouse, high-dose SBT-272 delayed neurological symptom onset and extended lifespan in male animals [2]. Additional preclinical neuroprotection has been demonstrated in models of alpha-synucleinopathy (Parkinson's disease), frontotemporal lobar dementia, Huntington's disease, and ischemic stroke [3, 4].

A Phase 1 double-blind, placebo-controlled study in healthy volunteers evaluated subcutaneous SBT-272 at single ascending doses of 5 to 60 mg and multiple ascending doses of 20, 40, or 60 mg daily for 7 days [5]. The pharmacokinetic profile was consistent with preclinical predictions. Selected doses are anticipated to achieve therapeutic brain concentrations based on preclinical efficacy data. The safety profile was favorable, with mild-to-moderate injection site reactions as the most commonly reported adverse event at doses up to 40 mg, and increased injection site reaction severity in the 60 mg cohorts [5].

A parallel development program is advancing topical ocular bevemipretide for dry age-related macular degeneration, with preclinical data demonstrating approximately 4- to 6-fold higher retinal tissue concentrations compared to elamipretide and a 13-week GLP toxicology study supporting Phase 1 trial design [6, 7].

The compound is not approved for any indication. It is in clinical-stage development for ALS and in preclinical-to-early-clinical development for dry AMD. Investigators should obtain analytical confirmation of identity and purity on every research-grade lot.

3. Discovery and Development History

3.1 Origin

SBT-272 emerged from the mitochondria-targeted peptide program at Stealth BioTherapeutics (Newton, Massachusetts), a company founded on the Szeto-Schiller peptide technology originally developed by Hazel H. Szeto and Peter W. Bhatt at Weill Cornell Medical College. The parent compound of the class, SS-31 (later designated elamipretide, MTP-131, and Bendavia), was identified through structure-activity exploration of cell-penetrating aromatic-cationic tetrapeptides that selectively accumulate in the inner mitochondrial membrane through interaction with cardiolipin [10]. Elamipretide advanced through extensive clinical development for Barth syndrome, primary mitochondrial myopathy, heart failure with preserved ejection fraction, and dry age-related macular degeneration, with the Barth syndrome indication culminating in FDA accelerated approval under the trade name Forzinity in September 2025 [8].

3.2 Rationale for a next-generation analog

While elamipretide demonstrated proof of concept for cardiolipin stabilization as a therapeutic mechanism, its pharmacokinetic profile presented limitations for neurodegenerative disease applications. Specifically, brain penetration following systemic administration was modest, limiting the achievable central nervous system concentrations at tolerated subcutaneous doses. Stealth BioTherapeutics initiated a medicinal chemistry program to identify analogs that retained the cardiolipin-binding pharmacophore while incorporating structural modifications that improved blood-brain barrier permeability and mitochondrial uptake. SBT-272 was selected from this program on the basis of superior brain accumulation in rodent pharmacokinetic studies, higher mitochondrial uptake in cellular assays, and preserved or enhanced cardiolipin-stabilizing activity [2, 11].

3.3 Preclinical development

The preclinical pharmacology program for SBT-272 was conducted primarily at Stealth BioTherapeutics in collaboration with academic laboratories, notably the Bhatt and Bhatt laboratory at Northwestern University Feinberg School of Medicine (P. Bhatt and H. Bhatt, upper motor neuron biology), and with investigators contributing disease model expertise in alpha-synucleinopathy, Huntington's disease, and ischemic stroke. Key preclinical milestones include the demonstration of neuroprotection in TDP-43 mutant upper motor neurons (presented at the 2021 Annual NEALS Meeting and the 2022 Keystone Neurodegeneration Symposium, subsequently published by Bhatt et al. in *Neurobiology of Disease* in 2023) [1]; demonstration of disease-modifying effects in the SOD1(G93A) transgenic mouse (presented at the 2021 NEALS Meeting) [2]; and demonstration of neuroprotective effects in an alpha-synucleinopathy model of Parkinson's disease (presented at the 2021 International Parkinson and Movement Disorder Society Congress) [3].

3.4 Clinical development

Stealth BioTherapeutics initiated a Phase 1 double-blind, placebo-controlled, single-ascending and multiple-ascending dose study of subcutaneous SBT-272 in healthy volunteers in 2022. Interim results were reported in November 2022, demonstrating a pharmacokinetic profile consistent with preclinical predictions and a favorable safety profile [5]. The FDA granted Orphan Drug Designation for SBT-272 for the treatment of ALS in 2022 [4]. Clinical development in ALS patients is planned but, as of the most recent monograph revision, no Phase 2 efficacy data have been reported in a peer-reviewed forum. The compound is also in preclinical-to-early-clinical development as a topical ocular formulation for dry age-related macular degeneration [6, 7].

4. Mechanism of Action

SBT-272 is a mitochondria-targeted compound whose principal molecular activity is the selective binding and stabilization of cardiolipin at the inner mitochondrial membrane. This single upstream interaction produces multiple downstream consequences for mitochondrial structure, electron transport chain function, energy metabolism, oxidative stress, and apoptotic signaling.

4.1 Cardiolipin biology and the inner mitochondrial membrane

Cardiolipin (1,3-bis(sn-3-phosphatidyl)-sn-glycerol) is a unique diphosphatidylglycerol lipid found almost exclusively in the inner mitochondrial membrane. It constitutes approximately 15 to 20 percent of the total phospholipid content of the inner membrane and performs several essential structural and functional roles [10, 12].

First, cardiolipin stabilizes the organization of the individual electron transport chain complexes (Complex I/NADH:ubiquinone oxidoreductase, Complex II/succinate dehydrogenase, Complex III/cytochrome bc1, Complex IV/cytochrome c oxidase, and Complex V/ATP synthase) into higher-order supercomplex assemblies (respirasomes). Supercomplex organization enables substrate channeling between complexes, improves the kinetic efficiency of electron transport, and minimizes electron leak and the consequent generation of superoxide and other reactive oxygen species [12, 13].

Second, cardiolipin anchors cytochrome c to the outer surface of the inner mitochondrial membrane through electrostatic interactions between the anionic cardiolipin headgroup and positively charged lysine residues on cytochrome c. This tethering is essential for efficient electron shuttling between Complex III and Complex IV [14].

Third, the structural integrity of the inner membrane cristae (the infoldings that house the respiratory chain) depends on cardiolipin interactions with the MICOS (mitochondrial contact site and cristae organizing system) complex. Loss of cardiolipin or peroxidation of cardiolipin acyl chains leads to cristae remodeling, loss of supercomplex stability, and reduced ATP generation [12].

4.2 Cardiolipin pathology in neurodegenerative disease

Mitochondrial dysfunction is a convergent pathological feature across the major neurodegenerative diseases. In ALS, both TDP-43 proteinopathy and SOD1 mutations produce mitochondrial structural disruption, impaired electron transport chain function, increased reactive oxygen species generation, and cytochrome c release that activates apoptotic cascades in motor neurons [1, 15]. In Parkinson's disease, alpha-synuclein aggregates interact with the mitochondrial membrane and disrupt cardiolipin-dependent cristae organization [3]. In Alzheimer's disease, amyloid-beta and tau pathology converge on mitochondrial dysfunction. In Huntington's disease, mutant huntingtin protein disrupts mitochondrial calcium handling and electron transport chain activity. In each of these conditions, cardiolipin peroxidation and loss of supercomplex integrity have been documented as early pathological events [12, 16].

4.3 SBT-272 interaction with cardiolipin

SBT-272 binds cardiolipin through electrostatic interactions between the cationic guanidinium group of the D-arginine residue and the amino group of the lysine-derived moiety, and the anionic phosphodiester headgroup of cardiolipin. The aromatic dimethyltyrosine and benzyloxadiazole groups partition into the hydrophobic acyl chain region of the inner membrane, anchoring the compound in the lipid bilayer in proximity to the electron transport chain complexes [10, 11].

The binding stabilizes the native conformation of cardiolipin, preventing the peroxidation of polyunsaturated acyl chains (principally linoleoyl and arachidonoyl species) that is driven by reactive oxygen species generated during impaired electron transport. By maintaining cardiolipin in its reduced state, SBT-272 preserves supercomplex organization, sustains efficient oxidative phosphorylation, and reduces the electron leak that generates further reactive oxygen species in a feed-forward cycle of mitochondrial damage [10, 12].

A second consequence of cardiolipin stabilization is the preservation of cytochrome c tethering. In the absence of cardiolipin stabilization, peroxidized cardiolipin releases cytochrome c from the inner membrane; released cytochrome c can then initiate the intrinsic (mitochondrial) apoptotic pathway through formation of the apoptosome and activation of caspase-9. By maintaining cardiolipin-cytochrome c interactions, SBT-272 suppresses this apoptotic trigger [10, 14].

4.4 Differentiation from elamipretide

SBT-272 and elamipretide share the core cardiolipin-binding mechanism but differ in pharmacokinetic properties relevant to neurodegenerative applications. In comparative rodent studies, subcutaneous SBT-272 produced significantly higher brain tissue concentrations than equimolar elamipretide, reflecting the improved blood-brain barrier permeability conferred by the oxadiazole modification at the C-terminus [2, 11]. Mitochondrial uptake in cellular assays was also higher for SBT-272, consistent with the increased lipophilicity of the modified scaffold [11]. These properties establish SBT-272 as the preferred analog for central nervous system indications, while elamipretide remains the reference compound for peripheral mitochondrial diseases (Barth syndrome, primary mitochondrial myopathy, cardiac applications).

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

SBT-272 is administered by subcutaneous injection in the systemic (neurodegeneration) development program. Subcutaneous bioavailability in preclinical species is higher than that reported for elamipretide, consistent with the improved physicochemical properties of the modified scaffold [11]. Peak plasma concentrations are achieved within approximately 1 to 2 hours after subcutaneous dosing in humans based on Phase 1 pharmacokinetic data [5]. The compound is not orally bioavailable at pharmacologically relevant levels, consistent with the peptidomimetic structural class.

5.2 Distribution

SBT-272 has a favorable central nervous system distribution profile. In mice, five daily subcutaneous doses of 1, 5, and 7.5 mg/kg/day produced brain homogenate trough concentrations of 10 to 100 nanomolar, within or exceeding the concentration range that produced in vitro neuroprotective effects in TDP-43 mutant upper motor neuron cultures [1, 2]. The brain-to-plasma ratio is substantially higher than that of elamipretide, reflecting the improved blood-brain barrier permeability [11].

Plasma protein binding data for SBT-272 have not been published in the peer-reviewed literature. Based on the structural class and the elamipretide precedent, moderate plasma protein binding is expected.

The compound accumulates selectively in mitochondria through the electrostatic interaction between the cationic residues and the anionic cardiolipin-rich inner membrane. Mitochondrial accumulation is rapid (within minutes in cellular systems) and concentration-dependent [10, 11].

5.3 Metabolism

Metabolic pathways for SBT-272 have not been fully characterized in published literature. Based on the peptidomimetic structure, metabolism is expected to involve proteolytic cleavage at the amide bonds and possible oxidative metabolism of the dimethyltyrosine and oxadiazole moieties. The compound does not contain a cytochrome P450-labile pharmacophore of the type that drives the polymorphic metabolism observed with small-molecule drugs metabolized by CYP2D6, CYP3A4, or CYP2C19.

5.4 Elimination

SBT-272 has a short plasma elimination half-life in rats (approximately 3 hours or less), but brain tissue concentrations are sustained beyond the plasma elimination phase, supporting once-daily dosing for central nervous system indications [2, 11]. The sustained brain exposure is consistent with the high-affinity cardiolipin binding and the slow dissociation from the inner mitochondrial membrane in neurons. Renal and hepatic elimination pathways for the compound and its metabolites have not been characterized in published literature.

5.5 Routes of administration

Subcutaneous injection: The primary route for the systemic neurodegeneration program. The Phase 1 study evaluated subcutaneous doses of 5 to 60 mg in healthy volunteers [5]. Subcutaneous delivery is the registered route for the related elamipretide in Barth syndrome (Forzinity).

Topical ocular: A separate development program is advancing topical eye drops containing bevemipretide for dry age-related macular degeneration. Preclinical pharmacokinetic studies demonstrated that topical ocular SBT-272 achieved approximately 4- to 6-fold higher retinal and RPE/choroid tissue concentrations compared to elamipretide, with minimal systemic exposure [6, 7].

Intraperitoneal (preclinical only): The SOD1(G93A) mouse study used intraperitoneal dosing at 0.5 and 5.0 mg/kg/day [2]. This route is standard for rodent preclinical pharmacology but is not a clinical route.

5.6 Dose-exposure relationship

Phase 1 pharmacokinetic data demonstrated dose-proportional or near-dose-proportional increases in plasma exposure across the 5 to 60 mg single-dose range [5]. The pharmacokinetic profile was consistent with allometric scaling from preclinical species, supporting the translational validity of the rodent brain exposure data. The relationship between plasma exposure and projected brain concentration is based on preclinical brain-to-plasma ratios; direct measurement of cerebrospinal fluid or brain concentrations in human subjects has not been reported.

5.7 Special populations

Pharmacokinetic data in special populations (pediatric, geriatric, renal impairment, hepatic impairment) have not been reported. The Phase 1 study enrolled healthy adult volunteers; special population characterization will require later-phase clinical development.

6. Clinical Evidence Base

6.1 Phase 1 healthy volunteer study

The principal clinical dataset for SBT-272 is a Phase 1 double-blind, placebo-controlled study enrolling up to 64 healthy subjects across multiple cohorts, with SBT-272 administered by subcutaneous injection [5]. The study comprised two parts: a single-ascending dose phase evaluating doses of 5, 10, 20, 40, and 60 mg, and a multiple-ascending dose phase evaluating once-daily doses of 20, 40, and 60 mg for 7 days. Each cohort included a smaller placebo control group.

Interim results reported in November 2022 demonstrated the following:

The pharmacokinetic profile of subcutaneous SBT-272 was consistent with non-clinical allometric scaling predictions. Plasma concentrations at the studied doses were in the range predicted to produce therapeutic brain concentrations based on the preclinical efficacy data in TDP-43 mutant motor neuron models and the SOD1(G93A) mouse model [5].

The safety profile was favorable. Injection site reactions were the most commonly reported adverse event at doses of 5 to 40 mg and were characterized as mild to moderate in severity, generally resolving within approximately 4 hours of dosing. In the 60 mg dose cohorts, injection site reaction severity increased relative to lower doses [5]. No dose-limiting toxicities, serious adverse events, or clinically significant laboratory, vital sign, or electrocardiographic findings were reported in the interim analysis.

6.2 Orphan Drug Designation

The FDA granted Orphan Drug Designation for SBT-272 for the treatment of ALS in 2022, based on the preclinical neuroprotective data and the rationale for mitochondrial-targeted therapy in a disease without curative treatment [4].

6.3 Clinical development in ALS patients

As of the most recent monograph revision, no Phase 2 efficacy data in ALS patients have been reported in a peer-reviewed forum or in registered conference proceedings. The Phase 1 safety and pharmacokinetic data support advancement to efficacy trials in ALS, and clinical studies in ALS patients are planned based on company communications [5].

6.4 Dry age-related macular degeneration

A separate development program is advancing topical ocular bevemipretide for dry AMD. Preclinical data presented at the 2024 Keystone Symposium and at ARVO 2024 and 2025 demonstrated that bevemipretide eye drops were well tolerated in a 13-week GLP toxicology study in rabbits, achieved target tissue concentrations (RPE/choroid and retina) at expected therapeutic levels, and maintained tissue concentrations through a 4-week recovery period [6, 7]. A Phase 1 study design informed by these preclinical data has been reported; clinical results have not been published as of monograph preparation.

7. Reported Research Dose Ranges

7.1 Preclinical doses

TDP-43 upper motor neuron model (in vitro): SBT-272 produced dose-dependent improvements in mitochondrial motility and axon outgrowth at concentrations in the low nanomolar to high nanomolar range [1].

TDP-43 transgenic mouse (in vivo): Chronic subcutaneous dosing for 60 days produced significant reductions in astrogliosis, microgliosis, and TDP-43 pathology in the motor cortex. Specific doses used in the in vivo chronic study have not been published in the peer-reviewed literature but are consistent with the 1 to 7.5 mg/kg/day range used in pharmacokinetic characterization [1].

SOD1(G93A) transgenic mouse: Intraperitoneal dosing at 0.5 and 5.0 mg/kg/day beginning at 8 weeks of age and continuing for 10 weeks. The 5.0 mg/kg/day dose produced significant effects on neurological symptom onset and lifespan in male mice [2].

Alpha-synucleinopathy model (Parkinson's disease): Two subcutaneous dose levels were tested; the higher dose produced significant protection against dopaminergic neuron loss and reduction of alpha-synuclein burden and neuroinflammation markers [3].

Pharmacokinetic characterization (mice): Subcutaneous doses of 1, 5, and 7.5 mg/kg/day for 5 days produced brain homogenate trough concentrations of 10 to 100 nanomolar [2].

7.2 Clinical doses

Phase 1 healthy volunteers (subcutaneous): Single ascending doses of 5, 10, 20, 40, and 60 mg. Multiple ascending doses of 20, 40, and 60 mg once daily for 7 days [5].

7.3 Topical ocular doses

Preclinical dose levels for topical ocular bevemipretide in the dry AMD program have not been fully disclosed; the 13-week GLP toxicology study evaluated multiple concentration levels of bevemipretide eye drops [6, 7].

8. Sourcing and Quality Verification

SBT-272 (bevemipretide) is available from research chemical suppliers as a research-grade preparation. Suppliers identified in public catalogues include Probechem Biochemicals, MedKoo Biosciences, and MedChemExpress, typically as the free base or hydrochloride salt at greater than 95 percent purity by HPLC.

Pharmaceutical-grade SBT-272 for clinical use is manufactured by Stealth BioTherapeutics and contract manufacturing organizations under current Good Manufacturing Practice conditions. The clinical-grade material is not available for general research purchase.

Investigators should confirm compound identity and purity on every research-grade lot through:

- Reverse-phase high-performance liquid chromatography area-percent purity, ideally greater than 95 percent
- Mass spectrometry confirmation of molecular weight (608.37 for the protonated free base $[M+H]^+$, or 607.36 for the monoisotopic neutral mass)
- Nuclear magnetic resonance spectroscopy (proton and carbon-13) to confirm structural identity, particularly the integrity of the oxadiazole heterocycle and the D-arginine stereochemistry
- Chiral HPLC or circular dichroism to confirm stereochemical purity
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography for common synthesis solvents (dimethylformamide, dimethyl sulfoxide, acetonitrile, methanol, trifluoroacetic acid)

The research-grade SBT-272 market is less established than that for elamipretide, and lot-to-lot variability is possible. On-receipt analytical confirmation is strongly recommended for any investigation where dose-response precision is important. Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis.

9. Reconstitution and Handling

SBT-272 is supplied as a lyophilized or crystalline solid and is reconstituted as needed for research applications.

Aqueous solutions: The compound is soluble in aqueous buffers at neutral to mildly acidic pH owing to the cationic guanidinium and amino groups. Stock solutions at 1 to 10 mM in phosphate-buffered saline (pH 7.4) or in sterile water are appropriate for in vitro applications. For subcutaneous injection in animal studies, solutions in sterile saline or phosphate-buffered saline at concentrations of 1 to 10 mg/mL are standard.

Organic solvent solutions: Dimethyl sulfoxide is the standard organic solvent for stock preparation at high concentrations (10 to 100 mM). The final DMSO concentration in biological assays should be maintained below 0.1 percent (volume/volume) to avoid solvent-mediated mitochondrial effects.

Storage: Lyophilized solid should be stored at minus 20 degrees Celsius, desiccated, and protected from light. Reconstituted aqueous solutions should be aliquoted for single use and stored at minus 20 degrees Celsius; stability at refrigerated conditions (2 to 8 degrees Celsius) for short-term use (up to 7 days) is expected based on the structural class, but formal stability data for research-grade SBT-272 have not been published. DMSO stock solutions are stable at minus 20 degrees Celsius for at least 6 months based on structural class precedent.

Handling: Standard laboratory precautions for peptidomimetic compounds apply. The compound should be handled with appropriate personal protective equipment. Avoid repeated freeze-thaw cycles of reconstituted solutions; aliquoting is recommended.

10. Stack Interaction Considerations

SBT-272 interacts with the inner mitochondrial membrane through a mechanism that is mechanistically distinct from conventional receptor-ligand pharmacology. Stack interaction considerations are therefore primarily pharmacodynamic rather than pharmacokinetic.

Other mitochondria-targeted compounds: Concurrent use with elamipretide is pharmacologically redundant, as both compounds target the same cardiolipin binding sites on the inner mitochondrial membrane. Concurrent use with other mitochondrial-targeted antioxidants (MitoQ, MitoTEMPO, SkQ1) produces partially overlapping pharmacology through different mechanisms (MitoQ and SkQ1 are ubiquinone and plastoquinone derivatives that accumulate through the triphenylphosphonium cation, not through cardiolipin binding). The combination has not been studied but may produce additive or synergistic mitochondrial protective effects.

Electron transport chain modulators: Compounds that directly inhibit or modulate electron transport chain complexes (rotenone, antimycin A, oligomycin in research settings; metformin at the Complex I level in clinical use) may partially counteract the supercomplex-stabilizing effect of SBT-272. Concurrent metformin is not expected to produce a clinically meaningful interaction at therapeutic doses, but investigators conducting in vitro studies with electron transport chain inhibitors should consider the opposing pharmacology.

Cytochrome P450 interactions: SBT-272 does not contain structural features associated with cytochrome P450 inhibition or induction. Based on the peptidomimetic structure, clinically significant CYP-mediated drug-drug interactions are not anticipated.

Riluzole and edaravone: As SBT-272 is being developed for ALS, concurrent use with approved ALS therapies (riluzole, edaravone, AMX0035/sodium phenylbutyrate-aurursodiol) is expected in clinical practice. The Bhatt et al. (2023) study compared SBT-272 directly to edaravone and AMX0035 in TDP-43 mutant upper motor neuron cultures and reported that SBT-272 produced superior restoration of

neuronal health metrics [1]. These findings suggest complementary rather than antagonistic mechanisms, though formal drug-drug interaction studies have not been conducted.

Coenzyme Q10 and NAD⁺ precursors: Investigational mitochondrial support compounds (coenzyme Q10, nicotinamide riboside, nicotinamide mononucleotide) act at different nodes of the mitochondrial energy production pathway and are mechanistically complementary to the cardiolipin-stabilizing mechanism of SBT-272. No interaction data are available; the combination is plausible for research applications.

11. Adverse Events and Safety

11.1 Preclinical safety

SBT-272 has been generally well tolerated in preclinical toxicology studies at the doses used in pharmacology experiments. The compound was administered for up to 60 days in the TDP-43 transgenic mouse model and for up to 10 weeks in the SOD1(G93A) mouse model without reported dose-limiting toxicities [1, 2]. Formal GLP toxicology data for the systemic (subcutaneous) program have not been published in the peer-reviewed literature but were sufficient to support the Phase 1 clinical trial initiation.

For the topical ocular program, a 13-week GLP toxicology study in rabbits demonstrated that bevemipretide eye drops reached ocular target tissues at expected therapeutic concentrations, with findings deemed non-adverse across dose levels and largely reversible following a 4-week recovery period [7].

11.2 Clinical safety (Phase 1)

The Phase 1 study in healthy volunteers reported the following safety findings from interim analysis [5]:

Injection site reactions: The most commonly reported adverse event at subcutaneous doses of 5 to 40 mg. These were characterized as mild to moderate in severity and generally resolved within approximately 4 hours of dosing. At the 60 mg dose level, injection site reaction severity increased relative to lower doses. The injection site reaction profile is consistent with the experience of the related elamipretide in clinical development and with the class effect of subcutaneously administered cationic peptides and peptidomimetics.

Systemic adverse events: No serious adverse events, dose-limiting toxicities, or clinically significant abnormalities in laboratory parameters, vital signs, or electrocardiographic parameters were reported in the interim analysis at any dose level [5].

11.3 Class-effect considerations from elamipretide

The elamipretide clinical development program provides relevant class-effect safety information. In the Barth syndrome registration program and in prior clinical studies in primary mitochondrial myopathy and heart failure, the principal adverse events of subcutaneous elamipretide were injection site reactions (pain, erythema, pruritus), which were the most commonly reported adverse event and the principal reason for treatment discontinuation in some patients. Systemic tolerability was otherwise favorable at doses up to 40 mg subcutaneously daily [8]. The SBT-272 clinical safety profile to date is broadly consistent with this class-effect pattern.

11.4 Theoretical safety considerations

Cardiolipin stabilization is a protective mechanism; no on-target toxicity mechanism has been identified or is expected from the pharmacology. The principal theoretical safety considerations are immunogenicity (relevant to any peptidomimetic administered chronically by injection, though not reported for elamipretide or SBT-272 in available data), injection site tolerability (the dose-limiting consideration based on Phase 1 data), and the unknown long-term consequences of chronic mitochondrial supercomplex stabilization in non-target tissues.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five mitochondria-targeted or neuroprotective candidates against SBT-272, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile (clinical or preclinical), and overall validation. The five candidates were selected as compounds that share either the mitochondrial-targeting mechanism or the neurodegenerative disease application space with SBT-272.

12.1 Elamipretide (SS-31, MTP-131, Bendavia, Forzinity)

Mechanism: Cardiolipin-binding tetrapeptide (D-Arg-Dmt-Lys-Phe-NH₂) that stabilizes electron transport chain supercomplexes at the inner mitochondrial membrane [10]. FDA-approved for Barth syndrome (September 2025) under the trade name Forzinity [8].

Novelty: Low relative to SBT-272 (the parent compound from which SBT-272 was derived). The mechanism is identical; the differentiation is pharmacokinetic rather than pharmacodynamic.

Effect size: In Barth syndrome, elamipretide produced statistically significant improvements in 6-minute walk distance and cardiac function in the TAZPOWER pivotal trial [8]. In primary mitochondrial myopathy (the MMPOWER trials), the compound did not meet its primary endpoint [17]. In the cardiovascular and ophthalmology programs, mixed results were reported. For neurodegenerative applications, elamipretide has shown preclinical activity in models of neuroinflammation and cognitive impairment but with lower brain concentrations than SBT-272 at equivalent systemic doses [11].

Promising potential: High for peripheral mitochondrial diseases (Barth syndrome approved; primary mitochondrial myopathy and cardiac applications in development). Low for neurodegenerative indications, where the limited brain penetration is a structural limitation that SBT-272 was specifically designed to overcome.

Side-effect profile: Favorable. The principal adverse event is injection site reaction (pain, erythema, pruritus) with subcutaneous administration. Systemic tolerability is well characterized through extensive Phase 2 and Phase 3 clinical experience [8].

Overall validation: High. The compound has FDA approval for Barth syndrome, extensive Phase 2 and Phase 3 clinical data across multiple indications, and a well-characterized safety profile. It serves as the reference compound for the cardiolipin-stabilizing class.

Comparison to SBT-272: Elamipretide is the parent compound and shares the core mechanism. SBT-272 is differentiated by superior brain penetration, higher mitochondrial uptake, and improved systemic bioavailability, properties that are specifically relevant for neurodegenerative applications. Elamipretide remains the preferred compound for peripheral mitochondrial diseases; SBT-272 is the preferred analog for CNS-targeted applications.

12.2 Edaravone (Radicava)

Mechanism: Free-radical scavenger (3-methyl-1-phenyl-2-pyrazolin-5-one) that quenches lipid peroxy radicals, hydroxyl radicals, and peroxynitrite. FDA-approved for ALS (May 2017) [18].

Novelty: Low. The free-radical scavenging mechanism is well established and non-specific. The compound does not target mitochondria selectively.

Effect size: In the Phase 3 ALS trial (Study 19), edaravone produced a 33 percent reduction in decline on the ALSFRS-R scale compared to placebo over 24 weeks in a highly selected patient population (early-stage ALS, definite or probable diagnosis, forced vital capacity greater than 80 percent, scores of 2 or greater on all ALSFRS-R items) [18]. The effect size in unselected ALS populations is smaller and has been debated. In the Bhatt et al. (2023) TDP-43 upper motor neuron model, SBT-272 produced superior neuroprotective effects compared to edaravone at pharmacologically relevant concentrations [1].

Promising potential: Moderate. The compound is approved and marketed for ALS but faces competition from newer therapies and questions about real-world efficacy in unselected populations.

Side-effect profile: Favorable for the oral formulation (Radicava ORS). The original intravenous formulation required infusion center visits and was associated with infusion-related reactions. Hypersensitivity reactions and sulfite sensitivity are noted in the prescribing label.

Overall validation: Moderate. FDA-approved for ALS with Phase 3 clinical evidence, but the magnitude of clinical benefit and the applicability to unselected patients remain subjects of clinical debate.

Comparison to SBT-272: Edaravone acts upstream as a nonspecific radical scavenger; SBT-272 acts at the inner mitochondrial membrane to prevent the generation of reactive oxygen species at their primary source. The mechanistic precision of SBT-272 (targeting the cardiolipin-supercomplex node) is greater than that of edaravone. Preclinical head-to-head comparison favored SBT-272 in TDP-43 motor neuron models [1]. SBT-272 has no clinical efficacy data in ALS patients; edaravone has FDA approval.

12.3 AMX0035 (Sodium phenylbutyrate/taurursodiol, Relyvrio)

Mechanism: Fixed-dose combination of sodium phenylbutyrate (endoplasmic reticulum stress modulator) and taurursodiol (mitochondrial permeability transition pore modulator). Initially approved by the FDA for ALS in September 2022 under the trade name Relyvrio; the marketing authorization was subsequently withdrawn following the negative Phase 3 PHOENIX trial results [19].

Novelty: Moderate. The combination of endoplasmic reticulum and mitochondrial stress modulation was a novel dual-targeting concept at the time of approval.

Effect size: The Phase 2 CENTAUR trial reported a 2.32-point per month slower decline on the ALSFRS-R compared to placebo [19]. The Phase 3 PHOENIX trial (n=664) failed to demonstrate a statistically significant effect on the primary endpoint, leading to voluntary withdrawal of the marketing authorization by Amylyx Pharmaceuticals in April 2024 [19].

Promising potential: Low. Development for ALS is discontinued following the Phase 3 negative readout and marketing authorization withdrawal.

Side-effect profile: The combination was associated with gastrointestinal adverse events (nausea, diarrhea, abdominal pain) and with palatability issues. Serious adverse events were uncommon.

Overall validation: Low. Initial FDA approval was based on Phase 2 data; the Phase 3 trial failed to confirm efficacy, resulting in market withdrawal.

Comparison to SBT-272: AMX0035 modulates mitochondrial permeability transition (through taurursodiol) by a mechanism distinct from cardiolipin stabilization. In the Bhatt et al. (2023) preclinical comparison, SBT-272 produced superior neuroprotective effects in TDP-43 motor neuron models [1]. The clinical failure of AMX0035 in Phase 3 underscores the challenge of ALS drug development and the importance of robust preclinical-to-clinical translation.

12.4 MitoQ (Mitoquinone mesylate)

Mechanism: Mitochondria-targeted antioxidant consisting of a ubiquinone (coenzyme Q10) moiety covalently linked to a triphenylphosphonium cation, which drives accumulation in the mitochondrial matrix through the membrane potential gradient [20]. MitoQ acts as an antioxidant in the mitochondrial matrix by accepting electrons and preventing lipid peroxidation.

Novelty: Moderate. The triphenylphosphonium-targeting strategy was an early innovation in mitochondria-targeted therapeutics and predates the SS-peptide class.

Effect size: In a Phase 2 trial in Parkinson's disease (the PROTECT study), MitoQ at 40 mg or 80 mg daily for 12 months failed to demonstrate a significant difference from placebo on the UPDRS Part III motor score [20]. In preclinical models of liver disease, cardiac ischemia-reperfusion injury, and oxidative stress, MitoQ has shown protective effects. The compound is marketed as a dietary supplement (not a regulated pharmaceutical) in multiple jurisdictions.

Promising potential: Low for neurodegenerative disease indications based on the negative Parkinson's disease Phase 2 trial. The compound continues as a marketed dietary supplement and as a research tool.

Side-effect profile: Well tolerated at studied doses. Gastrointestinal discomfort was the principal adverse event in clinical studies. The supplement market positioning means that long-term safety data from controlled clinical use are limited.

Overall validation: Low to moderate. The compound has a single negative Phase 2 trial in neurodegeneration and substantial preclinical data. It serves as the reference compound for the triphenylphosphonium-targeted mitochondrial antioxidant class.

Comparison to SBT-272: MitoQ accumulates in the mitochondrial matrix through the membrane potential gradient and acts as a general-purpose antioxidant; SBT-272 localizes to the inner mitochondrial membrane through cardiolipin binding and stabilizes supercomplex organization. The mechanisms are complementary at the pharmacological level. SBT-272 addresses the upstream cause of mitochondrial reactive oxygen species generation (supercomplex disassembly), while MitoQ scavenges reactive oxygen species after generation. SBT-272 has superior brain penetration and a more precisely defined molecular target. MitoQ is orally bioavailable (an advantage over subcutaneous SBT-272) but failed in the only neurodegenerative disease efficacy trial.

12.5 Omaveloxolone (Skyclarys)

Mechanism: Synthetic triterpenoid activator of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, a master transcriptional regulator of cellular antioxidant defense and mitochondrial biogenesis genes. FDA-approved for Friedreich's ataxia (February 2023) [21].

Novelty: Moderate. The Nrf2 activation mechanism is well characterized but was novel in the context of Friedreich's ataxia treatment.

Effect size: In the pivotal MOXIe trial in Friedreich's ataxia, omaveloxolone 150 mg daily produced a statistically significant 2.40-point improvement on the modified Friedreich's Ataxia Rating Scale (mFARS) compared to placebo over 48 weeks [21]. The effect size is clinically meaningful in the context of an unremitting neurodegenerative disease with no prior approved therapy.

Promising potential: High for Friedreich's ataxia (FDA-approved). Moderate for broader mitochondrial and neurodegenerative indications; the Nrf2 mechanism is being explored in Alzheimer's disease, Parkinson's disease, and ALS preclinical studies.

Side-effect profile: The principal adverse events are hepatotoxicity (alanine aminotransferase elevation, requiring hepatic function monitoring), nausea, headache, fatigue, and decreased appetite. The hepatotoxicity signal resulted in a

boxed warning in the prescribing label [21].

Overall validation: High. FDA-approved for Friedreich's ataxia with Phase 3 clinical evidence and a well-characterized safety profile.

Comparison to SBT-272: Omaveloxolone and SBT-272 both target mitochondrial pathology but through fundamentally different mechanisms. Omaveloxolone activates a nuclear transcription factor that upregulates endogenous antioxidant defenses and mitochondrial biogenesis; SBT-272 directly stabilizes the cardiolipin-supercomplex architecture at the inner membrane. The two mechanisms are complementary and could theoretically be combined. Omaveloxolone has the advantage of oral bioavailability and FDA approval; SBT-272 has the advantage of a more direct and mechanistically precise intervention at the mitochondrial membrane. The hepatotoxicity signal of omaveloxolone is a differentiating safety consideration; SBT-272 has not shown hepatotoxicity in available data.

12.6 Comparator summary

The five comparator compounds span the mitochondria-targeted and neuroprotective therapeutic landscape. **Elamipretide** is the parent compound and clinical reference for the cardiolipin-binding class, with FDA approval for Barth syndrome but limited brain penetration that restricts neurodegenerative applications. **Edaravone** is an approved ALS therapy with modest effect size and a nonspecific radical-scavenging mechanism that SBT-272 appears to surpass in preclinical comparisons. **AMX0035** represented a dual-targeting concept that ultimately failed in Phase 3, underscoring the difficulty of ALS drug development. **MitoQ** is a mitochondrial-matrix antioxidant that failed in Parkinson's disease Phase 2. **Omaveloxolone** is an Nrf2 activator approved for Friedreich's ataxia with oral bioavailability but hepatotoxicity concerns.

SBT-272 occupies a distinct position in this landscape: it is the only compound that combines cardiolipin-specific mitochondrial membrane stabilization with optimized central nervous system penetration. The preclinical data, particularly the head-to-head comparisons with edaravone and AMX0035 in TDP-43 motor neuron models, support the mechanistic advantage of targeting the upstream mitochondrial dysfunction rather than scavenging downstream reactive oxygen species or modulating parallel stress pathways. The compound is earlier in clinical development than most comparators, with Phase 1 data in healthy volunteers but no Phase 2 efficacy data in patients. The Orphan Drug Designation for ALS and the strong

preclinical evidence package position SBT-272 for advancement to patient efficacy trials, the outcome of which will determine whether the preclinical advantage translates to clinical benefit.

The principal question for investigators evaluating SBT-272 against this comparator landscape is whether the precision of the cardiolipin-stabilizing mechanism and the enhanced brain penetration will produce a clinically meaningful effect size in ALS and other neurodegenerative diseases that is superior to the effects achieved by the approved and failed comparators. The preclinical evidence is promising; the clinical proof remains to be established.

13. References

1. Bhatt N, Bhatt G, Kaya F, et al. SBT-272 improves TDP-43 pathology in ALS upper motor neurons by modulating mitochondrial integrity, motility, and function. *Neurobiol Dis.* 2023;178:106022.
2. Stealth BioTherapeutics. Stealth BioTherapeutics presents positive SBT-272 pre-clinical data at 2021 Annual Northeast Amyotrophic Lateral Sclerosis (NEALS) Meeting. Press release, October 13, 2021.
3. Stealth BioTherapeutics. Stealth BioTherapeutics presents positive SBT-272 pre-clinical data at International Parkinson and Movement Disorder Society Virtual Congress 2021. Press release, September 17, 2021.
4. Stealth BioTherapeutics. Stealth BioTherapeutics announces SBT-272 data updates and Orphan Drug Designation for the treatment of amyotrophic lateral sclerosis (ALS). Press release, November 8, 2022.
5. Stealth BioTherapeutics. Stealth BioTherapeutics announces new SBT-272 data and trial initiation. Press release, March 17, 2022.
6. Stealth BioTherapeutics. Next-generation ocular topical SBT-272 demonstrates optimized retina tissue exposure: building upon elamipretide for treating dry AMD. *Invest Ophthalmol Vis Sci.* 2024;65(7):ARVO abstract.
7. Stealth BioTherapeutics. Topical bevemipretide (SBT-272) eye drops in development for dry AMD: Phase 1 trial design informed by 13-week GLP study results. *Invest Ophthalmol Vis Sci.* 2025;ARVO abstract.
8. Stealth BioTherapeutics. Stealth BioTherapeutics announces FDA accelerated approval of Forzinity (elamipretide HCl), the first therapy for progressive and life-limiting ultra-rare genetic disease Barth syndrome. Press release, 2025.
9. United States Patent 12,252,554. Analogs that target mitochondrial diseases. Assigned to Stealth BioTherapeutics.
10. Szeto HH. First-in-class cardiolipin-protective compound as a therapeutic agent to restore mitochondrial bioenergetics. *Br J Pharmacol.* 2014;171(8):2029-2050.

11. Cognitive Vitality Report: SBT-272. Alzheimer's Drug Discovery Foundation. Available at: alzdiscovery.org/uploads/cognitive_vitality_media/GBT-272.pdf.
12. Paradies G, Paradies V, Ruggiero FM, Petrosillo G. Role of cardiolipin in mitochondrial function and dynamics in health and disease: molecular and pharmacological aspects. *Cells*. 2019;8(7):728.
13. Letts JA, Fiedorczuk K, Sazanov LA. The architecture of respiratory supercomplexes. *Nature*. 2016;537(7622):644-648.
14. Kagan VE, Tyurin VA, Jiang J, et al. Cytochrome c acts as a cardiolipin oxygenase required for release of proapoptotic factors. *Nat Chem Biol*. 2005;1(4):223-232.
15. Smith EF, Shaw PJ, De Vos KJ. The role of mitochondria in amyotrophic lateral sclerosis. *Neurosci Lett*. 2019;710:132933.
16. Area-Gomez E, Guardia-Laguarta C, Schon EA, Bhatt N. Mitochondria, OxPhos, and neurodegeneration: cells are not just running out of gas. *J Clin Invest*. 2019;129(1):34-45.
17. Karaa A, Haas R, Goldstein A, et al. Randomized dose-escalation trial of elamipretide in adults with primary mitochondrial myopathy. *Neurology*. 2018;90(14):e1212-e1221.
18. Writing Group on behalf of the Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2017;16(7):505-512.
19. Amylyx Pharmaceuticals. Amylyx Pharmaceuticals announces voluntary withdrawal of Relyvrio from the market following negative Phase 3 PHOENIX trial. Press release, April 2024.
20. Snow BJ, Rolfe FL, Lockhart MM, et al. A double-blind, placebo-controlled study to assess the mitochondria-targeted antioxidant MitoQ as a disease-modifying therapy in Parkinson's disease. *Mov Disord*. 2010;25(11):1670-1674.
21. Lynch DR, Chin MP, Delatycki MB, et al. Safety and efficacy of omaveloxolone in Friedreich ataxia (MOXIe study): a multicentre, randomised, double-blind, placebo-controlled, Phase 2 trial. *Lancet Neurol*. 2021;20(5):339-347.

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